



Pharmaceutically Active Compounds in the Environment: Risks, Trade-offs and Sewer Epidemiology

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ABSTRACT

The release of pharmaceutically active compounds (PhACs) into the environment has been a growing source of concern over the past decade. Only recently has it been demonstrated that the release of such contaminants can lead to the feminization of fish and has led to a dramatic decline in the population of other species in certain parts of the world. With such causally confirmed impacts and considerable uncertainty associated with the potential effects of almost 3,000 such pharmaceuticals in current use, it is prudent to be cautious and to aim to further understand the sources, the risks, and the trade-offs associated with the environmental presence and release of PhACs. Recognizing this, the overall objective of this thesis was to explore and model the relationships between the upstream patterns and level of use of PhACs and their resulting downstream mass loads in wastes and the environment and then to apply this understanding to address important human health and eco-toxicological issues.

In this research, the release and, hence, the environmental presence of PhACs are viewed from two distinct perspectives. The first is from an upstream perspective in which the degree of use or excretion of PhACs is used to estimate the environmental load of contaminants which, in turn, allows one to assess eco-toxicological and/or human-health concerns. Four unique evaluations were performed by adopting this perspective. The first evaluation resulted in the development of a model for the endogenous release of androgens, thyroids and their *in vivo* metabolites to the environment. The model was used to assess the eco-toxicological relevance of such contaminants and, from this, it was found that the endogenous release of androstenedione carries the potential to yield impacts on fish under a high exposure scenario. The second evaluation led to the development of an approach for the assessment of human-health and eco-toxicological risks posed by PhACs in urine that is applied to agricultural land. This approach was applied to evaluate 25 widely-used PhACs through six routes of exposure. Of the 25 PhACs evaluated, 14 were found to pose possible eco-toxicological or human-health risks. The third evaluation explored the sources and the human-health relevance regarding the aquatic release of 335 PhACs to the Canadian environment. The evaluation suggested that up to seven distinct sources can lead to the aquatic release of a given PhAC, with the importance of a given source term varying significantly from one case to another. PhACs appear to be predominantly released to the environment through their use in the general population but, in certain cases, their use in hospitals and their release through other sources (e.g., endogenous production, use of clinical precursors and illicit drugs) can also be important. When the human-health relevance regarding the potential presence of the 335 PhACs in drinking waters was evaluated, it was established that 323 of the PhACs are expected to pose a negligible risk to human-health. However, the results indicated that the following 14 PhACs warrant further study: triiodothyronine, thyroxine, ramipril and its

metabolite ramiprilat, candesartan, lisinopril, atorvastatin, lorazepam, fentanyl, atenolol, metformin, enalaprilat, morphine and irbesartan. Furthermore, it was demonstrated that environmental monitoring of PhACs is currently insufficient to properly assess their human-health impacts. In the fourth evaluation, an approach was developed to better understand and evaluate the relationships and trade-offs involved between a population's contraceptive choices and their respective load of steroidal estrogens to the environment. Counterintuitively, the analysis suggested that use of each contraceptive option, be it estrogen based or purely physical, prevents the release of steroidal estrogens to the environment. It was also shown that those who use ethinylestradiol-based oral contraceptives produce a lower estrogenic load on the environment than those who discontinue the use of such an option.

The second perspective adopted in this research was to use the downstream load of drug residues in wastewaters to gain information about the behaviour of an upstream population. Specifically research was conducted to use a sewer epidemiology approach to determine how best to translate measured loads of selected drug residues in wastewaters to the levels with which the parent illicit drugs are used in their respective upstream populations. To accomplish this, mass balances were developed for a number of illicit drugs in common use including amphetamine, cocaine, ecstasy, heroin, methamphetamine and tetrahydrocannabinol. Through the development of these mass balances, it was established that the extrapolation factors used in the literature that relate drug residue measurements in wastewaters to drug use in a population required significant refinement to improve their reliability and applicability.

RÉSUMÉ

Le rejet de composés pharmaceutiques actifs (PhACs) dans l'environnement est devenu une source d'inquiétude croissante dans la dernière décennie. Ce n'est que récemment qu'il a été établi que le rejet de tels polluants peut déclencher la féminisation des poissons et qu'il a conduit au déclin massif de populations d'autres espèces dans certains endroits du monde. Face aux conséquences avérées et à l'incertitude considérable qui entoure les effets potentiels des presque 3000 composés de la sorte utilisés actuellement, il est prudent de rester vigilant et de chercher à mieux comprendre les sources, les risques, et les compromis relatifs à la présence et au rejet des PhACs dans l'environnement. Dans cette perspective, l'objectif principal de cette thèse reposait sur la caractérisation et la modélisation des relations entre les tendances, ainsi que le niveau, d'utilisation des PhACs en amont et leur concentration résultante dans les déchets et l'environnement en aval, afin de s'attaquer à des problématiques cruciales de santé humaine et d'éco-toxicologie.

Au travers de cette étude, le rejet et, conséquemment, la présence des PhACs dans l'environnement sont considérés depuis deux perspectives différentes. La première est une perspective amont depuis laquelle le degré d'utilisation ou d'excrétion des PhACs est utilisé pour estimer la concentration des polluants dans l'environnement, ce qui, en retour, permet d'évaluer les inquiétudes liées à l'éco-toxicologie et/ou la santé humaine. Quatre évaluations uniques en leur genre ont été menées depuis cette perspective. La première évaluation a débouché sur le développement d'un modèle informatique pour le rejet endogène d'androgènes, d'hormones thyroïdiennes et leurs métabolites *in vivo* dans l'environnement. Le modèle a été utilisé pour évaluer la pertinence de tels polluants d'un point de vue éco-toxicologique et, en conséquence, il a été mis en évidence que le rejet endogène d'androstènedione comporte un risque d'impacts mesurables sur les poissons dans le cadre d'un scénario de forte exposition. La deuxième évaluation a conduit au développement d'une approche pour l'évaluation des risques liés à la santé humaine et à l'éco-toxicologie posés par les PhACs présents dans l'urine épandue sur les terres agricoles. Cette approche a été appliquée pour évaluer au travers de six voies d'exposition 25 PhACs abondamment utilisés. Des 25 PhACs évalués, 14 pourraient poser des risques d'éco-toxicologie ou pour la santé humaine. La troisième évaluation portait sur l'analyse des sources et la pertinence en termes de risques pour la santé humaine du rejet aquatique de 335 PhACs dans l'environnement au Canada. L'évaluation suggère qu'un maximum de sept sources distinctes peut mener au rejet aquatique d'un PhAC donné, avec l'importance du terme d'une source donnée variant de manière significative d'un cas à l'autre. Les PhACs s'avèrent être rejetés principalement dans l'environnement à travers leur utilisation au sein de la population en général, mais dans certains cas, leur utilisation dans les hôpitaux et leur rejet via d'autres

sources (production endogène, utilisation de précurseurs cliniques et de drogues illicites, par exemple) peuvent aussi être importants. Après évaluation de la pertinence en termes de risque pour la santé humaine de la présence potentielle des 335 PhACs dans les eaux potables, 323 de ces PhACs devraient poser un risque négligeable pour la santé humaine. Cependant, les résultats indiquent que les 14 PhACs suivants nécessitent des études plus approfondies : triiodothyronine, thyroxine, ramipril et son métabolite ramiprilat, candesartan, lisinopril, atorvastatin, lorazepam, fentanyl, atenolol, metformin, enalaprilat, morphine and irbesartan. De plus, il a été démontré que la surveillance environnementale des PhACs est présentement insuffisante pour évaluer de façon correcte leur impacts éco-toxicologiques et sur la santé humaine. Dans la quatrième évaluation, une approche a été développée pour mieux comprendre et évaluer les relations et compromis nécessaires entre les choix de contraception d'une population et leur concentration respective en estrogènes stéroïdiens dans l'environnement. De façon contre-intuitive, l'analyse a suggéré que l'utilisation de n'importe laquelle option de contraception, que ce soit à base d'estrogènes ou qu'elle soit purement physique, empêche le rejet d'estrogènes stéroïdiens dans l'environnement. Il a aussi été démontré que les femmes qui utilisent des contraceptifs oraux à base d'éthinylestradiol produisent une moindre concentration en estrogènes dans l'environnement que celles qui abandonnent l'utilisation d'une telle option.

La seconde perspective adoptée dans cette étude utilisait la concentration en aval de résidus de drogues dans les eaux usées pour obtenir des informations sur le comportement d'une population en amont. Une étude spécifique a été conduite pour utiliser une approche basée sur l'épidémiologie des eaux d'égout afin de déterminer comment mieux lier les concentrations mesurées de résidus de drogues sélectionnées dans les eaux usées aux niveaux d'utilisation de ces drogues illicites dans les populations respectives en amont. Pour parvenir à cette fin, des bilans massiques ont été développés pour un nombre de drogues illicites en circulation, notamment l'amphétamine, la cocaïne, l'ecstasy, l'héroïne, la métamphétamine et le tétrahydrocannabinol. Au travers du développement de ces bilans massiques, il a été établi que les facteurs d'extrapolation utilisés dans la littérature qui lient les mesures de résidus de drogues dans les eaux usées à l'utilisation de drogues dans une population nécessitent d'être affinés de manière significative pour améliorer leur fiabilité et leur applicabilité.

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CONTRIBUTIONS OF AUTHORS

This thesis is presented in a manuscript-based format. Chapters 2 to 8 present seven manuscripts detailing the methods, results and conclusions of the thesis. Five of these seven manuscripts have been published as peer reviewed journal articles in international journals and the two remaining have been submitted, as indicated below:

Chapter 2

Khan, U.; Nicell, J.A. "Assessment of the aquatic release and relevance of selected endogenous chemicals: androgens, thyroids and their in vivo metabolites." in Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations, Halden, R.U., Ed., American Chemical Society; Washington, DC, 2010, ACS Symposium Series 1048, Chapter 22, pp. 437-68.

Chapter 3

Khan, U.; Nicell, J.A. "Assessing the risk of exogenously consumed pharmaceuticals in land-applied human urine." Water Science and Technology (2010), 62(6), 1335-45.

Chapter 4

Khan, U.; Nicell, J.A. "Human-health relevance of exposure to selected pharmaceutically active compounds via drinking water". Submitted to Environment International, August, 2014.

Chapter 5

Khan, U.; Nicell, J.A. "Contraceptive options and their associated estrogenic environmental loads: relationships and trade-offs" PLOS ONE (2014) doi: 10.1371/journal.pone.0092630

Chapter 6

Khan, U.; Nicell, J.A. "Refined sewer epidemiology mass balances and their application to heroin, cocaine and ecstasy." Environment International (2011), 37(7), 1236-52

Chapter 7

Khan, U.; Nicell, J.A. "Sewer epidemiology mass balances for assessing the illicit use of methamphetamine, amphetamine and tetrahydrocannabinol." Science of the Total Environment (2012), 421-422, 144-162

Chapter 8

Khan, U.; Nicell, J.A. “Sewer epidemiology: Whom are we measuring.” Submitted to Environmental Science & Technology, August, 2014.

The author of the thesis is the primary author for all seven manuscripts. The respective roles of each author for the manuscripts presented in thesis are as follows:

- The PhD candidate, U. Khan conceptualized the studies performed, developed overall approaches, models and analysis tools, mined data from the literature, performed data and model analyses and prepared and revised manuscripts for publication.
- Prof. J. A. Nicell (Department of Civil Engineering & Applied Mechanics) was the supervisor of the PhD candidate over the course of the research. He participated in this work by helping to define the general direction of the research, supervising the research performed, providing suggestions for refining the work, contributing to the interpretation of the results, and framing the implications of the work and conclusions arising therein. He also contributed to the preparation of the manuscripts for publication.

Statement of Original Contributions to Knowledge

The body of work presented in this thesis significantly advances the understanding of the sources, risk, trade-offs and sewer epidemiology considerations as they relate to the environmental presence of PhACs. Numerous contributions are made both in terms of the extensive data sets compiled (see relevant appendices) and the modelling and analyses performed (see Chapters 2 to 8). The main original contributions to knowledge presented in thesis are as follows:

- For the first time, a model was developed for the endogenous human excretion of thyroids and androgens and their *in vivo* products. The model was applied to the situation in the USA to assess the environmental relevance of such contaminants. In turn, by evaluating the environmental relevance of such contaminants, it was established that the endogenous excretion of androstenedione has the potential to pose a threat to waterways in the USA under a high exposure scenario. The model for the endogenous release of thyroids and androgens was also applied for the first time to the Canadian context to assess the human-health relevance of such contaminants. It was established that endogenous thyroid hormones should be prioritized for further monitoring in finished drinking waters.
- An approach was developed for the first time to assess the eco-toxicological and human-health risks posed by applying urine on land for fertilization purposes. A particularly novel aspect of the work was the development of the concepts of “critical concentration” and “critical penetration”. The application of these concepts makes it possible to conduct screening-level risk evaluations in those cases where relevant consumption data is not available or is of questionable reliability.
- Comprehensive source models were developed for the first time for the release of 335 pharmaceutically active compounds (PhACs) to the environment by considering and quantifying for each an extensive range of potential source terms. The models were applied to the Canadian context and were used to estimate predicted exposure concentrations (PECs) for all 335 PhACs of interest. PEC estimates are of importance since they serve to establish at what concentrations various PhACs can be expected to occur in the environment. Moreover, PEC estimates are of critical importance when trying to evaluate the human and/or eco-toxicological risk posed by such contaminants. Prior to this, PEC estimates for only 15 PhACs had been furnished for Canada and it was unclear if all relevant sources of those PhACs had been considered in these cases. Outside Canada, the analysis presented here (see Chapter 4) is second only in

scale to a study conducted earlier in the United Kingdom. However, if scale, comprehensiveness and completeness are considered, the analysis presented here is the most substantial to date.

- The significance of non-clinical sources (i.e., endogenous and illicit use) to the environmental loads of relevant PhACs was also evaluated. Not only are such estimates the first of their kind for the Canadian context but also for a vast majority of the relevant cases they are the first furnished for any geographical location. Since the release of non-clinical sources of PhACs cannot be eliminated or mitigated by switching to alternative pharmaceutical preparations, it is important to understand the contributions to the overall load of individual PhACs that results from such sources.
- The significance of hospitals as a source was evaluated for 335 PhACs. It is of importance to understand what fractions of PhACs are sourced through hospitals since this can serve to indicate whether hospital wastewaters should be pre-treated for the presence of PhACs. Most of these evaluations were the first of their kind for Canada given that, prior to this study, hospital contributions had only been estimated for nine PhACs. Similarly, when studies conducted outside of Canada are considered, the assessment conducted here is amongst only a handful of analyses that evaluate the importance of hospitals as a point source of PhACs at a sufficient scale.
- A comprehensive approach was developed for the first time that integrates various points of departure for the effects of PhACs on human-health. This included the first wide -scale use of occupational exposure limits as a point of departure. The application of the approach resulted in acceptable daily intake (ADI) values being estimated for 335 PhACs.
- The human-health relevance of 335 PhACs with respect to their potential presence in Canadian drinking waters was established for the first time. Prior to the study presented herein, the human-health relevance for only a limited number of PhACs had been evaluated for the Canadian context. Even outside Canada, human health relevance evaluation presented here (see Chapter 4) is amongst the largest and most comprehensive conducted to-date.
- For the first time, a list of priority PhACs has been established on a scientifically sound basis whose monitoring in Canadian drinking waters is recommended. The study clearly demonstrated for the first time that most PhACs of relevance have yet to be monitored in Canadian surface and drinking waters,

which in turn served to highlight insufficiencies of existing monitoring data available for the presence of PhACs in Canadian surface and drinking waters.

- For the first time clinical, family planning and environmental fate data was integrated to understand and quantify the relationships and trade-offs involved between the contraceptive choices of a population and the corresponding environmental load of steroidal estrogens. The analysis is novel and brings a renewed vision to the field of risk assessment. Counterintuitively, it suggests that limiting the use of a given chemical in certain instances may not negate the associated environmental risk. Moreover, the analysis suggests that the possibility exists that by limiting use of a given chemical the associated environmental risk might be increased. The analysis is the first of its kind in terms of its concept, approach and methods and sets an important precedent for future research in this direction.
- The estrogenic trade-offs analysis (see in Chapter 5), established for the first time that the use of each contraceptive option when compared to using nothing at all prevents an estrogenic load from being released to the environment. Further, the analysis demonstrated for the first time that the use of contraception collectively averts an estrogenic load from being released to the environment. Also established for the first time was the result that those who use ethinylestradiol-based oral contraceptives produce a lower estrogenic load on the environment than those who discontinue the use of such an option. This result is clearly of importance when considering the pending environmental regulation of ethinylestradiol.
- For the first time, a systematic evaluation was performed to show how best to translate measured influent loads of selected drug residues into prevalence estimates for the use of parent illicit drugs (see Chapters 6 and 7). The analysis considered a number of aspects to develop sewer epidemiology mass balances for the illicit use of amphetamine, methamphetamine, cocaine, heroin, ecstasy and tetrahydrocannabinol. Specifically, for the first time, the following aspects were accounted for when developing mass balance expressions for each of the aforementioned illicit drugs: excretion patterns of an illicit drug for its various routes of administration, selection of an appropriate drug residue, illicit and licit sources that could lead to the release of the selected drug residue, sorption of the drug residue onto sewer-laden suspended solids, and the potential for the drug residue to degrade during sewer transmission.
- For the first time a very important, yet unrecognized, limitation of the field of sewer epidemiology is explored (see Chapter 8). That is, it is demonstrated that influent loads of certain residues of illicit drug

use are expected to be highly sensitive to a small number of users, thereby making it difficult to interpret geographical and temporal variations in the measured influent loads of a relevant drug residue. This represents an important contribution to the field of sewer epidemiology and establishes future directions for research in this field of growing importance.

1. INTRODUCTION

1.1 Pharmaceutically Active Compounds in the Environment

Pharmaceutically active compounds (PhACs) have been widely used for more than half a century, but it is only over the last two decades that their environmental release has been viewed with significant concern. Such concerns largely arose from evidence first gathered in England, which suggested that estrogens being released via sewage treatment effluents were causing fish in the receiving environment to become feminized (1). Among the causative estrogens identified were estradiol, estrone, estriol and ethinylestradiol (2). In addition to being endogenously produced, the first three can also result from the use of hormone replacement therapeutics. In contrast, ethinylestradiol is not naturally produced by humans and, therefore, is entirely released to the environment due to its clinical use in medications such as birth control pills (3). Therefore, this was the first case where the use of clinical preparations was shown to have a causal impact on the environment. The causal impacts of such contaminants have not only been limited to aquatic life as is demonstrated by the fact that diclofenac, which is administered for veterinary purposes and has subsequently been found in cattle carcasses, has led to a greater than 95% decline in the population of oriental white-backed vultures in Pakistan and India (4). To-date, globally, a total of 275 PhACs have been detected in various environmental matrices (5). However, with exceptions of the two causal impacts described above, it remains unclear whether the detectable presence of PhACs have significant impacts on the health of humans, aquatic life and wildlife. In light of such uncertainty, it is prudent to be cautious and aim to further understand the sources, the risks, and the trade-offs associated with the environmental presence and release of such contaminants.

1.1.1 PhACs in Canadian Surface and Finished Drinking Waters

In Canada, nearly nine thousand measurements have been performed on surface waters samples to assess the environmental presence of PhACs (see Table 1.1). Of the 8,997 analyses reported, 1,230 yielded a positive detection for a PhAC. Therefore, PhACs have been detected in Canadian surface waters with an overall detection frequency of 14%. These nearly nine thousand measurements include the analyses of 66 PhACs covering 20 therapeutic classes of drugs (see Table 1.1). Of the 66 PhACs sought, 47 have been detected in at least one sample. However, extensive monitoring data (i.e., number of samples analyzed, n , > 100) is only available for 26 PhACs. Of those that have been extensively monitored, carbamazepine is most often detected in Canadian surface waters with an overall detection frequency of 51%. Carbamazepine is typically used for the treatment of epilepsy and bipolar disorder. The highest concentration reported thus far for a PhAC in Canadian surface waters has been for the painkiller

ibuprofen at a level of 6,400 ng/L (7). Overall, the data compilation indicates that a number of PhACs are present in Canadian surface waters with concentrations varying from below detection limits to as high as the microgram per litre range.

Table 1.1 PhACs in Canadian surface water samples.

PhAC	Therapeutic Use	$n^{(a),(b)}$	$FOD^{(a),(c)}$	MEC_{Max}	Reference for MEC_{Max}
			%	ng/L	
Acetaminophen	Analgesic	212	26	3600	(7)
Amitriptyline	Anti-depressant	2	100	3.7	(16)
Atenolol	Beta-blocker	19	47	53	(20)
Atorvastatin	Lipid modifying agent	27	33	59	(17)
Bezafibrate	Lipid modifying agent	446	9	470	(7)
Bupropion	Anti-depressant	10	60	96	(23)
Carbamazepine	Anti-epilepsy drug	453	51	749	(14)
Celecoxib	Anti-inflammatory drug	9	56	14	(20)
Chloramphenicol	Antibiotic	276	0	<LOD ^(d)	
Ciprofloxacin	Antibiotic	160	3	114	(30)
Citalopram	Anti-depressant	19	89	206	(23)
Clarithromycin	Antibiotic	12	50	20	(20)
Clofibric Acid	Metabolite of clofibrate (a lipid lowering agent)	329	8	103	(6)
Codeine	Opioid	9	33	125	(20)
Cyclophosphamide	Anti-cancer drug	33	6	54	(36)
Diclofenac	Anti-inflammatory drug	443	3	194	(22)
Doxycycline	Antibiotic	281	2	73	(19)
Enalapril	Cardiovascular agent	4	25	63	(10)
Equilin	Estrogen	51	4	1.92	(13)
Erythromycin	Antibiotic	367	8	232	(31)
Estradiol	Estrogen	287	15	17	(21)
Estriol	Estrogen	262	0.4	0.48	(13)
Estrone	Estrogen	275	8	5.3	(13)
Ethinylestradiol	Estrogen	279	0	<LOD	
Fenofibrate	Lipid modifying agent	58	0	<LOD	
Fenoprofen	Anti-inflammatory drug	184	4	142	(22)
Fluoxetine	Anti-depressant	114	11	141	(23)
Gemfibrozil	Lipid modifying agent	510	26	580	(7)
Hydrochlorothiazide	Diuretic	9	0	<LOD	
Ibuprofen	Anti-inflammatory drug	496	30	6400	(7)
Indomethacin	Anti-inflammatory drug	407	2	150	(7)
Ketoprofen	Anti-inflammatory drug	210	7	80	(20)
Lovastatin	Lipid modifying agent	1	0	<LOD	
Medroxy-Progesterone	Progestogen	2	0	<LOD	
Methotrexate	Immunosuppressant	4	0	<LOD	

PhAC	Therapeutic Use	n ^{(a),(b)}	FOD ^{(a),(c)}	MEC _{Max}	Reference for MEC _{Max}
			%	ng/L	
Metoprolol	Beta-blocker	16	31	22	(20)
Nadolol	Beta-blocker	7	71	2	(18)
Naproxen	Anti-inflammatory drug	514	29	4500	(7)
Norethisterone	Progestogen	26	0	<LOD	
Norfloxacin	Antibiotic	93	3	107	(30)
Norfluoxetine	Metabolite of fluoxetine (an anti-depressant)	24	13	4	(23)
Nortriptyline	Beta-blocker	2	100	0.7	(16)
Ofloxacin	Antibiotic	9	22	57	(36)
Omeprazole	Proton pump inhibitors	9	0	<LOD	
Orlistat	Peripherally acting antiobesity products	1	0	<LOD	
Paroxetine	Anti-depressant	29	14	7	(23)
Penicillin G	Antibiotic	26	0	<LOD	
Pentoxifylline	Peripheral vasodilator	86	5	38	(36)
Progesterone	Progestogen	153	0	<LOD	
Propranolol	Beta-blocker	16	19	4.4	(20)
Rosuvastatin	Lipid modifying agent	16	44	75	(17)
Roxithromycin	Antibiotic	367	5	66	(14)
Sertraline	Beta-blocker	20	20	17	(23)
Simvastatin	Lipid modifying agent	1	0	<LOD	
Sotalol	Beta-blocker	7	0	<LOD	
Sulfacetamide	Antibiotic	9	0	<LOD	
Sulfadiazine	Antibiotic	26	0	<LOD	
Sulfapyridine	Antibiotic	38	34	61	(30)
Sulfisoxazole	Antibiotic	18	0	<LOD	
Sulfamethoxazole	Antibiotic	364	16	578	(35)
Temazepam	Anti-depressant	9	67	89	(20)
Testosterone	Androgen	97	2	3	(13)
Tetracycline	Antibiotic	214	3	35	(14)
Trimethoprim	Antibiotic	369	16	134	(31)
Venlafaxine	Anti-depressant	20	100	901	(23)
Warfarin	Antithrombotic agent	151	0	<LOD	
All	20 Therapeutic Classes	8997	14	6400	(6-36)

Notes: (a) Based on data compiled from the following sources: (6-36); (b) n = number of samples analyzed; (c) FOD = frequency of detection; (d) <LOD = less than limit of detection; (e) From reference (37).

Not only have PhACs been detected in Canadian surface waters, they have also been sought and detected in finished (i.e. treated) Canadian drinking waters, making their environmental release of direct relevance to human-health. Thus far, 5,690 measurements specifically seeking PhACs in finished Canadian drinking

waters have been performed (see Table 1.2). Of these, 170 have yielded positive detection results, which corresponds to a detection frequency of 3% in finished Canadian drinking waters. Through such monitoring of finished Canadian drinking waters, the presence of 47 PhACs has been sought and, of those, only 20 have been detected in at least one finished drinking water sample. As in the case of surface waters, extensive monitoring data ($n > 100$) is only available for 26 PhACs in drinking water. Of these, ibuprofen is the most frequently detected with an overall detection frequency of 22%. The highest concentration reported thus far for a PhAC in Canadian drinking waters has been for carbamazepine at a level of 601 ng/L (14). Overall, the data indicates that a number of PhACs are present in Canadian finished drinking waters with concentrations varying from below detection limits to as high as the hundreds of nanograms per litre.

Table 1.2 PhACs in Canadian finished drinking waters.

PhAC	Therapeutic Use	$n^{(a),(b)}$	FOD ^{(a),(c)}	MEC _{Max}	Reference for MEC _{max}
			%	ng/L	
Acetaminophen	Analgesic	176	3.4	29	(21)
Bezafibrate	Lipid modifying agent	218	1.4	2.9	(31)
Bupropion	Anti-depressant	1	0	<LOD ^(d)	
Carbamazepine	Anti-epilepsy drug	221	19	601	(14)
Chloramphenicol	Antibiotic	155	0	< LOD	
Ciprofloxacin	Antibiotic	159	0.6	7	(31)
Citalopram	Anti-depressant	1	0	< LOD	
Clarithromycin	Antibiotic	3	0	< LOD	
Clofibric Acid	Metabolite of clofibrate (a lipid lowering agent)	219	0.9	1.1	(36)
Cyclophosphamide	Anti-cancer drug	7	0	< LOD	
Diclofenac	Anti-inflammatory drug	186	0.5	n.r.	(15)
Doxycycline	Antibiotic	155	0	< LOD	
Enalapril	Cardiovascular agent	3	0	< LOD	
Equilin	Estrogen	159	0.6	n.r. ^(d)	(15)
Erythromycin	Antibiotic	214	6.1	155	(15)
Estradiol	Estrogen	237	0	< LOD	
Estriol	Estrogen	236	0	< LOD	
Estrone	Estrogen	237	0.4	1	(31)
Ethinylestradiol	Estrogen	236	0	< LOD	
Fenofibrate	Lipid modifying agent	59	0	< LOD	
Fenoprofen	Anti-inflammatory drug	63	0	< LOD	
Fluoxetine	Anti-depressant	65	1.5	6	(21)
Gemfibrozil	Lipid modifying agent	218	12	4	(14)
Ibuprofen	Anti-inflammatory drug	219	22	75	(21)
Indomethacin	Anti-inflammatory drug	218	0	< LOD	
Ketoprofen	Anti-inflammatory drug	218	1.4	1	(31)
Methotrexate	Immunosuppressant	3	0	< LOD	

PhAC	Therapeutic Use	$n^{(a),(b)}$	$FOD^{(a),(c)}$	MEC_{Max}	Reference for MEC_{max}
			%	ng/L	
Naproxen	Anti-inflammatory drug	219	0.5	26	(21)
Norethisterone	Progestogen	32	0	< LOD	
Norfloxacin	Antibiotic	159	0.6	n.r.	(14)
Ofloxacin	Antibiotic	4	50	1.6	(36)
Paroxetine	Anti-depressant	1	0	< LOD	
Penicillin G	Antibiotic	32	0	< LOD	
Pentoxifylline	Peripheral vasodilator	63	0	< LOD	
Progesterone	Progestogen	155	0	< LOD	
Roxithromycin	Antibiotic	214	4.7	41	(14)
Sertraline	Anti-depressant	1	0	< LOD	
Sulfacetamide	Antibiotic	4	0	< LOD	
Sulfadiazine	Antibiotic	32	0	< LOD	
Sulfamethoxazole	Antibiotic	221	1.4	2	(14)
Sulfapyridine	Antibiotic	4	0	< LOD	
Sulfisoxazole	Antibiotic	4	0	< LOD	
Testosterone	Androgen	68	0	< LOD	
Tetracycline	Antibiotic	214	2.3	15	(14)
Trimethoprim	Antibiotic	221	0.5	15	(14)
Venlafaxine	Antibiotic	1	0	< LOD	
Warfarin	Antithrombotic agent	155	0	< LOD	
All	14 Therapeutic Classes	5,690	3	601	(6, 10, 14, 21, 23, 31, 36)

Notes: (a) Based on data compiled from the following sources: (6, 10, 14, 21, 23, 31, 36); (b) n = number of samples analyzed; (c) FOD = frequency of detection; (d) <LOD = less than limit of detection; (e) From reference (37).

The comprehensive collection of Canadian data summarized in Tables 1.1 and 1.2 clearly indicate that PhACs are present in Canadian surface and drinking waters. However, since some estimates suggest that more than 3,000 drugs may be currently in use (60), the very limited scope of the current monitoring data for Canada becomes fairly obvious, especially given that extensive surface and drinking water occurrence data ($n > 100$) has been reported for only 26 PhACs (see Table 1.1 and 1.2) and given the only slightly higher number of PhACs that have been monitored in sewage treatment plants (38-40).

1.2 Sources of PhACs to the Environment

Given that a number of PhACs have been positively detected in Canada and elsewhere, it is of interest to determine how such chemicals enter the environment in the first place. Depending on the PhAC being considered, human and/or veterinary sources may be of significance. PhACs that result from human

sources are primarily released to the environment through the discharge of untreated and treated wastewaters (39).

The presence of a PhAC in sewage and, hence, wastewater treatment plant influents can result from a number of sources. The PhAC could be released via the excreta of those who clinically use the chemical in the general population and in hospitals (41). In addition, greywater could also be an important source of such contaminants since some PhACs are topically applied and therefore are highly likely to be released to the environment through bathing and laundering activities (42). Topically-applied PhACs typically demonstrate low absorption through human-skin and are therefore unlikely to undergo human metabolism to a significant degree (30, 42). Therefore, they are expected to be present in greywater and ultimately released to the environment largely as the parent compound. If the same PhAC or another PhAC is administered in a manner that involves human intake (i.e., oral ingestion, intravenous injection, etc.), the PhAC becomes available for human metabolic action and, depending on the PhAC being considered, could result in little to almost complete metabolism of the chemical (43). To illustrate the impact of route of administration on the environmental load of a PhAC, consider the example of estradiol. This estrogen can be administered either orally or topically (37). Oral estradiol is extensively metabolised upon ingestion, with only 10% of the administered dose being excreted unchanged via urine (44). In contrast, when estradiol is applied topically, as much as 83% of the applied dose remains unabsorbed and therefore carries the potential to be released “as is” to the environment (45). Unfortunately, routes with which a PhAC is administered are rarely considered when estimating the environmental loads (42). Therefore, given the major role of metabolism in many PhACs there is a substantial need to consider such routes of administration when estimating the environmental loads of PhACs.

As introduced above, a PhAC could be clinically administered or made available for human use in the general population via pharmacies and/or through hospitals. Intuitively hospitals are often considered to be an important source of PhACs to the environment (46). However, it often remains unclear as to which PhACs are predominantly used in or sourced through hospitals and, by extension, what fraction of a given load of a PhAC originates in hospitals. Such information is of importance since it can serve to indicate whether hospital wastewaters should be pre-treated for the presence of PhACs. More specifically, in Canada, the relative importance of hospitals as a source for PhACs has only been evaluated for 9 PhACs to date (47). Therefore, there is much room to advance our understanding about the importance of Canadian hospitals as point sources for the clinical use and/or dispensing of PhACs. Even outside of Canada, only a handful of analyses of sufficient scale have been performed evaluating the importance of hospitals as a point source of PhACs (42, 48- 50).

In addition to the clinical use of a PhAC itself, the same PhAC could also be present in wastewater influents due to the clinical use of other preparations that are metabolized by humans to the PhAC of interest. To account for such sources, all metabolic precursors for a given PhAC must be identified and, following that, clinical literature must be analysed in order to arrive at the metabolic fraction with which each precursor is converted to the PhAC being considered. Such precursor models for the environmental release of a PhAC have only been developed for a limited number of cases (51) and, even then, they are often found to lack sufficient detail. As one example, it has yet to be recognized in environmental studies that morphine can be released to the environment through the use of clinical precursors including codeine, ethylmorphine and nicomorphine (52-54). Thus, overall, there is a need to better grasp the clinical precursors that could lead to the environmental loading of a PhAC.

In addition to clinical sources, PhACs can also be found in wastewater influents due to non-clinical anthropogenic sources. One potential non-clinical source for the release of a given PhAC is its endogenous excretion. Typically, endogenous excretions are most relevant for PhACs that are natural hormones (54), but exceptions to this generalisation do exist. Consider that both morphine and codeine have been reported to be endogenously present in human excretions (55). The endogenous release of a PhAC can typically be accounted for by developing models that consider how the excretion of a given PhAC varies with age, gender, reproductive status and other contributing factors (56). Thus far, an endogenous excretion model has only been developed for estrogens (56) and, therefore, there is a need for the development of a model that can account for the endogenous release of other natural hormones such as androgens and thyroids.

Beyond the obvious interest in accounting for endogenous contributions to the net environmental load of a given PhAC, there is also an interest in understanding such contributions from a risk management perspective. Consider that if a PhAC that is almost entirely or predominately released from endogenous sources is found to pose a human-health and/or environmental risk, one would have no choice but to facilitate the removal of the PhAC in sewage and/or drinking-water treatment plants. Conversely, if a PhAC that almost entirely results from the exogenous use of relevant pharmaceutical preparations is found to pose unacceptable human-health and/or eco-toxicological risk, the possibility of managing the risk by either limiting the use of this PhAC or by substituting it with alternative pharmaceutical preparations can be considered.

A PhAC could also be released to the environment due to its illicit use (i.e., non-clinical). Such contributions are obviously important for those PhACs that are exclusively used illicitly (e.g., MDMA which is commonly referred to as “ecstasy”) and have no clinical application. However, there are PhACs for which both clinical and illicit sources are important. For example, while amphetamine is most widely known as an illicit drug, it is also used clinically for the treatment of attention deficit hyperactivity disorder (58). In addition to these, the presence of amphetamine in sewage samples could also be ascribed to more than 10 other precursor clinical drugs, all of which are metabolised by humans to amphetamine (59). Recognition of the importance of illicit sources and incorporation of these in estimating the environmental loads of many PhACs has either not been addressed at a sufficient level of detail or has largely been ignored.

Overall, there is a need to account for the variety of aforementioned sources for individual PhACs in order to develop their respective environmental loading models. For example, to-date, no investigation has considered that morphine could be released from the range of sources identified in Figure 1.1. Such models need to be developed for individual PhACs in order to allow one to fully understand the origins of the compounds of interest, provide more realistic estimates of environmental loadings, conduct risk assessments, and explore risk management options. Such an analysis can also serve to evaluate whether existing monitoring data is sufficient.

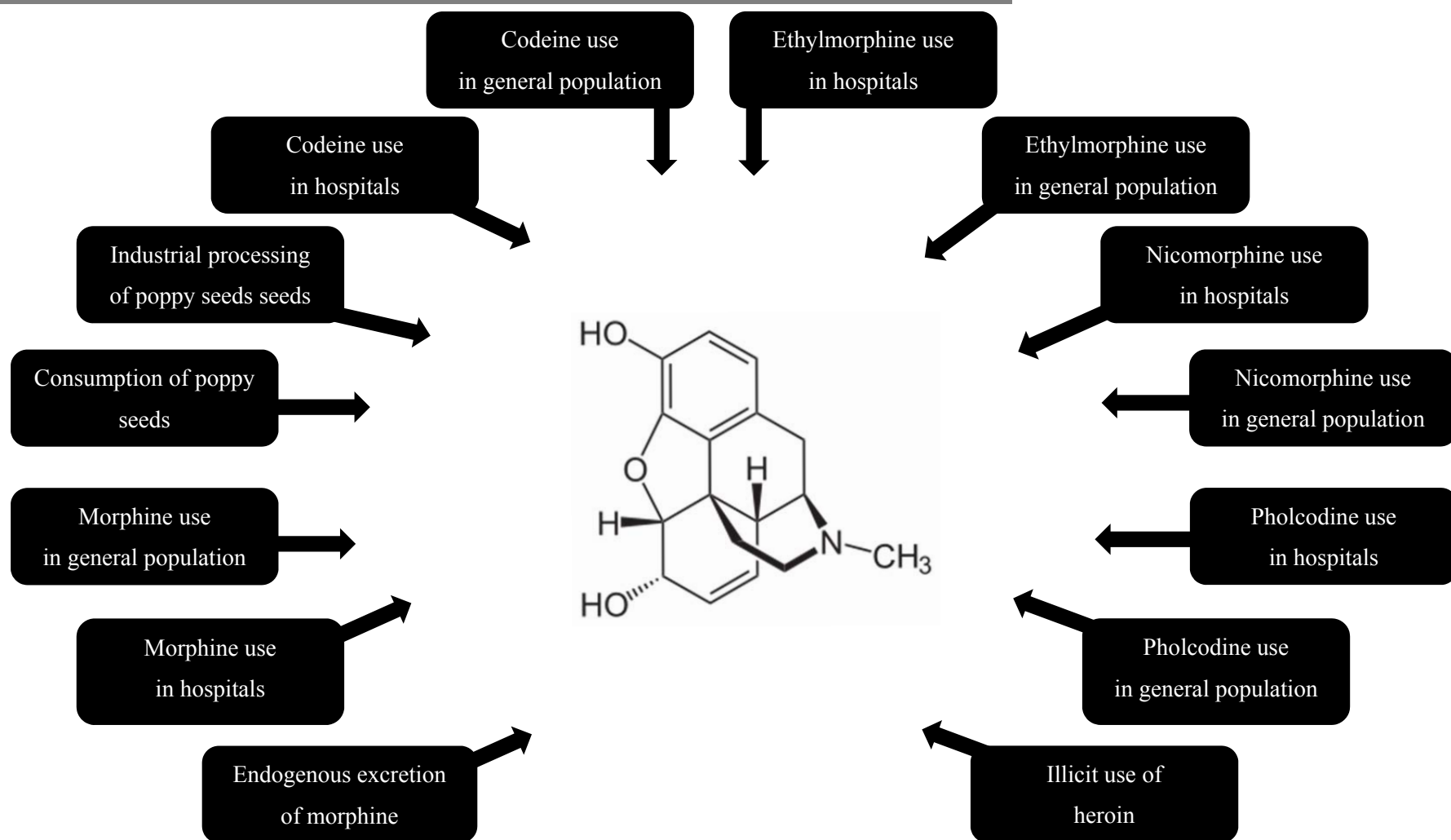


Figure 1.1 Sources of morphine to the environment.

1.3 Risk Evaluation and Prioritization

As described above, nearly 3,000 PhACs are currently in use and yet only 26 PhACs have been monitored extensively in Canada (see Tables 1.1 and 1.2). Even for those that have been extensively monitored, it remains unclear in the literature why these PhACs were specifically selected for extensive monitoring. Were they selected because they carry the highest potential to occur in the environment? Or was it because they are particularly potent in their action on human and/or aquatic life? Or is it because of a combination of the two aforementioned factors in the form of high potential to cause risk to human-health and/or aquatic life? Some have suggested that the reason some PhACs have been extensively monitored is not because they are the most abundant or toxic or pose the highest risk, but just because others have chosen to monitor those PhACs (60). In other words the existing monitoring data for PhACs appears to be marred by the “Matthew” or the “bandwagon” effect (60). As an illustrative exercise, consider the top 20 drugs dispensed in Canada to the general population (see Table 1.3). These top 20 drugs include 17 distinct PhACs. Of these, only one and five PhAC/s have been monitored in Canadian drinking and surface waters, respectively. The single PhAC that was monitored in drinking water was done through the analysis of a single sample, whereas in surface waters at most 20 samples have been analysed for a PhAC in the list (see Table 1.3). Therefore, it is clear from Table 1.3 that PhACs that are widely used in Canada either have not yet been monitored at all or have only been monitored in a limited number of samples. Compare this to a PhAC such as fenoprofen for which 184 samples in surface waters and 63 samples in drinking waters have been analysed and yet the PhAC has been discontinued from use in Canada since 2002. Overall, the limited monitoring data that is available seems to not reflect the importance of the release of those PhACs that are widely used by Canadians.

In light of the limited monitoring data that is available and the possibility that the data available is biased to what everyone else is measuring and/or the availability of suitable analytical methods, there is a need to perform a screening level assessment for a large number of PhACs. The goal of such an analysis would be to screen the human-health relevance of a selected evaluation set of PhACs and, in turn, develop a list of PhACs whose monitoring in drinking waters can be recommended on a scientifically justifiable basis. The development of such a list would not only consider exposure but also potential effects on human-health. Therefore, a risk based evaluation, which combines both exposure and effects assessment, is best suited for the need to evaluate and prioritize the human health relevance for a large set of PhACs. Such an exercise is yet to be performed for Canada. Even for populations outside Canada, such evaluations have not been performed at sufficient levels of scale and/or detail (62-64).

Table 1.3 Twenty top ranked drugs according to number of units dispensed and the reported number of Canadian drinking water and surface water samples that have been analyzed for their presence.

Rank ^(a)	Drug Name	PhAC	Number of samples that have been analyzed for their presence	
			Surface Water ^(b)	Drinking Water ^(c)
1	Synthroid	Levothyroxine	– ^(d)	–
2	Crestor	Rosuvastatin	16	–
3	Lipitor	Atorvastatin	19	–
4	Apo-Furosemide	Furosemide	–	–
5	Teva-Amoxicillin	Amoxicillin	–	–
6	Nexium	Esomeprazole	–	–
7	Teva-Venlafaxine XR	Venlafaxine	20	1
8	Apo-Ramipril	Ramipril	–	–
9	Apo-Hydro	Hydrochlorothiazide	9	–
10	Plavix	Clopidogrel	–	–
11	Apo-Atorvastatin	Atorvastatin	19	–
12	Teva-Rabeprazole	Rabeprazole	–	–
13	Ativan	Lorazepam	–	–
14	Coversyl	Perindopril	–	–
15	Celebrex	Celecoxib	9	–
16	Apo-Salvent CFC FR	Salbutamol	–	–
17	Apo-Lorazepam	Lorazepam	–	–
18	Avapro	Irbesartan	–	–
19	Diovan	Valsartan	–	–
20	Eltroxin	Levothyroxine	–	–

Notes: (a) Drug ranked based on the number of units dispensed to the Canadian general population during 2010 (61); (b) Surface water counts based on data compiled from references (6) to (36); (c) Based on data compiled from all studies reporting on the presence of PhACs in finished Canadian drinking waters (6, 10, 14, 21, 23, 31, 36); (d) not measured.

Exposure assessments can be performed using predicted and/or measured environmental concentrations (65). In the absence of sufficient measurements, which seems to be the case for most PhACs, predicted environmental concentrations (PEC) can be used for screening purposes provided it can be established that PEC estimates can conservatively account for the environmental release of a given PhAC (66,67). It is also important to recognize that even though measured environmental concentrations are considered to be a gold standard, such data may not have been collected under high exposure conditions (e.g., low flow conditions in vulnerable regions).

In order to estimate predicted environmental concentrations from environmental loading estimates, a number of additional variables need to be parameterized. These include the volume of wastewater

generated on a per capita basis, the levels with which the PhAC is removed in primary and secondary treatment plants and, finally, the dilution available to effluents upon their discharge to the environment under low flow conditions. Therefore, there is a need to establish such parameters that specifically describe the Canadian context.

Effects assessment for the potential exposure to PhACs via drinking waters is typically accomplished by extrapolating the lowest oral therapeutic dose (LOTD) of a given PhAC to assumed safe levels through the use of safety factors that can typically range in value from 1,000 to 10,000 (68, 69). However, the use of such an approach can be questioned since the point of departure (i.e., the LOTD) from which an extrapolation to safe levels is being made still yields a response in humans. Further, LOTD values for a given PhAC may not be available since it is not orally administered. As an alternative to the LOTD approach, some have suggested that the point of departure could be occupational exposure limits (OEL) developed by pharmaceutical manufacturers for the protection of their workers (70). The advantage of an OEL-based approach is that these limits are truly derived with a goal of protecting human-health. An additional advantage of such an approach is that pharmaceutical manufacturers may have derived these limits using clinical data that is not readily available in the public domain. This, however, also implies a lack of transparency since such limits are typically developed internally by various pharmaceutical manufacturers. In addition, OEL values for certain PhACs may not have been promulgated by their respective manufacturers. Despite some of the advantages of the OEL approach over the one based on LOTDs, an OEL-based approach to date has only been applied to derive human-health protective benchmarks for 4 PhACs (70,71). Clearly there is a need for wider application of the OEL approach to assess the human-health relevance for the potential presence of PhACs in drinking waters.

For PhACs that are genotoxic carcinogens, neither the LOTD nor the OEL approach may be conservative enough, especially if a highly conservative “one-hit” model is assumed (68,72). Genotoxic carcinogenic chemicals are typically assumed to present an added lifetime cancer risk at all levels of exposure. However, an added lifetime cancer risk of a 1 in 10^6 or 1 in 10^5 for the exposure to such contaminants is accepted (72), since such an added risk for cancer over a lifetime is less than what can be associated with common human activities.

In light of the above, there is an overall need for the development and application of an approach that integrates the various points of departure for the effects of PhACs on human-health.

Exposure of human populations to PhACs via drinking water derived from surface waters is not the only exposure route of concern. For example, in many areas of the world, the application of wastes to agricultural land is an important objective that can be used to simultaneously reduce the burden of wastes on receiving surface water bodies while also creating a product that has value in terms of its fertilizing or soil conditioning properties. Nutrients such as phosphorus and nitrogen, which if not treated sufficiently in wastewaters before release, can lead to eutrophication of water bodies with important impacts on ecosystems and drinking water supplies (90). However, these nutrients can be of high value if they can be isolated from the wastes and then applied in a controlled manner to agricultural land for food production, leading to a beneficial reduction in the need for artificial fertilizers that may be either inaccessible or unaffordable to some populations. In recognition of this, researchers and waste management practitioners in many areas of the developing world are exploring source separation technologies in which wastes such as urine are collected separately and applied to agricultural land (91). While this valorization process is certainly beneficial as described above, it may lead to complications associated with the PhACs that will be in orders-of-magnitude higher concentrations in these separated wastes than in typical wastewater treatment plant effluents (92). Therefore, their application to agricultural land may lead to environmental impacts as well as possible health affects due to human consumption of food grown on such lands. As a result, research is required to address several important questions. For example, it should be asked whether the presence of PhACs in human urine present an eco-toxicological or a human-health risk if it is applied on land untreated? And, if so, which PhACs should be monitored during the pre-treatment of urine? And, of these prioritized pharmaceuticals, what are the exposure routes and endpoints that they are likely to be affected?

1.4 Trade-offs

Typically the use, and hence the environmental release, of a PhAC is viewed to pose some level of environmental and/or human-health risk. By logical extension it is commonly assumed that if the use of the PhAC is eliminated the associated risk will be completely negated. As much as this holds true for a given PhAC, it may not hold true for a group of contaminants whose sources and environmental impacts are inter-related. Therefore, when evaluating the relevance of such a group of contaminants, it is important to understand and evaluate the relationships and trade-offs that exist in defining their environmental release.

In particular, steroidal estrogens of human origin are a group of contaminants whose net environmental release is characterized by previously unrecognized relationships and trade-offs. Evidence collected over more than a decade suggests that steroidal estrogens released via sewage treatment plants are, at the very

least, partially responsible for feminizing effects seen on fish in the receiving water environment (73-76). Concerns associated with the release of steroidal estrogens have grown to such an extent that they are being considered for regulation in various parts of the world (77-80). Steroidal estrogens of human origin whose environmental release has drawn attention include estrone (E_1), estradiol (E_2), estriol (E_3) and ethinylestradiol (EE_2) (2, 3). In the environment, these PhACs are known to act in an additive manner (2, 3). However, even though these estrogens are known to act in an additive manner, their respective ecotoxicological potencies are not equal. That is, EE_2 , E_1 and E_3 are 10, 0.33 and 0.04 times as potent as E_2 , respectively (3, 79-82). E_1 , E_2 , and E_3 are endogenously produced by humans with higher basal levels being excreted by women than men (2, 3). Additionally, in women, the initiation of pregnancy leads to a significant, but temporary, gestational-age dependent upturn in the excretion of E_1 , E_2 , and E_3 . (83). In the United States, the majority of the anthropogenic mass load of E_1 , E_2 and E_3 's is released over the course of pregnancy events experienced by the population (84, 85). These three estrogens are also released due to their exogenous use in clinical hormone replacement formulations (2, 3). However, in the United States only a minor fraction of the total anthropogenic mass load of E_1 , E_2 and E_3 load is released due to their use in clinical hormone replacement formulations (84, 85). EE_2 is a synthetic estrogen and is exclusively released to the environment due to its use in oral contraceptives (2, 3).

To date, the load of natural estrogens released over the course of all pregnancy events and that of EE_2 released due to the use of oral contraceptive pills has been treated in the literature as being completely independent of each other (e.g., 56, 86, 87). However, such a treatment is far too simplistic and fails to recognize the relationships involved between a population's contraceptive choices, the direct estrogenic content released via the use of chosen contraceptive options, the efficacy with which the population uses available contraceptive options, the number of pregnancies experienced, and the load of estrogens released as a consequence of experienced pregnancies. The failure to recognize the relationships between these elements leads to the misconception that the use of an ethinylestradiol-based oral contraceptive (EE_2 -OC) is the only form of contraception that has an estrogenic load associated with its use and, by extension of this, that other forms of contraception are presumed to not have any associated estrogenic loads (86, 87). This also leads to the added misconception that if a population was to stop the use of EE_2 -OC, a net reduction in the estrogenic load equal to that arising from the direct use of EE_2 -OC can be expected (88). Such misconceptions largely originate in the erroneous belief that only the use of an estrogen-based contraceptive has an estrogenic load associated with it (86, 87). However, if one recognizes that all contraceptive options fail to some extent, it becomes clear that this is not true. That is, the failure of a contraceptive option leads to unintended pregnancies (89), which in turn results in a temporary and yet significant upturn in the excretion of natural estrogens. Hence, at the very least, a mass

load of natural estrogens can be associated with the choice to use each contraceptive option. In turn, it can be stated that a fraction of the overall pregnancy load of natural estrogens (E_1 , E_2 and E_3) results from a population's contraceptive choices. On the other hand, since each contraceptive option prevents pregnancies from occurring, as they are inherently designed to do, their use can also be regarded as preventing an estrogenic load from being released to the environment. Therefore, as estrogenic trade-off is associated with the choice to use each contraceptive option.

Overall, there is an urgent need to examine through a multifaceted approach the relationships between the choice of using a given contraceptive option and the net loading of estrogens to the environment. This is especially important and timely given that the regulation of steroidal estrogens, and particularly EE_2 (74), is likely to engender substantial public debate. To-date, the aforementioned relationships and trade-offs remain to be conceptually recognized and studied.

1.5 Sewer Epidemiology

Thus far the discussion has focused on relating the upstream information concerning the consumption of a PhAC at the source to its downstream release into the environment where impacts can occur. However, information can also be gleaned by gathering information at the downstream point of release and then using this to gain insights of what is happening upstream. Specifically, by measuring concentrations of a given chemical residue in sewage or influents to wastewater treatment plants one can gather information about the use of the parent chemical in the upstream population. In turn such estimates can be used to understand and track the epidemiology of the parent drug in the upstream population connected to a sewer system. Thus far, such an approach has been utilized to track an upstream population's use of illicit drugs (93), ADHD drugs (94), flu medication (95), alcohol (96), tobacco (97) and also sildenafil (98), which is a lifestyle PhAC that is commonly used for the treatment of erectile dysfunction. Among these, there is particularly strong interest in using a sewage-based approach to estimate the use of illicit drugs in a community, since the level with which such drugs are used in a given population is often highly uncertain. It almost goes without saying that from a public health and a law enforcement perspective it is of paramount importance to estimate the level with which illicit drugs are used within a community.

Even though the chemical residues from the use of a given illicit drug can be readily detected in wastewater influents (93, 99) there is a need to know how to best to translate the measured drug loads into estimates for the use of the parent illicit PhAC in the upstream population (57). Aspects that need further consideration include the excretion pattern of an illicit drug for its various routes of administration (e.g.,

inhalation, injection), selection of an appropriate drug residue for monitoring, illicit and licit sources that could lead to the release of the selected drug residue, sorption of the drug residue onto sewer-laden suspended solids, and the potential for the drug residue to degrade during sewer transmission. As an example of the analysis that needs to be performed, consider just the one need related to defining the illicit and licit sources that could lead to the release of an appropriate drug residue. It has been suggested that wastewater influent loads of morphine should be used to track an upstream population's use of heroin, since morphine is a major metabolite of heroin use (99). However, as described above, morphine can be released to sewers due to licit and illicit sources (see Figure 1.1). In fact, heroin use is only one of 14 sources that could lead to the presence of morphine in wastewater influents. Therefore, from a sewer epidemiology perspective the utility of morphine to track an upstream population's use of heroin can only be justified for those populations whose environmental loads of morphine primarily results from the use of heroin.

1.6 Objectives

Based on the review presented above, there are numerous aspects associated with the environmental presence of PhACs that warrant further investigation. As such, the global objective of this work is to explore and model the relationships between the upstream patterns and level of use of PhACs and their resulting downstream mass loads in wastes and the environment and then to apply this understanding to address important human health and eco-toxicological issues. In addressing such a global objective, the work aims to understand sources, risks, trade-offs and sewer epidemiology aspects as they relate to the environmental presence and release of PhACs.

The scope of the research is limited to the specific objectives listed below:

1. To develop models for the endogenous release of PhACs to the environment and apply them to assess the environmental risks posed by such contaminants with a particular focus on androgens, thyroids and their *in vivo* metabolites;
2. To develop and apply an approach for the assessment of human-health and eco-toxicological risks posed by PhACs in urine that is applied to agricultural land;
3. To develop a better understanding of the relative importance of sources through which a selected set of PhACs are released to the environment including the contributions of loads that are sourced through their clinical use in the general population and in hospitals, released through endogenous excretions, arise from the metabolism of precursors, and/or originate from the use of illicit drugs;

4. To develop and apply an approach that integrates the various points of departure (e.g., OEL, LOTD) to assess the potential effects of PhACs on human-health;
5. To perform a screening-level assessment of the human-health risks posed by a selected set of PhACs and, in turn, develop a list of prioritized PhACs whose monitoring in drinking waters can be recommended on a scientifically sound basis;
6. To develop and apply a multidisciplinary approach to better understand and evaluate the relationships and trade-offs involved between a population's contraceptive choices and the respective loads of steroidal estrogens to the environment; and
7. To develop an understanding on how best to relate measurements of selected drug residues in wastewaters to the levels with which the parent illicit drugs are used in their respective upstream populations.

1.7 Organization of Present Work

This is a manuscript-based thesis in which the objectives stated above have been addressed in a series of journal articles that have either already been published in peer reviewed journals or have been submitted for publication.

Objectives #1 and #2 are addressed in Chapters 2 and 3, respectively. The body of work presented in Chapter 4 addresses objectives #3, #4 and #5. Objective #3 is also addressed from a sewer epidemiology perspective in Chapters 6 and 7. Objective #6 is addressed in Chapter 5. Finally, objective #7 is covered in Chapters 6, 7 and 8. Chapter 9 provides a summary of the conclusions arising from the entire body of the work presented in the thesis.

Note that extensive supplementary materials have been provided for many of the journal articles, all of which represent important contributions in their own right. These are presented in the Appendices to the thesis. These Appendices contain multiple sub-sections and are organized in the same manner in which they were published along with their corresponding journal articles.

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Chapter 2: Assessment of the Aquatic Release and Relevance of Selected Endogenous Chemicals: Androgens, Thyroids and Their *in Vivo* Metabolites

PREFACE

This chapter addresses the objective of the thesis related to developing a model for the endogenous release of PhACs to the environment. The developed model is applied to estimate the release of androgens, thyroids and their *in vivo* metabolites to the environment in the context of the USA. In turn, where possible, the environmental risk posed by these PhACs is also assessed.

The appendices for this chapter can be found at the end of this thesis.

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Assessment of the Aquatic Release and Relevance of Selected Endogenous Chemicals: Androgens, Thyroids and Their in-Vivo Metabolites

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ABSTRACT

Endogenous chemicals released through anthropogenic excretions enter the environment on a continuous basis. Therefore, it is important to establish their rate of introduction into the environment. An approach was developed to establish such environmental loads for any given endogenous chemical that is likely to be released in anthropogenic excretions. The approach developed was used to quantify influent, effluent and surface water loads of 25 endogenous chemicals including androgens, thyroids and their in vivo metabolites, using the United States as an illustrative case. The predicted surface water concentrations matched up well with the limited monitoring data presently available. The environmental relevance of the surface water presence could only be assessed for 5 of the 25 endogenous chemicals due to limited availability of eco-toxicological data. Data available thus far suggest that testosterone, dihydrotestosterone, thyroxine, triiodothyronines are unlikely to pose a risk to the receiving aquatic ecosystem when considered individually. However, androstenedione is predicted to pose a potential risk to the receiving environment in situations where the surface water dilution of the effluents is expected to be low.

2.1 INTRODUCTION

The detectable presence of pharmaceutically active compounds (PhACs) in the aquatic environment has garnered increasing attention from the scientific community as is evident from the relevant literature compilation maintained by the United States Environmental Protection Agency (1), which on its last update cited 8,882 publications related to the subject of pharmaceuticals and personal care products. (PhACs is defined here to include pharmaceuticals, endogenous hormones and their metabolites generated *in vivo*). Such scientific interest and activity is also gradually leading to the establishment of regulatory guidelines for a number of such contaminants in the form of environmental quality standards (2, 3), water quality standards (4), and acceptable daily intakes for human exposure (5).

Among PhACs that are likely to be present in the environment, special attention is paid to those that are likely to interact with the endocrine system. This largely stems from the eco-toxicological evidence available to date which suggests that endocrine-modulating or disrupting PhACs are likely to manifest significant effects at environmentally relevant concentrations (6). Such contaminants are typically released in human urinary and fecal excretions (7). In the present day wastewater treatment context, anthropogenic excretions are diluted by large amounts of grey water; i.e., water that is partially contaminated. This relatively dilute and complex mixture is then transferred to sewage treatment plants where such contaminants, after undergoing varying levels of treatment, are ultimately discharged into the receiving environment.

Endocrine-disrupting PhACs that are eventually released into the environment can be broadly categorized into two classes:

1. Endogenously-produced hormones that are naturally produced by and are present in living organisms and therefore logically have high potential for interactions with the endocrine system; and
2. Exogenously-consumed hormones/pharmaceuticals, that are typically not naturally produced and therefore are not naturally present but can nevertheless interact with the endocrine system in either expected or unexpected manners.

Perhaps the greatest distinction between the two categories from an environmental standpoint would be that if an exogenous compound is deemed to be detrimental to the receiving ecosystems, its release could

be mitigated by switching to a “greener” alternative or an alternative may be developed if none is available. However, no such alternatives are available with respect to the release of endogenous chemicals, which are a fixed characteristic of our human biology. Given this, the presence of endogenous chemicals in anthropogenic excretions, and therefore wastewater treatment effluents and hence aquatic ecosystems, can be considered to be omnipresent. Therefore, it is imperative that one makes an attempt to quantify the environmental release and the environmental relevance of such contaminants.

Attempts have been made by others to precisely address such concerns by developing models for the environmental release of endogenous estrogens (8–10). Considerably less attention has been paid to the release and eventual fate of endogenous androgens, thyroid hormones and their *in vivo* metabolites. In vertebrates, androgens modulate sexual characteristics by interacting with the androgen receptor (11, 12). Similarly, thyroid hormones regulate a wide range of physiological endpoints including, reproductive ones, by interacting with the thyroid receptor (13–16). The presence of such receptors with a high degree of homology to the respective human receptors has been confirmed in eco-toxicologically relevant aquatic taxons such as fish (12, 17, 18). Therefore, from an environmental perspective, the question is not whether excreted endogenous androgens and thyroid hormones making their way into the environment interact with associated receptors in relevant aquatic taxa but, rather, whether the interactions are expected to be significant from an eco-toxicological standpoint. Furthermore, anthropogenic excretions are not only likely to contain active hormones but also their *in vivo* metabolites. As these *in vivo* metabolites will also make their way into the receiving environment their release loads and environmental relevance is also worth investigating.

In order to address such concerns the first logical step is to develop a model for the environmental release of endogenous chemicals (androgens and thyroids and their *in vivo* metabolites) originating from anthropogenic excretions. Therefore, the overall objectives of the research presented herein were to:

1. Develop a model for estimating the quantities (i.e., load and concentrations) of the endogenous chemicals of interest here in the influents and effluents of wastewater treatment plants;
2. Where possible to assess the environmental relevance of such contaminants making their way to the environment; and
3. Highlight knowledge gaps that need to be addressed before the next logical iterative refinement of the developed model is undertaken.

The application of the proposed methodology will be demonstrated using data corresponding to the United States, as an illustrative case.

2.2 Model Development

The mass balance model suggested by Johnson and Williams (8) for quantifying the load of a particular contaminant expected to reach the influent of a treatment plant can be logically extended to establish such loads for any given endogenous chemical that is likely to be present in anthropogenic excretions. Therefore, the general form of their model is adapted here and modified, where necessary. Appropriate simplifications and enumerations of the various parameters of the general form that is relevant to the chemicals being considered here are included in the model development.

2.2.1 Estimating Influent Loads of Endogenous Chemicals

Following modification of the general form of the model of Johnson and William (8), the total amount of an endogenous chemical expected to arrive in the influent of a wastewater treatment plant (H_{T-inf} , in kg/d) can be expressed as:

$$H_{T-inf} = [(1 - k_d) \cdot (P \cdot C(U_t + F_t) + G + X)] \quad (1)$$

where k_d is the fraction of the endogenous chemical that is degraded during sewer transit; P is the total population of the community; C is the fraction of the total population that is connected to the wastewater treatment and collection train; U_t is the amount of the endogenous hormone that is excreted in the urine of population P on a per capita basis ($\mu\text{g}/\text{cap} \cdot \text{d}$); F_t is the amount of the endogenous chemical that is excreted in the fecal matter of population P on a per capita basis ($\mu\text{g}/\text{d}$); G is the potential rate of generation of the endogenous chemical arising from the degradation of another contaminant ($\mu\text{g}/\text{d}$); and X is the contribution to the influent load due to exogenous consumption of the endogenous chemical itself or the consumption of another chemical/pharmaceutical preparation that may be metabolized by humans to the endogenous chemical being considered ($\mu\text{g}/\text{d}$).

Furthermore, U_t can be represented as a summation of the endogenous chemical excreted by relevant human population cohorts:

$$U_t = \sum_{i=1}^I f_i U_i \quad (2)$$

where: I is the number of population cohorts excreting different amounts of the compound of interest; f_i is the fraction of population P that belongs to cohort i ; and U_i is the amount of the endogenous chemical that is excreted in urine by cohort i on a per capita basis ($\mu\text{g}/\text{cap}\cdot\text{d}$).

The amount of a given endogenous chemical that is excreted by a given cohort i in urine on a per capita basis is likely to be composed of three distinct components (11, 19–23): namely, a fraction that is excreted as the free endogenous chemical itself (F_u), a further fraction that is excreted conjugated to glucuronic acid (G_u), and an additional fraction that is excreted as sulphate conjugates (S_u). Considering this, equation (2) can be expanded as follows:

$$U_t = \sum_{i=1}^I f_i (F_u + G_u + S_u) U_i \quad (3)$$

where, by definition, the sum of the fractions, $F_u + G_u + S_u$, must be equal to one. Similar development can lead to the expansion of the F_t term in equation (1):

$$F_t = \sum_{i=1}^I f_i (F_f + G_f + S_f) F_i \quad (4)$$

where: F_i is the amount of the endogenous chemical that is excreted in fecal matter by cohort i on a per capita basis ($\mu\text{g}/\text{cap}\cdot\text{d}$); F_f is the fraction of F_i that is excreted as the free endogenous chemical itself; G_f is a further fraction of F_i that is excreted conjugated to glucuronic acid; and S_f is an additional fraction of F_i that is excreted as sulfate conjugates.

However, data available to-date regarding fecal excretions of androgens (24) and thyroids (25, 26) suggest that such endogenous chemicals are primarily excreted in the form of free chemical in fecal matter. This is largely a consequence of the intestinal flora acting on conjugated fractions to liberate free chemicals (24, 25). Therefore, equation (4) can be simplified to the following:

$$F_t = \sum_{i=1}^I f_i F_f F_i \quad (5)$$

Further, recognizing that $F_f \approx 1$, equation (5) can be simplified to:

$$F_t = \sum_{i=1}^I f_i F_i \quad (6)$$

The load, X , added due to exogenous use of the chemical itself or another chemical/pharmaceutical-preparation that may be metabolized to the endogenous chemical being considered can be calculated as follows:

$$X = N \cdot C \cdot P(X_u + X_f) \cdot (Mw_{eh} / Mw_p) \quad (7)$$

where: N is the total per capita daily consumption of the pharmaceutical preparation ($\mu\text{g}/\text{cap} \cdot \text{d}$); X_u is the fraction of the administered daily dose of the preparation that is excreted in urine as the endogenous chemical of interest; X_f is the fraction of the administered daily dose that is excreted in fecal matter as the endogenous chemical of interest; Mw_{eh} is the molecular weight of the endogenous chemical being considered; and Mw_p is the molecular weight of the pharmaceutical preparation that is metabolized to the endogenous chemical of interest. Note that the pharmaceutical preparation could be the exogenous form of the endogenous chemical of interest and, in such cases; the molecular weight adjustment (Mw_{eh}/Mw_p) would be equal to 1.

Substitution of equations (7), (6) and (3) into equation (1) leads to the following model that can be used to estimate the amount of a given endogenous androgen or a thyroid chemical that is expected to reach treatment plants in their influents:

$$H_{T-\text{inf}} = (1 - k_d) \cdot (P \cdot C \left(\sum_{i=1}^I f_i (F_u + G_u + S_u) U_i + \sum_{i=1}^I f_i F_i^f \right) + G + N \cdot P \cdot C (X_u + X_f) \cdot (Mw_{eh} / Mw_p)) \quad (8)$$

2.2.2 Quantifying Parameters to Estimate Influent Loads of Endogenous Chemicals

Influent Loads

In order to quantify influent loads of a given endogenous chemical ($H_{T-\text{inf}}$), the various daily excretions parameters (i.e., values of U_i and F_i) of equation (8) were quantified. This was accomplished by performing a comprehensive literature search for all studies reporting urinary and fecal excretion profiles of endogenous chemicals of interest here (androgens, thyroids and their in vivo metabolites) by mining the following literature databases: MEDLINE, EMBASE, SCOPUS and Scifinder Scholar. No language restrictions were applied in the retrieval of relevant literature and search keywords were kept very generic so as to capture as diverse a body of relevant literature as possible.

In the initial phase, all studies that demonstrated one or more of the following criteria were excluded: (1) excreta to be analyzed had been collected for durations of less than 24 hours; and (2) results reported were

normalized to creatinine content of the sample without stating the adjustment creatinine level that was used. The former data was excluded because collection durations of less than 24 hours or analysis of spot urine are unlikely to yield accurate estimates of the daily excretion of the endogenous chemical being considered. Additionally, the use of creatinine-adjusted results, where such adjustment levels were not stated in the original reference, would entail that one multiply reported results (i.e., $\mu\text{g}/\text{mg}$ of creatinine) by the typical daily creatinine excretion (i.e., $\text{mg}/24 \text{ hr}$) thereby, adding an additional degree of variability to the daily excretion values of the endogenous chemical being considered. The validity of applying such a correction to data can further be questioned considering the wide range that constitutes “typical” daily excretion of creatinine (27).

After initial screening of the studies, the estimated per capita daily excretions of the various chemicals ($\mu\text{g}/\text{cap}\cdot\text{d}$) from the remaining studies were compiled. The compiled dataset was used to identify the number of population cohorts excreting different amounts of the compound of interest, i , for each endogenous chemical. Identification of the cohorts allowed one to further refine the collection of reported data. At this level of screening, studies were excluded that reported data encompassing more than one relevant cohort. The screening at this stage is best illustrated with the aid of an example: that is, it is known that testosterone levels in women decreases with age (28), therefore a study like Doberne and New (29) which presented mean testosterone excretion for 14 women whose ages were between 22 and 67 is too broad as it combines many different excreting cohorts into one.

From all remaining studies, means and standard deviations (σ 's) were extracted from the reported data. In cases where data was only presented in graphical form, the images were digitized and the dimensions of the extracted images was subsequently used using DigitizeIt™ (30) to estimate means and standard deviations of the reported data. Often, studies reported either the standard error or the range of data rather than the desired σ . In cases where standard error was reported, it was converted to standard deviation by multiplying it with the square root of the number of observations. For those cases where the range was reported, σ was approximated by dividing the range by four as described by Massart et al. (31). Means from different studies within a relevant population cohort, i , were combined by weighting each mean by the number of subjects monitored in the study. Standard deviations were also combined by the number of subjects, specifically according to the pooled standard deviation method suggested by Massart et al. (31).

Population Parameters

Since the case study reported here had the objective of estimate the release of such contaminants to United States waterways, the national population of the United States was used for P . The base simulation

year used here is 2005, because it is the latest year for which certain population cohorts of interest have been enumerated (i.e., number of pregnancies in a given year). The fraction of the national population that is connected to the wastewater treatment and collection trains, C , was reported to be 98.1% (32). Once the appropriate cohorts were identified for the various endogenous chemicals of interest, the fraction of population corresponding to each cohort, f_i , were derived from United States Census Bureau (33) data for the simulation base year of 2005.

Degradation and Sewer Transit Parameters

Typical sewer transit times reported in literature are on the order of a few hours (34, 35). Furthermore, considering that anaerobic conditions set in fairly early on during the transit process (36), it is reasonable to assume that the contaminants considered here won't be significantly transformed en-route to the treatment plant. Hence, it is conservatively assumed here that the total daily loads of endogenous androgens, thyroids and their in vivo metabolites released in human urinary and fecal excretions are transmitted to the influents of wastewater treatment plants unchanged (i.e., k_d and $G \approx 0$).

However, the conjugated fraction of the total loads is expected to change during the sewer transit process. Research primarily with conjugated fractions of endogenous estrogens suggests that the glucuronide fraction will be essentially deconjugated to the free form (i.e., $G_u \rightarrow F_u$), while the sulphate fraction will survive the transmission (35, 37). These assertions are assumed to hold true for the excreted conjugated fractions of the endogenous chemicals being considered here.

Exogenous Chemical Parameters

Besides being an endogenous hormone that is present in anthropogenic excretions, testosterone is also used exogenously by the human population, primarily by those undergoing treatment for hypogonadism (38). Current consumption rates of exogenous testosterone were not available for the United States. However, consumption data from Canada (39) and Sweden (40) suggests that the population-normalized consumption of exogenous testosterone is between 73 and 120 $\mu\text{g}/\text{cap}\cdot\text{d}$. The mean of this range ($\approx 96 \mu\text{g}/\text{cap}\cdot\text{d}$) is used here as N . Canadian data further suggests that (39) on a mass basis testosterone is predominately applied topically or transdermally, with intravenous administration amounting to a minor fraction of the total administered mass. Further, considering that only 10% of topical administered testosterone is absorbed (41) and that up to 98% of a transdermal dose may remain as residue in a used transdermal patch (42); therefore, it is conservatively assumed here that the exogenous mass of testosterone utilized enters the sewer unmetabolized in the free form (i.e., $X_u + X_f = 1$).

Levothyroxine, the synthetic form of the endogenous hormone thyroxine, is among the top 10 prescribed drugs in the United States (43) and is primarily used for the treatment of hypothyroidism (38). Again, actual consumption data with respect to the use of levothyroxine was not available for the United States. However, population-normalized Canadian (39) and French data (44) suggests that the consumption of levothyroxine in those countries ranged between 2.6 and 4.6 $\mu\text{g}/\text{cap}\cdot\text{d}$. The mean of this range (3.6 $\mu\text{g}/\text{cap}\cdot\text{d}$) is assumed here for N . Reports on disposition of levothyroxine suggest that on average 30% of the administered dose is excreted in fecal matter as thyroxine ($X_f = 0.3$ for thyroxine) while on average 9% of the administered dose is excreted in urine as thyronine ($X_u = 0$ for thyroxine and $X_u = 0.09$ for thyronine) (45, 46).

2.2.3 Effluent Loads of Endogenous Chemicals

The effluent load of a particular endogenous chemical that is likely to be released to the receiving environment, $H_{T\text{-eff}}$ (kg/d), can be calculated from $H_{T\text{-inf}}$ by multiplying it by one minus the removal efficiency expected during the treatment process (Eff):

$$H_{T\text{-eff}} = (1 - Eff) H_{T\text{-inf}} \quad (9)$$

Based on considerations discussed in the preceding section, the influent load ($H_{T\text{-inf}}$) arriving at the influent of the wastewater treatment facility will be composed of endogenous chemicals in free form (which includes the excreted glucuronide fraction that has been assumed to be fully cleaved to the free form) and the sulphate conjugates of the endogenous chemical. Evidence reported to date in literature regarding sulphate conjugates of endogenous estrogens (8, 37) suggests that this fraction is likely to survive the treatment process. Hence, it is assumed here that this will be the case with the sulphate conjugates of endogenous chemicals being considered here. Incorporation of such an assumption leads to the following modification of equation (9):

$$H_{T\text{-eff}} = (1 - Eff) \cdot (H_{T\text{-inf}} - H_{T\text{-infs}}) + H_{T\text{-infs}} \quad (10)$$

where $H_{T\text{-infs}}$ is the total load of the endogenous chemical that is conjugated to sulphate ions and can be stated as:

$$H_{T\text{-infs}} = P \cdot C \sum_{i=1}^I f_i S_u U_i \quad (11)$$

Since measurements of removal efficiencies (Eff) from full-scale treatment plants entails that specific monitoring studies measuring both influent and effluent concentrations of the contaminant of interest, such data is rare and rarer still for the compounds being considered here, as will become evident below.

Therefore, in cases where such data is not available or where the data available is limited to a small number of samples, Eff was estimated using the STPWINTM software of the USEPA (47).

2.2.4 Predicting Surface Water Load and Concentrations of Endogenous Chemicals

The expected load of a given endogenous chemical in surface water immediately downstream of wastewater treatment plants, H_{T-sw} , can be estimated by dividing H_{T-eff} by the dilution expected of the effluent in the receiving surface water:

$$H_{T-sw} = \frac{H_{T-eff}}{DF} \quad (12)$$

where: DF is the dilution factor and is indicative of the number of times a typical wastewater effluent is diluted in the receiving surface water. Based on the work of Rieses et al. (48), Lyndall et al (32) suggested DF values of between 4 and 130 for environmental exposure assessment purposes for United States waterways. A DF of 4 was suggested to represent a “high-end” exposure scenario while the value of 130 was considered to represent a “typical” exposure scenario. These suggested values of DF were used here.

The concentration of a particular endogenous chemical in surface waters immediately downstream of wastewater treatment plants, C_{T-sw} (ng/L), can then be derived from H_{T-sw} using the following relationship:

$$C_{T-sw} = \frac{H_{T-sw}}{P \cdot W \cdot C} = \frac{H_{T-eff}}{DF \cdot P \cdot W \cdot C} \quad (13)$$

where W is the average daily water use per capita in the United States, which was estimated to be 677 L/cap·d based on the work by Hutson et al. (49).

2.2.5 Environmental Relevance

The environmental relevance of any contaminant making its way into the aquatic environment can be assessed by deriving the contaminant’s Predicted No-Effect Concentration ($PNEC$). A contaminant-specific $PNEC$ is typically derived from the lowest available eco-toxicological endpoint by dividing it by an assessment factor (AF). The magnitude of AF is dependent on the nature of the lowest available eco-toxicological endpoint (i.e. whether it was obtained after an acute or chronic exposure) and the overall diversity of the eco-toxicological data when chronic eco-toxicological data is available. When the lowest available eco-toxicological endpoint was derived after an acute exposure, a value of 1000 is suggested for AF (50, 51). However, in cases where the lowest eco-toxicological endpoint was established after chronic

exposure, the magnitude of AF depends on the number of chronic endpoints available for different taxa. The typical value used for AF when chronic endpoints are available from only one taxon is a 100, and in cases where chronic endpoints are available from two or three taxa the suggested values are 50 and 10, respectively (50, 51).

The derived $PNEC$ of a given contaminant could subsequently be compared to its predicted surface water concentration (C_{T-sw}) to derive an environmental risk quotient (RQ):

$$RQ = \frac{C_{T-sw}}{PNEC} \quad (14)$$

A risk quotient greater than or equal to one would indicate unacceptable risk of the contaminant being considered, while a value of less than one is indicative of no risk in light of the eco-toxicological data used to derive respective the contaminant's $PNEC$.

2.3 Results and Discussion

2.3.1 Influent Loads

Per Capita Release of Androgens and Their in Vivo Metabolites

Through the data mining strategy employed here, 19 endogenous androgens and their in vivo metabolites were identified for which varying degrees of information were available with respect to their anthropogenic excretions. The methodology used to quantify influent loads for these is clarified below by illustrating the methodology as applied to three of these compounds. These three represent typical cases of the diversity that were encountered in terms of availability of relevant excretion data. The process for the remaining compounds was similar to the three cases illustrated here and has been summarized in tables presented in Appendix A.

Case 1 – Example for Which Extensive Data Was Available for All Relevant Cohorts - Testosterone

The body of literature reporting the urinary excretion of testosterone indicated that the urinary excretion of testosterone is dependent on the age the subject (52); gender of the subject (53) and the trimester of pregnancy for pregnant women (54), while the variation due to the day of the menstrual cycle and the onset of menopausal state is likely to be insignificant when compared to observed inter-individual variation (56, 57). The urinary excretion of testosterone for both sexes was reported to rise during

puberty, peaking in the late-teens to mid-twenties and then decline steadily thereafter (52, 53). It was shown that females excrete considerably lesser amounts throughout their life cycle than males (53). The effect of pregnancy was suggested to be significant only during the third trimester, with significantly higher amounts being excreted during the third trimester while excretions profile during the first two trimesters was suggested to be similar to those of normal (i.e. non-pregnant) women (54). Considering these excretion trends and the resolution of data available, the relevant cohort's (i 's) for the excretion of testosterone were defined to be: gender, age cohorts within each of the gender cohorts, and pregnant women in the third trimester cohort within the cohort of women that are likely to be pregnant (i.e., assumed to be 15-40 year old females (58)). Urinary excretion (U_i 's) data for each of these cohorts is summarized in Table 2.1. U_t for the whole population was obtained by multiplying U_i values with their respective f_i 's (from (33)) and subsequently summing these for all cohorts (i 's), as indicated in equation (2). The analysis (Table 2.1) suggests that, on a demographic normalized basis, the daily urinary excretion of testosterone on a per capita basis is expected to be $25 \mu\text{g}/\text{cap}\cdot\text{d}$ (U_t). Of this total per capita load, $18 \mu\text{g}/\text{cap}\cdot\text{d}$ is expected to be conjugated to the glucuronide moiety while the majority of the remaining is expected to be conjugated to sulphate ions (i.e., $7 \mu\text{g}/\text{cap}\cdot\text{d}$).

In contrast to the vast body of literature reporting urinary excretions of testosterone, the fecal excretions of endogenous androgens is rarely studied. To date, only one study has analyzed human fecal excretions for their androgen content (24). In that study, upon analysis of 18 fecal samples of young males, aged 21-36, it was suggested that the average testosterone content of the analyzed human fecal samples was $10 \mu\text{g}/\text{cap}\cdot\text{d}$ (24). The average urinary excretion of testosterone for such individuals based on our analysis is expected to be between 66 and $85 \mu\text{g}/\text{cap}\cdot\text{d}$ (Table 2.1). If one were to use the mean of this range ($\approx 75 \mu\text{g}/\text{d}$) as the likely urinary excretion for such individuals, their reported fecal excretion of $10 \mu\text{g}/\text{cap}\cdot\text{d}$ amounts to 13% of the urinary excretions. Since no other data is available regarding fecal excretions, it was assumed here that the fecal excretions for all cohorts of interest amounted to 13% of the respective urinary excretions. Such an approximation allows one to estimate F_t as $3.3 \mu\text{g}/\text{cap}\cdot\text{d}$; this fecal load is expected to be in free form in light of previously mentioned considerations. Therefore, the total per capita daily load of testosterone released by humans in fecal and urinary excretions (i.e., $U_t + F_t$) amounts to $28 \mu\text{g}/\text{cap}\cdot\text{d}$. Recalling that the fraction conjugated to the glucuronide moiety is expected to revert to the free form during sewer transit, $21 \mu\text{g}/\text{cap}\cdot\text{d}$ of this load is expected to arrive in the influents of wastewater treatment plants in the free form and therefore would be available for treatment. The remaining $7 \mu\text{g}/\text{cap}\cdot\text{d}$, would arrive at the treatment plant “as-is” in the form of sulphate conjugates and, as assumed earlier, would not be available for treatment.

Table 2.1 Total per capita daily urinary excretion of testosterone (U_t) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$)

Androgen		U _t						Conjugated Fraction of U _t					
		Quantifying U _i				f _i ^a	U _i .f _i x ± σ				Reference		
		Reference	l	n	U _i (x ± σ)			F _u	G _u	S _u			
			Age (yr)/status	# of samples	(μg/cap.d)		(μg/cap.d)	(%)	(%)	(%)			
Testosterone	Male	(59-60)	0-<5	23	1.4	0.04	0.1	0.3	70	30	(74)		
		(59-63)	5-<10	88	5.6	0.03	0.2						
		(52,59,61,62,64,65)	10-<15	298	20	0.04	0.7						
		(52,53,59,62-71)	15-<30	205	85	0.11	9.1						
		(52, 53, 55, 59, 63, 64, 67-69)	30-<40	74	66	0.07	4.6						
		(52, 53, 59, 63, 64, 67-69)	40-<50	63	49	0.08	3.7						
		(52, 53, 59, 64, 69)	50+	57	31	0.13	4.1						
	Female	(60)	0-<5	16	1.2	0.03	0.1	4	75	21	(74)		
		(53, 60, 61, 63)	5-<10	7	8.1	0.03	0.3						
		(60, 63,71)	10-<20	39	6.1	0.07	0.4						
		(53, 63, 64, 67, 71, 72)	20-<40	79	6.5	0.13	0.9						
		(53, 63, 67, 71,73)	40+	56	4.6	0.23	1.1						
		(54)	3rd trimester	32	17	0.01	0.1						
	U _t =Σf _i .U _i (n=1037) ^b						25	F _u .U _t ^c	0.2	G _u .U _t ^d	18	S _u .U _t ^e	7.3

(a) Based on demographic data for the simulation base year 2005 (33); (b) Total per capita daily load of testosterone excreted in human urine ($\mu\text{g}/\text{cap.d}$); (c) Total per capita daily load of testosterone excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of testosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of testosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$); (f) Based on the number of pregnancies in the year 2005 (58).

Case 2 – Example for which a reasonable data set was available, but with information lacking on certain cohorts – Androstenedione

As with the excretion of testosterone, the literature suggested that daily urinary excretion of androstenedione was dependent on the age of the subject (69); gender of the subject (69, 76) and the trimester of pregnancy for pregnant women (54). Therefore the relevant cohorts (*i*'s) for androstenedione were defined to be: gender, age cohorts within each of the gender cohorts, and women in the third trimester within the cohort of women likely to be pregnant. Sufficient data was available to quantify each of the age cohorts for the males; however, this was not possible for all the female cohorts (Table 2.2). For females, limited data was available; the three identified studies reported daily urinary excretion of androstenedione by adult women (20-40 age cohort) (75, 76) and pregnant women in their third trimester (54). The approach taken here to estimate excretion by women of other age cohorts than the 20 to <40 year olds is best illustrated with the aid of an example. For example, data presented in Table 2.2 suggest that males in the age cohort of 10 to <15 years excrete approximately 30% of the levels excreted by those males in the 20 to <40 year cohort; therefore, the approximation made here was to multiply the female 20 to <40 year cohort reported data (75, 76) by 30% to generate the excretion profile for the female age cohort of 10 to <15 years. A similar approach was used to quantify all female age cohorts for which no data was available.

The analysis presented in Table 2.2 suggests that total daily urinary excretion of androstenedione (U_t) on a per capita basis is expected to be approximately 19 $\mu\text{g}/\text{cap}\cdot\text{d}$. Of this total per capita urinary load, 4.3 $\mu\text{g}/\text{cap}\cdot\text{d}$ is likely to be present in urinary excretions in the form of glucuronide conjugates, 14 $\mu\text{g}/\text{cap}\cdot\text{d}$ as the sulphate conjugates, and the minor amount of 0.6 $\mu\text{g}/\text{cap}\cdot\text{d}$ as free androstenedione.

Due to the paucity of data on the fecal disposition of endogenous chemicals, it remains unclear what levels of such chemicals are eliminated in fecal excretions. However, it is possible to suggest whether fecal elimination is likely to be a major elimination route for a given chemical of interest. In particular, Yang et al. (90) suggested that the molecular weight of a chemical was a major determinant of the likelihood of a chemical ending up in biliary excretions rather than being eliminated in urinary excretions. Specifically, a threshold 475 Da was suggested, where chemicals having a molecular weight greater than this threshold were likely to appear in biliary excretions. Further, recognizing that fecal excretions may originate in biliary excretions, the importance of fecal disposition of an endogenous chemical can be assessed by comparing the molecular weight of the endogenous chemical to the threshold of 475 Da. The molecular weight of all androgens and their *in vivo* metabolites of interest here was well below this

threshold and therefore the fecal excretion of such chemicals is expected to be low compared to their elimination in urine. This is consistent with the earlier derived fecal-to-urine ratio of 13% for testosterone, the only androgen which has been quantified in human fecal excretions.

Considering this, and given the lack of data reporting the fecal excretion of androstenedione, the fecal load was assumed to be equal to 13% of the total urinary load based on the ratio of fecal to urinary excretion of testosterone. Hence, F_t was assumed to be 13% of androstenedione's U_t and is therefore equal to $2.5 \mu\text{g}/\text{cap}\cdot\text{d}$. This suggests that the total load (i.e., $U_t + F_t$) of androstenedione arriving in the influents of the wastewater treatment plants is likely to be $21.5 \mu\text{g}/\text{cap}\cdot\text{d}$ and, of this, $7.4 \mu\text{g}/\text{cap}\cdot\text{d}$ will be in the free form ready to undergo treatment and the remainder will be present as the treatment-resistant sulphate conjugated fraction.

Table 2.2 Total per capita daily urinary excretion of androstenedione (U_t) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$)

Androgen		U _t					Conjugated Fraction of U _t				
		Quantifying U _i			f _i ^(a)	U _i f _i	F _u	G _u	S _u	Reference	
		I	n	U _i							
		Reference	Age (yr)/status	# of samples	(µg/cap.d)	(µg/cap.d)	(%)	(%)	(%)		
Androstenedione	Male	(62)	<10	5	0.0	0.07	0.0	3.7	23	73	(74)
		(62)	10-<15	16	6.2	0.04	0.2				
		(62)	15-<20	11	16	0.04	0.6				
		(69)	20-<30	6	57	0.07	4.0				
		(69)	30-<40	4	47	0.07	3.3				
		(69)	40-<50	8	38	0.08	2.9				
		(69)	50-<60	9	28	0.06	1.7				
		(69)	61+	7	20	0.07	1.4				
	Female	Approx ^(f)	0-<10	-	0.0	0.07	0.0	2.0	22	76	(74)
		Approx ^(f)	10-<15	-	2.0	0.03	0.1				
		Approx ^(f)	15-<20	-	5.4	0.03	0.2				
		(77, 78)	20-<40	29	17	0.12	2.1				
		Approx ^(f)	40-<50	-	12	0.08	1.0				
		Approx ^(f)	50-<60	-	9.0	0.06	0.6				
		Approx ^(f)	61+	-	6.3	0.10	0.6				
		(54)	3 rd trimester	32	6.4	0.01 ^g	0.1				
	Total (µg/cap.d)		U _t =Σf _i U _i (n=106) ^(b)			19	F _u .U _t ^(c) = 0.6 G _u .U _t ^(d) = 4.3 S _u .U _t ^(e) = 14				

(a) Based on demographic data for the simulation base year 2005 (33); (b) Total per capita daily load of androstenedione excreted in human urine ($\mu\text{g}/\text{cap.d}$); (c) Total per capita daily load of androstenedione excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of androstenedione excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of androstenedione excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$); (f) Approximated by relative ratio from associated male cohorts (see text for details); (g) Based on the number of pregnancies in the year 2005 (58).

Case 3 – Example with Limited Data Availability, but with Information Available for Adult Male and Female Cohorts – Dihydrotestosterone

Since, dihydrotestosterone is produced upon *in vivo* metabolism of endogenously produced testosterone (38), one would expect its urinary excretion to be distinctly different depending on the age of the subject, gender of the subject, and the trimester of pregnancy for pregnant women. However, daily urinary loads of dihydrotestosterone are rarely reported in literature. In total, two studies were identified reporting daily urinary excretions of dihydrotestosterone in human urinary excretions, one for adult males (77), while the other one reporting on excretions of adult females (78). Given the lack of data, no option is available except to assume all the males in the population excrete as adult males and all the females as adult females. Obviously, the estimate loads generated with such assumptions will be an overestimate, but from an environmental relevance perspective the estimate would be a conservative one.

In light of the assumption that all males and females within the population excrete dihydrotestosterone as adults, the total daily urinary excretion of dihydrotestosterone on a per capita basis (U_t) is expected to be 19 $\mu\text{g}/\text{cap}\cdot\text{d}$ (Table 2.3). Again, data on the fecal disposition of endogenous dihydrotestosterone was lacking and was approximated to amount to 13% of U_t , as was used above, allowing one to estimate F_t as 2.3 $\mu\text{g}/\text{cap}\cdot\text{d}$. Enumeration of U_t and F_t further allows one to estimate the total load of dihydrotestosterone expected to arrive in influents of wastewater treatment plants as 21.3 $\mu\text{g}/\text{cap}\cdot\text{d}$, where all of this is expected to be available for treatment since the fraction of urinary dihydrotestosterone bound to sulphate ions is expected to be negligibly small (79).

Table 2.3 Total per capita daily urinary excretion of dihydrotestosterone (U_t) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$)

		U _t						Conjugated Fraction of U _t			
Androgen		Quantifying U _i				f _i ^(a)	U _i f _i	F _u	G _u	S _u	Reference
		Reference	I	n	U _i			(%)	(%)	(%)	
			Age (yr)/status	# of samples	(μg/cap.d)		(μg/cap.d)				
Dihydrotestosterone	Male	(77)	Adults	14	32	0.5 ^(b)	16	minor	100	0	(18), (79)
	Female	(78)	Adults	5	5.1	0.5 ^(b)	2.5	minor	100	0	Assumed ^(g)
		Total (μg/cap.d)	U _t = Σf _i U _i (n=19) ^(c)				19	F _u ·U _t ^(d) ≈ 0	G _u ·U _t ^(e) = 19	S _u ·U _t ^(f) ≈ 0	

(a) Based on demographic data for the simulation base year 2005 (33); (b) Due to lack of data it is conservatively assumed here that the whole male and female populations excrete dihydrotestosterone as adults; (c) Total per capita daily load of dihydrotestosterone excreted in human urine ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of dihydrotestosterone excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of dihydrotestosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (f) Total per capita daily load of dihydrotestosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$); (g) assumed to be equal to the conjugated and unconjugated proportions of male urinary excretions.

Per Capita Release of Thyroids and Their *in Vivo* Metabolites

The literature survey identified 6 different endogenous thyroids and their *in vivo* metabolites for which varying degrees of information were available with respect to their anthropogenic excretion rates. In general, excretions of endogenous thyroids have not been extensively studied. The process to calculate influent loads is detailed below for the two biologically active thyroids, thyroxine and triiodothyronine, while the process is summarized for the remaining four *in vivo* metabolites in Appendix A and briefly discussed below to highlight some key assumptions.

Triiodothyronine and Thyroxine

Urinary excretion of triiodothyronine was shown to vary significantly with gender (80) and age of the subject (80, 81). While urinary excretion of thyroxine was shown to vary significantly with gender only, the reported age effect was statistically insignificant (80); indicating that inter-individual variation was more pronounced than any age induced effect. Onset of pregnancy and the day of the menstrual cycle were shown to be not significant factors with respect to urinary excretions of either thyroxine or triiodothyronine (82, 83). Therefore, the relevant cohorts (*i*'s) for triiodothyronine were defined to be gender and age cohorts within each of the gender cohorts, and gender only for thyroxine. The urinary excretions (U_i) data for each of these cohorts along with the subsequently derived daily urinary loads (U_i) are summarized in Tables 2.4 and 2.5.

The analysis for triiodothyronine (Table 2.4) suggests that its net daily urinary load (U_i) is expected to be 2.2 $\mu\text{g}/\text{cap}\cdot\text{d}$, and all of this is expected to be available for treatment as the fraction of triiodothyronine excreted as sulphate conjugates has been reported to be negligibly small (21). As was the case with fecal disposition of endogenous androgens, the endogenous thyroid content of fecal samples is rarely measured. The lone study quantifying daily fecal content of triiodothyronine (25), reported analyses of daily feces samples from children and found that the daily load present in their fecal excretions amounted to 10.6 $\mu\text{g}/\text{cap}\cdot\text{d}$. Iversen and Pedersen (80) measured the daily load of free triiodothyronine in children's urinary excretions and suggested that this amounts to 1.55 $\mu\text{g}/\text{cap}\cdot\text{d}$. Further, recognizing that urinary loads not only include the free fraction but also the two conjugated fractions, this daily urinary load of free triiodothyronine must be corrected for the conjugated fraction. Literature suggests that approximately 32.4% (i.e., a sample weight mean of data from three sources: (21, 84, 85) of the total urinary load of triiodothyronine is present as conjugated triiodothyronine. Using this value along with the free daily load measured by Iversen and Pedersen (80), the total daily load of triiodothyronine in children's urinary excretion can be estimated to be 2.3 $\mu\text{g}/\text{cap}\cdot\text{d}$. This, along with the reported fecal content 10.6 $\mu\text{g}/\text{cap}\cdot\text{d}$

Table 2.4 Total per capita daily urinary excretion of triiodothyronine (U_t) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$)

		U _t						Conjugated Fraction of U _t (µg/cap.d)			
Thyroid		Quantifying U _i				f _i ^(a)	U _i .f _i	F _u	G _u	S _u	Reference
		Reference	l	n	U _i ^(b)			(%)	(%)	(%)	
Triiodothyronine	Male	(80)	<60	61	2.5	0.42	1.0	68.1	31.9	≈ 0	(21,84,85)
		(80)	61+	11	1.8	0.07	0.1				
	Female	(80)	<50	68	2.1	0.35	0.7	68.1	31.9	≈ 0	(21,84,85)
		(80)	51+	15	1.7	0.16	0.3				
	Total (µg/cap.d)		U _t =Σf _i .U _i (n=155) ^(c)				2.2	F _u .U _t ^(d) = 1.5 G _u .U _t ^(e) = 0.7 S _u .U _t ^(f) ≈ 0			

(a) Based on demographic data for the simulation base year 2005 (33); (b) Total urinary loads calculated from reported free fraction (80) and sample weighted correction for level of conjugation from (21,84, 85); (c) Total per capita daily load of triiodothyronine excreted in human urine ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of triiodothyronine excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of triiodothyronine excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (f) Total per capita daily load of a triiodothyronine excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$).

Table 2.5 Total per capita daily urinary excretion of thyroxine (U_t) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$)

Thyroid		U_t					Conjugated Fraction of U_t			
		Quantifying U_t			$f_i^{(a)}$	$U_i f_i$	F_u	G_u	S_u	Reference
		Reference	I	n						
			Age (yr)/status	# of samples	$U_i^{(b)}$ ($\mu\text{g}/\text{cap.d}$)	($\mu\text{g}/\text{cap.d}$)	(%)	(%)	(%)	
Thyroxine	Male	(80)	All	61	2.5	0.5	70	30	≈ 0	(21,84,86)
	Female	(80)	All	68	2.1	0.5	70	30	≈ 0	(21,84,86)
	Total ($\mu\text{g}/\text{cap.d}$)	$U_t = \sum f_i U_i$ ($n=127$) ^(c)				2.3	$F_u \cdot U_t^{(d)} = 1.7$	$G_u \cdot U_t^{(e)} = 0.7$	$S_u \cdot U_t^{(f)} \approx 0$	

(a) Based on demographic data for the simulation base year 2005 (33); (b) Total urinary loads calculated from reported free fraction (80) and sample weighted correction for level of conjugation from (21,84, 86); (c) Total per capita daily load of thyroxine excreted in human urine ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of thyroxine excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of thyroxine excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (f) Total per capita daily load of a thyroxine excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$).

(25), suggests that the daily fecal load of triiodothyronine (F_t) amounts to be 4.4 times higher than the net urinary load (U_t). Therefore, F_t can be estimated to be $9.7 \mu\text{g}/\text{cap}\cdot\text{d}$. This along with U_t allows one to estimate that the total load of triiodothyronine in anthropogenic excretions to be $11.9 \mu\text{g}/\text{cap}\cdot\text{d}$.

The analysis for thyroxine (Table 2.5) suggests that its daily urinary load (U_t) is expected to be $2.3 \mu\text{g}/\text{cap}\cdot\text{d}$. Again, recognizing the limitation that the one study (25) reporting fecal content for thyroxine involved the analysis of samples from children only, the fecal to urinary load ratio for children was used here to estimate net fecal loads of thyroxine (F_t) from the determined net urinary loads (U_t). Using an analysis similar to that used to establish fecal-to-urinary load ratio for triiodothyronine explained in the preceding section, one can estimate the net fecal loads of thyroxine to be 4 times the net urinary loads of thyroxine (21, 25, 84, 86). Hence, F_t can be estimated to be $9.2 \mu\text{g}/\text{cap}\cdot\text{d}$ and the total load due to anthropogenic excretion ($U_t + F_t$) for thyroxine can be approximated as $11.5 \mu\text{g}/\text{cap}\cdot\text{d}$.

In Vivo Metabolites

The evaluation of the urinary loads for the remaining four *in vivo* metabolites is summarized in Appendix A. As is evident from the tabulated data, these chemicals have not been extensively studied. Since these compounds originate from *in vivo* metabolism of thyroxine and triiodothyronine (91), one might expect a gender and possibly an age dependency. But no data exists to support or negate such a hypothesis. Given the lack of data, it is assumed here that the limited data available and presented in Appendix A are representative excretion profiles for the whole population. Considering that this data largely stems from studying adult excretions, the excretion values generated in this manner might be overestimated, but from an environmental relevance perspective these estimates are expected to be conservative.

As with other compounds of interest, data on the fecal disposition of these chemicals was missing. Recognizing that reverse triiodothyronine, 3',5'-diiodo-L-thyronine, 3,3'-diiodothyronine have molecular weights above the biliary excretion threshold as is the case with triiodothyronine and thyroxine, the daily fecal disposition (F_t) for these three was assumed to be equal to 4.2 times their respective daily urinary loads (U_t), where 4.2 is the mean of the thyroxine and triiodothyronine fecal-to-urine load ratio derived earlier. Thyronine's molecular weight is well below the threshold and one would expect its fecal excretion to be of minor importance compared to its urinary excretion and definitely not as high as the values derived earlier for triiodothyronine and thyroxine. Hence, it is conservatively assumed here that the F_t for thyronine is equal to its U_t . Such an assumption warrants verification in future studies.

Influent Loads

The influent loads of the various endogenous chemicals released in anthropogenic excretions in the United States were estimated by enumerating the various parameters of equation (8). The U.S. nationwide influent loads for endogenous androgens and their *in vivo* metabolites are summarized in Table 2.6, ranging from 6 kg/d (epitestosterone) to 763 kg/d (5 α -androstanedione). The U.S. nationwide influent loads of the various endogenous thyroids and their *in vivo* metabolites were considerably lower and have been summarized in Table 2.7. The estimated loads varied from 0.5 kg/d (3', 5'-diiodo-L-thyronine) to 3.8 kg/d (thyroxine).

Three of the twenty five endogenous chemicals (i.e., testosterone, thyroxine and thyronine) also had exogenous contributions to their total influent loads. Exogenous consumption of relevant pharmaceutical preparations amounted to approximately 77%, 8% and 1% of the total influents loads of testosterone, thyroxine and thyronine, respectively. The minor contribution of exogenous use of levothyroxine to the influent loads of thyroxine and thyronine suggests that when the developed approach is applied to different geographical locations, it is not necessary to ascertain the use of levothyroxine in the local population. Typical values, as used here, may suffice since the consumption of levothyroxine is not expected to vary drastically among developed countries. Even if one considers the consumption of the levothyroxine to be variable, an error of 100% in the exogenous consumption of levothyroxine will only manifest itself as an 8.6% and 1.4% error in the influent loads of thyroxine and thyronine, respectively.

Conversely, the analysis suggests that exogenous testosterone will likely be a major contributor to the influent load of testosterone, where an increase of a 100% in the exogenous load of testosterone manifests itself as an increase of 77% in the total influent load of testosterone. Therefore, where the interest is in predicting the influent loads of testosterone, estimation of the consumption of exogenous testosterone in the local population is desirable.

2.3.2 Effluent Loads

The effluent loads for the various thyroids and androgens were calculated using equation (10). As justified earlier, the sulfate conjugate fractions of the influent loads were assumed to be unavailable for treatment. Literature reporting removal efficiencies (*Eff*) at full-scale treatment plants were only available

Table 2.6 Summary of the modeled influent loads, effluent loads and surface water concentrations of endogenous androgens and their in vivo metabolites in U. S. waterways

Androgens	Parameters for H_{T-inf}			Influent			Effluent		Surface Water	
	$U_t^{(a)}$	$F_t^{(b)}$	N	$H_{T-inf}^{(d)}$	$H_{T-infs}^{(e)}$	$H_{T-inf} - H_{T-infs}$	$Eff^{(f)}$	$H_{T-eff}^{(i)}$	$C_{T-sw-high}^{(j)}$	$C_{T-sw-typical}^{(k)}$
	$\mu\text{g/cap.d}$			kg/d			-	kg/d	ng/L	
5 α -Androstanedione	2329	303		763	238	525	0.29	613	781	6.0
Androst-4-ene-3,6,17-trione	1332	173		436	363	73	0.12	428	545	4.2
Androstane-3,17-dione, (5 β)	1577	205		517	124	393	0.29	405	515	4.0
11 β -Hydroxyandrosterone	710	92		233	0	233	0.46	125	159	1.2
Dehydroepiandrosterone	395	51		129	106	23	0.35	121	154	1.2
5 β Androstane-3-11-17-trione	351	46		115	64	51	0.46	92	117	0.9
Androstane-3,11,17-trione, (5 α)	303	39		99	39	60	0.46	72	92	0.7
Androstenetriol	393	51		129	0	129	0.48	67	85	0.7
11-Ketoetiocholanolone	365	47		120	0	120	0.46	65	82	0.6
11 β Hydroxyetiocholanolone	336	44		110	0	110	0.46	59	75	0.6
11-ketoandrosterone	333	43		109	0	109	0.46	59	75	0.6
5 β Androstane-3 α 17 β diol	396	51		130	43	87	0.88	53	68	0.5
Androsterone	1463	190		479	30	450	0.99 ^(g)	34	43	0.3
Etiocholanolone	1492	194		489	22	467	0.99 ^(g)	26	34	0.3
5 α Androstane-3 α 17 β diol	100	13		33	14	19	0.89	16	20	0.2
Androstenedione	19	2		6	4	2	0.12	6	7.5	0.1
Epitestosterone	17	2		5	1	5	0.38	4	4.7	0.04
Testosterone	25	3	96 ^(c)	37	2	35	0.99 ^(h)	3	3.4	0.03
Dihydrotestosterone	18	2		6	0	6	0.70	2	2.3	0.02

(a) From tables 2.1-2.3 in main text and tables in appendix A; (b) Estimated to be 13% of the respective U_t (from testosterone urine to fecal load ratio for adult males- see text for details); (c) Exogenous testosterone consumption estimated consumption data (see text for details); (d) From equation (8); (e) Using equation (11); (f) Estimated using STPWIN (47), unless otherwise indicated; (g) From (86,87); (h) From (87); (i) Equation (10); (j) Equation (13) with a DF of 4 ; (k) Equation (13) with a DF of 130.

Table 2.7 Summary of the modeled influent loads, effluent loads and surface water concentrations of endogenous thyroids and their in vivo products in U.S waterways

Thyroids	Parameters for H_{T-inf}			Influent			Effluent		Surface Water	
	$U_t^{(a)}$	F_t	N	$H_{T-inf}^{(e)}$	$H_{T-infs}^{(f)}$	$H_{T-inf} - H_{T-infs}$	$Eff^{(g)}$	$H_{T-eff}^{(h)}$	$C_{T-sw-high}^{(i)}$	$C_{T-sw-typical}^{(j)}$
	$\mu\text{g/cap.d}$			kg/d			-	kg/d	ng/L	
Triiodothyronine	2.2	9.7		3.4	0.0	3.4	0.14	3.0	3.8	0.03
Thyroxine	2.3	9.2	3.6 ^(d)	3.6	0.0	3.6	0.37	2.3	2.9	0.02
3,3'-Diiodothyronine	1.3	5.5 ^(b)		2.0	0.2	1.9	0.23	1.6	2.0	0.02
Thyronine	4.1	4.1 ^(c)	3.6 ^(d)	2.4	0.0	2.4	0.75	0.6	0.8	0.01
Reverse triiodothyronine	0.5	2.1 ^(b)		0.8	0.1	0.7	0.14	0.7	0.9	0.01
3',5'-Diiodo-L-thyronine	0.4	1.5 ^(b)		0.5	0.1	0.5	0.26	0.4	0.5	0.004

(a) From Tables 2.4-2.5 in main text and in appendix A; (b) Estimated to be 4.2x the respective U_t (see text for details); (b) Estimated to be 1.0x the respective U_t ; (d) Due to exogenous levothyroxine consumption estimated (see text for details); (e) From equation (8); (f) Using equation (11); (g) Estimated using STPWIN (47); (h) Equation (10); (i) Equation (13) with a DF of 4; (j) Equation (13) with a DF of 130.

for three of the endogenous androgens (i.e., testosterone (87), androsterone (86, 87) and etiocholanolone (86, 87)) and none of the thyroids. Such data gaps were addressed by modeling *Eff* for the remaining compounds of interest using the USEPA's STPWIN™ software (47). The modeled and reported (when available) *Eff*'s along with the subsequently derived effluent loads are summarized in Tables 2.6 and 2.7.

It is worth noting that even though a 100% increase in the use of exogenous testosterone manifests as a 77% increase in the influent load, the resultant increase in the effluent load would approximately amount to 10%. This is largely due to the assumption that all the exogenously-applied testosterone was available for treatment due to its mode of administration, the high removal efficiency that has been reported for its removal during sewage treatment, and the assumption that the sulphate conjugates are not available for treatment.

2.3.3 Surface Water Concentrations

Surface water concentrations were estimated from the derived effluent loads with the aid of equation (13). Two scenarios could be modeled using this equation and incorporating the range of dilution factors (*DF*) suggested by Lyndall et al. (32). Estimated surface water concentrations calculated using a *DF* of 4 were likely to be encountered in a “high-end” exposure scenario, while an evaluation with a *DF* of 130 would generate concentrations likely to be relevant in a typical exposure scenario. By evaluating the surface water concentrations for these two scenarios one can get a better grasp of the range of concentrations that are likely to be encountered upon conducting an extensive monitoring campaign.

The modeled surface water concentrations for endogenous androgens and their in vivo metabolites evaluated for a “high-end” exposure scenario (Table 2.6) ranged from a few ng/L to almost 800 ng/L. In contrast, when evaluated for a typical exposure scenario (*DF* = 130), the range in surface water is expected to range from less than 0.1 ng/L to a maximum of 6 ng/L. Of the 19 endogenous androgens and their in vivo metabolites whose surface water concentrations have been estimated here, only 2 have been actually monitored in United States surface waters; testosterone and androsterone (89). The range predicted here for testosterone covering the two scenarios was from less than 0.1 ng/L to 3.4 ng/L. In comparison, in a surface water monitoring study conducted all across the United States (89), 70 samples were analyzed and, of these, only 2 had testosterone concentrations above the detection limit of 5 ng/L. This suggests that the concentration in the majority of the samples was less than 5 ng/L. For androsterone, the predicted range here encompassing the two scenarios was 43 ng/L to 0.7 ng/L. In the same study mentioned above (89), 10 positive detections were reported from the analysis of 70 samples for androsterone, with a median for the detected samples of 17 ng/L and with a detection limit of 5 ng/L.

Both comparisons suggest that the estimates generated here for surface water concentrations appear to be reasonable surrogates for actual field measurements.

The modeled surface water concentrations for endogenous thyroids evaluated for a “high-end” exposure scenario (Table 2.7) ranged from less than 1 ng/L to almost 4 ng/L, while for a typical exposure scenario all the predicted concentration were less than 0.1 ng/L. To date, it appears that no attempts have been made in the United States or elsewhere to quantify the environmental concentrations of endogenous thyroids.

2.3.4 Environmental Relevance

Before one can assess the environmental relevance of the endogenous chemicals being considered here, their *PNECs* must be established. In order to establish contaminant-specific *PNECs*, eco-toxicological data was sought for each of the 25 endogenous chemicals. However, a literature survey indicated that relevant data was available for only 5 of the 25 endogenous chemicals of interest. The data used to derive *PNECs* along with the derived *PNECs* for these five chemicals is summarized in Table 2.8. The derived *PNECs* for testosterone, androstenedione and dihydrotestosterone are considered to be more robust than those derived for thyroxine and triiodothyronine, as the *PNECs* for the androgens were derived from classical eco-toxicological endpoints. A conservative application factor of 1000 was used to derive the *PNECs* for the two thyroids since the lowest reported endpoints still yielded a response in the test fish.

The environmental relevance for those chemicals for which *PNEC* values could be established was assessed for the two exposure scenarios using equation (14). The resultant risk quotients (*RQ*) are presented in Table 2.8. The *RQs* derived indicate that under a typical exposure scenario none of the five hormones are likely to pose a risk; however, when assessments were conducted for a high exposure assessment scenario, only androstenedione was found to pose unacceptably high risk to the receiving aquatic ecosystem. This suggests that androstenedione is likely to pose a risk to the receiving aquatic ecosystem in only those locations where the dilution of wastewater effluents is low.

The lack of relevant eco-toxicological data for the remaining chemicals prevents one from estimating their *PNECs*. However, *in vivo* and *in vitro* potency data can be used to indicate the potential of the remaining chemicals to acts as endocrine disrupting chemicals. The *in vivo* and *in vitro* potency data suggests that the majority of the remaining chemicals are weak modulators of the appropriate receptors (99–110). However, three important exceptions to this generalization were identified:

androsterone, which was shown to be 2.6 times more potent than testosterone in inducing secondary male characteristics in exposed *O. Latipes* (99); androstane-3,11,17-trione, which was 5 times more potent than dihydrotestosterone in binding to the androgen receptor extracted from the ovaries of *M. undulates* (105); and 5 α -androstanedione, which was found to be twenty times more potent than dihydrotestosterone in binding to the androgen receptor extracted from the brains of *M. undulates* (105). Therefore, there exists real potential for these chemicals to modulate the androgen receptor in fish, particularly so in the case of androsterone, since effects were demonstrated *in vivo*. Therefore, these three chemicals should be prioritized for eco-toxicological testing.

For the remaining chemicals (not including the five known hormones for which *PNECs* were derived and the three that are likely modulators) the likely relevance is less certain. It is known that most of them are weak modulators based on *in vitro* binding affinity to appropriate receptors (100–110) but what such weak binding to the receptors means in terms of toxic potential is less certain.

Table 2.8 Predicted No-Effect Concentrations (PNECs) and Risk Quotients (RQs) for endogenous hormones for which eco-toxicological data was available

Hormones	Endpoint	Taxon	Species	Duration	Effect	Concentration	Reference	AF	PNEC	RQ	
				d		µg/L			ng/L	high	typical
Testosterone	NOEC	Fish	<i>O. tshawytscha</i>	29	Sex differentiation	1	(92)				
	NOEC	Algae	<i>S. subspicatus</i>	3	Growth	335	(93)	10 ^(a)	100	3.4x10 ⁻²	2.6x10 ⁻⁴
	NOEC	Crustacean	<i>B. calyciflorus</i>	4	Females fertilized	1	(94)				
Androstenedione	NOEC	Fish	<i>G. affinis</i>	24	Mascluziation	0.04	(95)	10 ^(b)	4	1.9x10 ⁰	1.44x10 ⁻²
	NOEC	Crustacean	<i>D. magna</i>	21	Abnormalities	2291	(96)				
Dihyrdotestosterone	NOEC	Fish	<i>G. aculeatus</i>	18-35	Spiggin induction	2	(97)	100 ^(c)	20	1.2x10 ⁻¹	8.8x10 ⁻⁴
Thyroxine	LOEC	Fish	<i>C. auratus</i>	25d	Standard length	10	(98)	1000 ^(d)	10	2.9x10 ⁻¹	2.2x10 ⁻³
Triiodothyronine	LOEC	Fish	<i>C. auratus</i>	40d	Tail fin length	10	(98)	1000 ^(d)	10	3.8x10 ⁻¹	2.9x10 ⁻³

(a) AF=10 used, considering 3 chronic endpoints from three different taxa were available; (b) AF =10 used, even though only data from two taxa was available because the chronic endpoint for algae is unlikely to below the one reported for fish; (c) AF =50 even though only one chronic endpoint was available because the chronic endpoint for algae is unlikely to below the one available for fish; (d) AF =1000 is used conservatively, as the endpoint available was an LOEC.

2.3.5 Overall Perspective

Very little attention has been paid to the environmental release and relevance of endogenous androgens, thyroids and their *in vivo* metabolites. The intent here was to develop a systematic approach that allows one to conservatively quantify the loads of such chemicals released in anthropogenic excretions. The compiled data set made it possible to generate mean loads of such compounds in urinary and fecal excretions (i.e., U_i and F_i) of various population cohorts of interest. These loads should be applicable to any situation where the desire is to quantify net loads of such contaminants. Considering that population demographics in most instances are not expected to vary drastically between communities, the derived population-normalized net urinary and fecal loads (U_i and F_i) could even be used on an individual treatment plant level to conservatively estimate the likely loads of such contaminants in the influents of treatment plants. Such predicted loads could also be coupled to influent monitoring data to understand the sewer behavior of such contaminants. If the predicted loads are found to be consistently higher than the measured loads, degradation/transformation of the excreted load is a likely cause. In this case, it is suggested that a comparison of the monitored and predicted values should be made on a daily load basis. That being said, it is important to understand that if the interest lies in predicting the maximum risks posed or the environmental relevance of such contaminants, then the assumption that the excreted loads are conserved during sewer transit is a conservative one. In order to calculate effluent loads, it was assumed that the sulphate conjugates of the endogenous chemicals are likely to be resistant to treatment in sewage plants. It is worth investigating the effect of this assumption on the predicted effluent loads. If one were to assume the converse, i.e., that the sulphate conjugates are completely available for treatment, the effluent loads for a number of the endogenous chemicals will be significantly reduced, while for others minimal to no reduction in effluent loads would be observed (see Figure A.1 of Appendix A). From an environmental relevance perspective, the assumption that the sulphate conjugates are not available for treatment is a conservative one. Therefore, if the interest lies in risk assessment and environmental relevance of such contaminants such an assumption may suffice at the preliminary assessment stage until readily useable data is available indicating otherwise.

Overall, from an environmental assessment perspective, these assumptions are only worth investigating in further detail for those compounds that pose a significant risk according to the analysis described above. In this way, impact assessments could be conducted more efficiently by only focusing efforts on investigating compounds that have a reasonable possibility of triggering important eco-toxicological impacts.

2.4 Conclusions

In the strategy employed here to translate the derived excretion loads from anthropogenic excretions to the environment, justifiable but conservative assumptions were made where data was found lacking. Therefore, the predicted surface water concentrations should represent conservative estimates of their likely presence in the environment. The estimates were subsequently used to assess the environmental relevance of the chemicals for which *PNECs* could be derived. The conservative analysis suggests that all of the endogenous chemicals for which *PNECs* could be derived are unlikely to pose a risk to receiving ecosystems when evaluated for a typical exposure scenario. When the relevance was evaluated even more conservatively by considering a high exposure scenario, exposure to only androstenedione raises concern. Therefore, it is suggested that the conservative nature of the assumptions used here be investigated for androstenedione only, in the event that its predicted surface water concentrations are overestimates and the resultant risk is overstated.

Overall, it is suggested that the strategy developed here could be used to conduct a preliminary risk assessments of any endogenous chemicals in order to identify compounds of concerns. Those compounds that are identified as having a potential risk could then be investigated in further detail to assess their impacts in greater detail and with greater accuracy. An additional utility of the generated surface water estimates produced here is that they can serve as detection limit bench marks for analytical chemists or regulatory bodies that are interested in detecting or monitoring such chemical.

2.5 Suggestions for Further Development

The focus here has been to establish a nationwide release inventory of all major endogenous androgens, thyroid hormones and their *in vivo* metabolites, as they make their way to receiving environment through the wastewater treatment and collection train. However, other potential sources that may be important on a regional scale including the contributions of surface runoffs from feedlots and sludge application sites, slaughterhouse facilities discharging endogenous chemical-laden wastes, and/or industrial effluents that themselves may have significant androgenic or thyroidal content.

Further, the analysis here was limited to a range of dilution factors that are relevant for a nationwide assessment. However, the combination of factors yielding surface water concentrations on a local level may be very different. In certain instances, a combination of factors could lead to a situation where a dilution factor of less than the lower limit of 4 used here may be appropriate under low flow conditions (i.e. 7Q10). In other cases no secondary treatment may be available for a wastewater stream being

discharged into the environment. Furthermore, each of the parameters used to estimate surface water concentrations has variability associated with it, which is not accounted for in a deterministic risk assessment. Therefore, the next logical step of the strategy developed here would be to move from the national deterministic realm to the probabilistic geo-referenced regional realm by incorporating probabilistic considerations into geographical information system (GIS) contaminant fate models such as GREAT-ER (111) or PhATE (112). Such an analysis will allow one to go beyond a national assessment and identify regional hot spots, where contaminants identified in a nationally assessment as low risk may indeed pose a risk to the local environment.

Lastly, the interest here has been on risk posed by individual chemicals and, as such, the net androgenic and thyroidal potential of mixtures of such chemicals hasn't been considered. Work with mixtures of endogenous estrogens suggests that the concept of concentration addition can be used to reasonably predict the worst case impact of chemical mixtures that manifest their effects by interacting with a receptor (113). Since endogenous thyroids and androgens also act through similar receptor-mediated modes of action as endogenous estrogens, it is plausible that mixtures of such chemicals would also act in a concentration-additive manner. Ideally, sufficient toxicity data or *in vivo* effect data would be available for each of the endogenous chemicals so that one can establish environmental relevance of the mixture being discharged. Unfortunately, such data are rare for the chemicals of interest here. In such cases where enough toxicity data or *in vivo* effect data not readily available, an *in vitro* surrogate typically used is the receptor binding potency of the chemical (114). Therein lays the limitation of using such an approach as it implicitly assumes that the biological response of a chemical can be predicted by considering the chemical's binding potential. The limited *in vivo* data available for such chemicals further raises questions about exclusively relying on *in vitro* binding data. For example, work by Sperry and Thomas (105) suggested that for the androgen receptors of *M. undulatus* the binding potency of testosterone was 37 to 625 times higher than the binding potency of androsterone. However, *in vivo* data reported by Kawamoto (99) suggests that it is actually androsterone that is 2.6 times more potent than testosterone in inducing secondary male characteristics in exposed *O. latipes*. Considering such dramatic discrepancies between *in vitro* and *in vivo* data and the limited availability of *in vivo* data, it is perhaps too premature to robustly establish the eco-toxicological relevance of the mixtures of interest here. However, as relevant data becomes available such mixture effects could be, and should be, considered.

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Chapter 3: Assessing the Risk of Exogenously-consumed Pharmaceuticals in Land-applied Human Urine

PREFACE

Chapter 2 was focussed on evaluating the release of PhACs via effluents of sewage treatment plants. In the following chapter, further studies are done in recognition that the application of human urine to agricultural land as a fertilizer is another totally distinct and important route through which PhACs can be released to the environment. Specifically, this chapter addresses the objective of the thesis related to developing and applying an approach for the assessment of human-health and eco-toxicological risks posed by PhACs in urine that is applied to agricultural land. Exposure to 25 PhACs through six routes was evaluated, three with respect to eco-toxicological risk and three for human-health risk. Overall, the risk assessment approach developed and applied attempted to address the following questions: (1) does the presence of certain PhACs in human urine present an eco-toxicological or a human-health risk if it is applied on land untreated?; (2) if so, which PhACs of the ones studied should be monitored during the pretreatment of urine?; (3) of the prioritized pharmaceuticals what are the exposure routes and endpoints that they are likely to be affected? and (4) what knowledge gaps need to be addressed before the next logical iterative refinement of the developed framework is undertaken? A particularly novel aspect of the developed approach was the formulation of the concepts of “critical concentration” and “critical penetration”. The development of such concepts allows for risk evaluation for those populations for which relevant consumption data for PhACs is not readily available or is of questionable reliability.

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Assessing the Risk of Exogenously-consumed Pharmaceuticals in Land-applied Human Urine

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ABSTRACT

Once separated, the use of urine as fertilizer is a particular attractive proposition and can significantly mitigate the release of nutrients and pharmaceutically active compounds (PhACs) to the environment. In the current study, a simple methodological framework is proposed for assessing risks that are posed by the land application of urine, which contains PhACs, in terms of 6 selected environmental and human-health endpoints. In total, 25 commonly-used PhACs were conservatively assessed using the proposed methodology and results indicated that 14 of them may pose a risk with respect to either eco-toxicological or human-health endpoints. The receiving terrestrial environment was identified as the most susceptible of the eco-toxicological endpoints and hazard to human-health was most significant through food-chain transfer. The results highlight the need to consider the potential impacts associated with pharmaceuticals and the need to pre-treat urine to address the presence of problematic PhACs before it is applied on land.

Keywords: Fertilizer; land application; pharmaceuticals; risk assessment; source separation; urine

3.1 INTRODUCTION

One of the fastest growing concerns in the wastewater treatment industry is the environmental fate and impacts of pharmaceutically active compounds (PhACs). Such compounds are primarily excreted by humans in urine, either in an unchanged form or as metabolites (Lienert et al., 2007). In the present day treatment context, urine is collected simultaneously with fecal matter and diluted by large amounts of grey water and infiltrating water. This relatively dilute and complex mixture is then transferred to sewage treatment plants, where the use of tertiary advanced treatment techniques is often suggested to treat copious amounts of wastewater in which PhACs are frequently present at nanogram per liter concentrations (Jones et al., 2007). This is a particularly difficult challenge and, as such, source separation of human excreta must be given serious consideration (Larsen et al., 2004). The exploration of source separation strategies initially stemmed from the understanding that human urine is an important source of nutrients in wastewaters and has the potential to be exploited as a sustainable source of fertilizer (Jönsson et al., 2004). Therefore, source separation of human urine would not only allow one to effectively manage the problems of PhAC and nutrient releases to the environment but would also permit one to valorize human urine through agricultural use. However, before land application of human urine is considered, one needs to first assess the risks posed by its PhAC content.

Therefore, the purpose of this paper is to present a proposed approach to evaluate the risks posed by PhACs present in human urine. Risks posed by a selection of widely-used yet chemically diverse pharmaceuticals were considered. Altogether, six exposure routes were considered; three considering eco-toxicological endpoints and another three considering human-health endpoints. Overall, the risk assessment approach was developed in an attempt to answer the following questions: (1) does the presence of certain PhACs in human urine present an eco-toxicological or a human-health risk if it is applied on land untreated?; (2) if so, which PhACs of the ones studied should be monitored during the pretreatment of urine?; (3) of the prioritized pharmaceuticals what are the exposure routes and endpoints that they are likely to be affected? and (4) what knowledge gaps need to be addressed before the next logical iterative refinement of the developed framework is undertaken?

3.2 APPROACH DEVELOPMENT

3.2.1 Urine Application Rate and Frequency

Before one can establish the initial concentration and subsequent fate of a particular PhAC in the soil matrix following land applications of urine, the rate and frequency of urine application must be

ascertained. A reasonable assumption regarding the frequency of application is once per year, which is consistent with the suggested minimum storage duration of six months for collected urine to mitigate its inherent microbial or viral risks (Schönning and Stenström, 2004). As to the rate of application, this can be estimated by considering the per litre nutrient content of urine and the per unit area nutrient requirement of the land to which it is being applied. The urine nutrient content is dependent on the excreting individual's diet and is expected to vary between 5.2 - 10.9 g of nitrogen (N) and 0.5 - 1.1 g of phosphorus (P) on a daily per capita basis (Jönsson et al., 2004). This daily nutrient content is excreted in approximately 1.5 litres of human urine (Jönsson et al., 2004). Therefore, the average per litre nutrient content of human urine is expected to be 3.5 - 7.3 g of N and 0.3 - 0.7 g of P. A conservative maximum application rate for urine can be calculated by assuming that urine is applied at a rate so that the European Union regulatory limit of 17 g/m² for the maximum amount of nitrogen that can be applied per unit area of land fertilized is met (Spaepen et al, 1997; EMEA, 2007). Using this regulatory limit and the nitrogen content of urine, the maximum application rate of urine is likely to be between 2.3 - 4.9 L/m². These calculated maximum values correspond well with urine application rates of 2 - 4 L/m² used in on-fields studies (Heinonen-Tanski and Wijk-Sijbesma, 2005). In summary, the annual urine application rate (AR_{urine}) was conservatively assumed to be 4.9 L/m².

3.2.2 Risk to the Terrestrial Environment

To assess the risk of PhACs to the terrestrial environment, one can extend van Leeuwen's (2003) approach for the risk assessment of contaminants present in land-applied sewage sludge and calculate the initial concentration of particular PhAC in soil upon urine application (C_{s0}) using the following equation:

$$C_{s0} = \frac{Cu \times AR_{urine}}{D_{mix} \times \rho_{soil}} \quad (1)$$

where: Cu is the concentration of a particular PhAC in urine at the time of application (mg/L); D_{mix} is the mixing depth of urine upon application (m); and ρ_{soil} is the density of soil (kg/m³). AR_{urine} is as described above and is assumed to be 4.9 L/m². D_{mix} was set conservatively equal to 0.05 m, which is a typical mixing depth value used for undisturbed soil (Spaepen et al, 1997; EMEA, 2007). The density of the soil was assumed to be 1,700 kg/m³ (van Leeuwen, 2003).

The typical approach to using such an equation to assess the risk posed by a particular PhAC present in urine to the soil environment would be to utilize the net consumption of the PhAC for a population in a

given location to estimate C_u . Once estimated, C_u would then be used to calculate C_{s_o} according to eq. (1) which can be compared to a predicted no-effect concentration for that PhAC for the terrestrial environment ($PNEC_{soil}$) to generate a risk index. However, PhAC consumption patterns for the urine-contributing communities are expected to show considerable geographical variations. Indeed, the WHO estimates that in 1999 approximately 15% of the world's population living in high-income countries consumed about 90% of the total medicines by cost (WHO, 2004). Conversely, it is conceivable that other drugs, such as antimalarial and antituberculosis medications, may be used in disproportionately higher quantities in low-income countries.

As an alternative approach, it is proposed here that C_{s_o} be set equal to a relevant terrestrial toxicity endpoint in eq. (1) and then a critical urine concentration (i.e., $C_u = C_{u_c}$) be calculated. In other words, C_{u_c} is the minimum PhAC concentration in urine that would entail a risk to the terrestrial ecosystem when urine is applied to land. Typically, the fate of contaminants in soils is assumed to follow first-order decay kinetics (Spaepen et al, 1997; van Leeuwen, 2003) and therefore repeated applications of urine could lead to terrestrial accumulation of PhACs, particularly for compounds with longer half-lives. As a consequence, C_{s_o} cannot be directly set equal to $PNEC_{soil}$ and should be corrected for the accumulation over a number of repeated applications. A worst case exposure assumption typically used in this regard is 10 successive applications (van Leeuwen, 2003), which translate to 10 years of urine application once per year for the current assessment. Furthermore, in year 10 itself the contaminant would demonstrate first-order decay, hence the question arises as to which point in time in year 10 one should use for risk assessment purposes. A typical strategy is to consider an average tenth year exposure concentration where the suggested averaging duration for terrestrial ecosystem exposure is the first 30 days of year 10 (van Leeuwen, 2003). Using this approach, C_{s_o} can be related to $PNEC_{soil}$ as follows:

$$C_{s_o} = \frac{PNEC_{soil}}{AcF \times AvgF} \quad (2)$$

where AcF (accumulation factor) and $AvgF$ (averaging factor), which incorporate soil decay rates, can be calculated, respectively, using eqns. (62) and (55) from van Leeuwen (2003). Now that the initial soil concentration has been related to a toxicity endpoint, we can equate eqns. (1) and (2) and solve for the critical urine concentration (C_{u_c}), as follows:

$$Cu_c = \frac{PNEC_{soil} \times D_{mix} \times \theta_{soil}}{AcF \times AvgF \times AR_{urine}} \quad (3)$$

One could use such critical values to assess the risk posed by a local situation by measuring the concentration of PhACs in the urine storage tank just before application is undertaken. Where such an analysis is not possible (i.e., where sophisticated analytical equipment and expertise are unavailable), it is proposed that the use of a critical penetration factor ($Fpen_c$) in the urine-contributing community be calculated from Cu_c as follows:

$$Fpen_c (\%) = \frac{Cu_c}{Cu_{100\%}} \times 100 \quad (4)$$

A penetration factor represents the fraction or percentage of a population that is currently using a particular medication at any given time. Therefore, the factor, $Fpen_c$, defined by eq. (4) represents the minimum penetration factor and therefore the minimum net usage of particular drug within the urine-contributing community that would entail a risk through a particular exposure pathway. $Cu_{100\%}$ represents the expected PhAC urine concentration in the urine storage tank if 100% of the urine-contributing population was taking the drug. It can be estimated by:

$$Cu_{100\%} = \frac{DDD \times F_{ex}}{U} \quad (5)$$

where: DDD (mg) is the defined daily dose of a particular PhAC as compiled by the World Health Organization (WHO, 2009); F_{ex} is the fraction of the consumed dose that is excreted in urine either as the parent compound or as its conjugates (obtained from such references as Dollery, 1998; Moffat et al., 2004; McEvoy et al., 2009); and U is the average volume of urine excreted per day, which was earlier established above to be 1.5 L/cap/d. Thus, combining (4) and (5) leads to:

$$Fpen_c (\%) = \frac{Cu_c \times U}{DDD \times F_{ex}} \quad (6)$$

$Fpen_c$ values can then be compared to the knowledge of local drug consumption patterns in the urine-contributing community to assess if the use of a particular PhAC is likely to pose a risk. Furthermore, and

more importantly for screening level assessment studies like the present one, the magnitude of $Fpen_c$ could immediately indicate if the presence of a particular PhAC in urine is ever likely to pose a risk through the exposure pathway being considered. That is, if the $Fpen_c$ for a particular PhAC and exposure pathway combination is greater than 100%, it would be from a practical standpoint virtually impossible for it to ever pose a risk. Moreover, the drug penetration factors in national populations from high per capita drug-consuming countries suggest that for most pharmaceuticals the penetration factor is expected to be less than 2%. For example, data indicate that the upper 95th percentile for population penetration factors for 800 drugs used in Germany in 2001 was 0.95% (EMEA, 2006) while for more than 300 high-use Canadian drugs consumed in 2006 it was 1.9% (Khan and Nicell, in preparation). Note that for the Canadian dataset, it was found that only one drug had a penetration factor greater than 5%; i.e., acetaminophen at 6.7%. Therefore, it is conservatively assumed that for most drugs an $Fpen_c$ value greater than 5% is unlikely to pose a significant risk. This threshold will be used in the analysis presented below. Possible exceptions to this suggested upper limit may be drugs used to treat locally prevalent diseases (e.g., antimalarial and antituberculosis drugs) in low-income countries for which comparative penetration factors countries such as Canada and Germany are likely insufficiently conservative. In summary, barring those drugs used to treat endemic and pandemic disease outbreaks, an $Fpen_c$ value greater than 5% should be indicative of minimal risk.

3.2.3 Eco-toxicological Exposure Assessment

Considering that PhACs introduced into the soil environment through urine application will inevitably be distributed into groundwater and surface waters, three distinct exposure routes were considered for eco-toxicological exposure assessment: (1) exposure to the terrestrial environment; (2) exposure to the groundwater ecosystem; and (3) exposure to the surface water ecosystem. The relevant equations for Cu_c and $Fpen_c$ for terrestrial environmental exposure were developed in the preceding section. Similar equations can be developed for the eco-toxicological risks posed to groundwater and surface water ecosystems. For this purpose, the concentration of PhACs in groundwater upon leaching from the soil layer can be conservatively estimated using van Leeuwen's (2003) approach, which approximates the concentration in groundwater as equal to the concentration in soil pore water. For the case of surface water exposure, the suggested approach of Metcalfe et al. (2009) was extended, which conservatively estimates the concentration in surface water as a tenth of the concentration in the pore water. Using similar approximations and approaches presented for the terrestrial exposure routes, surrogates for equation (1), (2), (3) and (6) that were developed for terrestrial environments can also be developed for groundwater and surface water exposure. These equations are summarized in Table 3.1.

Table 3.1 Summary of equations for eco-toxicological and human-health exposure pathways.

Endpoints	Basic assessment equation	Toxicity endpoint	Critical urine concentration (Cu _c)	Critical penetration factor (Fpen _c)
Eco-toxicological endpoints				
Terrestrial	$C_s = \frac{Cu \times AR_{urine}}{D_{mix} \times \rho_{soil}}$	$C_s = \frac{PNEC_{soil}}{AcF \times AvgF}$	$Cu_c = \frac{PNEC_{soil} \times D_{mix} \times \rho_{soil}}{AcF \times AvgF \times AR_{urine}}$	$Fpen_c (\%) = \frac{Cu_c \times U}{DDD \times F_{ex}} \times 100$
Groundwater	$C_{gw} = \frac{Cu \times AR_{urine}}{D_{mix} \times K_{soilwater} \times 1000}$	$C_{gw} = \frac{PNEC_{daphnia}}{AcF \times AvgF}$	$Cu_c = \frac{PNEC_{daphnia} \times D_{mix} \times K_{soilwater} \times 1,000}{AcF \times AvgF \times AR_{urine}}$	
Surfacewater	$C_{sw} = \frac{Cu \times AR_{urine}}{D_{mix} \times K_{soilwater} \times 10,000}$	$C_{sw} = \frac{PNEC_{aquatic}}{AcF \times AvgF}$	$Cu_c = \frac{PNEC_{aquatic} \times D_{mix} \times K_{soilwater} \times 10,000}{AcF \times AvgF \times AR_{urine}}$	
Human-health endpoints				
Food chain transfer	$C_s = \frac{Cu \times AR_{urine}}{D_{mix} \times \rho_{soil}}$	$C_s = \frac{(ADI / S - TDI) \times BW \times B}{AcF \times AvgF \times \sum (I_i \times f_i \times K_{spi} \times FD_i)}$	$Cu_c = \frac{\rho_{soil} \times D_{mix} \times (ADI / S - TDI) \times BW \times B}{AcF \times AvgF \times \sum (I_i \times f_i \times K_{spi} \times FD_i) \times AR_{urine}}$	$Fpen_c (\%) = \frac{Cu_c \times U}{DDD \times F_{ex}} \times 100$
Groundwater intake	$C_{gw} = \frac{Cu \times AR_{urine}}{D_{mix} \times K_{soilwater} \times 1000}$	$C_{gw} = \frac{(ADI / S - TDI) \times BW \times B}{V \times AcF \times AvgF}$	$Cu_c = \frac{(ADI / S - TDI) \times D_{mix} \times K_{soilwater} \times BW \times B \times 1,000}{V \times AcF \times AvgF \times AR_{urine}}$	
Surfacewater intake	$C_{sw} = \frac{Cu \times AR_{urine}}{D_{mix} \times K_{soilwater} \times 10,000}$	$C_{sw} = \frac{(ADI / S - TDI) \times BW \times B}{V \times AcF \times AvgF}$	$Cu_c = \frac{(ADI / S - TDI) \times D_{mix} \times K_{soilwater} \times B \times BW \times 10,000}{V \times AcF \times AvgF \times AR_{urine}}$	

Notes: ρ_{soil} (kg/m^3) = Soil density = 1,700; AcF= Accumulation factor [estimated using equations in van Leeuwen (2003)]; ADI (mg/kg/day) = Acceptable daily intake [see Table 2 for values and associated references]; AR_{urine} (L/m^2) = Application rate = 4.9; AvG= Averaging factor [estimated using equations in van Leeuwen (2003)]; B= Coefficient of background exposure set to 0.5 (WHO 2002); BW= human body weight= 60 kg (WHO 2002); C_{gw} (mg/L) = Concentration in groundwater; C_s (mg/kg) = Concentration in soil; C_{sw} (mg/L) = Concentration in surface water; C_u (mg/L) = Concentration in urine; DDD (mg) = Defined daily dose [see Table 2 (WHO 2009)]; D_{mix} (m) = Mixing depth = 0.05 (EMEA 2007); Fd_i = Fresh water to dry weigh conversion factor for the i^{th} group (WHO 2002); $F_{\text{excretion}}$ = Fraction excreted in urine-parent compound plus parent compound associated conjugates [see Table 3.2 for values and associated references]; f_i = Fraction of the i^{th} food group affected by land application = assumed to be 1.0 (WHO 2002); I_i (kg/day)= Daily consumption of i^{th} food group (WHO 2002); K_{sp_i} = Plant/soil partition factor for the i^{th} food group [estimated using equations in WHO (2002)]; $K_{\text{soil-water}}$ = Soil–water partitioning coefficient [estimated using equations in van Leeuwen (2003)]; $\text{PNEC}_{\text{aquatic}}$ (mg/L) = Toxic endpoint for aquatic species (algae, daphnia and fish) [see Table 2 for values and references]; $\text{PNEC}_{\text{daphnia}}$ (mg/L) = Toxic endpoint for daphnia [see Table 3.2 for values and associated references]; $\text{PNEC}_{\text{soil}}$ (mg/kg) = Toxic endpoint for terrestrial environment [calculated using equilibrium partitioning method van Leeuwen (2003), see Table 3.2 for values]; s-TDI (mg/kg/day) = Surrogate tolerable daily intake [see Table 3.2 for values and associated references]; U (L/cap.d) = Per capita urine production = 1.5 (Jonsson et al. 2004); V (L/cap.d) = Daily consumption of water = 2 (NEPC 2008).

3.2.4 Human-Health Exposure Assessment

PhACs introduced into the soil environment through urine application may also present a human-health risk. The WHO (2002) identified seven pathways through which humans may be exposed to contaminants present in land applied sewage sludge. Of the seven pathways, the authors prioritized food chain transfer of pollutants for further quantitative analysis due to the consumption of grains, vegetables, roots/tubers and fruits. The rationale for this being that food-chain transfer is the primary route through which humans are exposed to environmental pollutants and that 75% of the load transferred through such a route is via the consumption of the grains, vegetables, roots/tubers and fruits. Therefore, one of the human-health exposure routes considered for the current study was the transfer of PhACs from urine-fertilized soil to plant material to humans through dietary intake. The other two exposure pathways considered exposure to PhACs via consumption of either groundwater or surface water to meet daily human drinking water requirements. Using similar logic as that presented in the preceding sections, one can extend equations suggested in the WHO report and develop relevant equations for Cu_c and $Fpen_c$ for the human–health exposure routes being considered here. Resultant equations for these critical factors as well as the equations used to derive them are summarized in Table 3.1.

3.3 RESULTS AND DISCUSSION

A total of 25 PhACs were selected to demonstrate the assessment procedure proposed above and are listed in Table 3.2. The intent behind the selection of these particular compounds was to capture a set of chemically diverse PhACs that meet one or more of the following selection criteria: prevalent global use, environmental persistence, eco-toxicity potential, human-health hazard potential and lastly, possible use in endemic disease situations. Extensive chemical/fate data was required for each of the PhACs as data input for the Cu_c and $Fpen_c$ equations in Table 3.1. The collected and calculated data are presented in Table 3.2 along with associated literature sources or calculation procedures. Table 3.3 presents the assessment results for the selected 25 PhACs.

The utility of the calculated Cu_c and $Fpen_c$ values is demonstrated by the fact that their relative magnitudes can immediately be used to identify the most sensitive exposure pathways for a particular PhAC. That is, for the 25 compounds, the terrestrial environment was identified as the most susceptible of the eco-toxicological endpoints and for humans the most significant exposure pathway was through food-chain transfer. Furthermore, an $Fpen_c$ value greater than 5% for most PhAC and exposure pathway combinations is immediately indicative of minimal risk. It is also important to note that, even though they don't have any real

meaning, $Fpen_c$ values greater than 100% are a measure of the margin of safety for each PhAC and exposure pathway combination.

The suggested utility of $Fpen_c$ for risk prioritization and screening purposes is also demonstrated in Table 3.3 in a two-tier evaluation process. It is suggested that in a “Tier A” assessment the most sensitive $Fpen_c$ of the pathways considered be compared to the 5% benchmark and risk posed be characterized either as “minimal risk” (i.e., most sensitive $Fpen_c > 5\%$) or “possible risk” (i.e., most sensitive $Fpen_c < 5\%$). The application of such a methodology to the 25 PhACs presented in Table 3 eliminates 5 of the 25 drugs as posing “minimal risk”. It is important to note that the results of a Tier A assessment would typically be globally applicable regardless of the local drug consumption patterns. However, for some compounds further consideration is required. For example, chloroquine was one of the drugs to be classified to present “minimal risk” upon Tier A assessment. However, chloroquine is commonly used to treat malaria infections and, as suggested earlier, such drugs could conceivably surpass the 5% benchmark being used for Tier A assessment. Therefore, its “minimal risk” classification warrants further discussion, with the most sensitive exposure pathway for chloroquine requiring an $Fpen_c$ of 52%. The likelihood that 52% of the population will be consuming the defined daily dose for chloroquine each day for a given year (i.e., because urine is collected for one year before application) is essentially zero considering that malaria is an acute condition and a yearly drug consumption penetration of 52% would translate into an epidemiological prevalence of malaria in the region greater than 100%.

In a “Tier B” assessment, it is suggested that $Fpen_c$ values for drugs classified as being of “possible risk” in a Tier A assessment be compared to the local drug penetration factors ($Fpen_{local}$), thereby providing a basis for the calculation of a risk index (i.e., $Fpen_{local}/Fpen_c$). For which a value of greater than one would be indicative of risk and less than one would suggest little or no risk according to the endpoints used for assessment. A Tier B assessment is demonstrated in Table 3 using national Canadian drug penetration factors, and is therefore relevant for situations where application of human urine to land is being considered within Canada (Note: For the sake of completeness, Tier B assessments were also conducted for compounds identified as being of minimal risk under the Tier A assessment). The Tier B assessment using Canadian data classified an additional 6 PhACs as posing “minimal risk” for the Canadian context. An alternative Tier B assessment strategy could be used to measure the concentration of all Tier A drugs of “possible risk” in the urine storage tank at the time of urine application for comparison to the associated Cu_c values.

The assessment results suggest that a number of the drugs present in human urine are likely to pose a risk once introduced into the soil matrix. Of the 14 drugs classified as risky following Tier B assessment using

Table 3.2 Collection and estimation of chemical and fate data required as inputs.

PhACs	Therapeutic class	Log P^1	Log K_{oc}	K_H^{11}	$t_{1/2}$ (biodegradation)	DDD ¹⁹	$F_{exc}^{20,21,22}$	ADI/S-TDI ²³	$PNEC_{aquatic}^{27}$	$PNEC_{soil}^{28}$	$PNEC_{daphnia}^{27}$
			L/kg	Pa-m ³ /mole	d	mg	%	mg/kg/d	mg/L	mg/kg	mg/L
Acetaminophen	Analgesic	0.5	2.4 ⁴	6.5x10 ⁻⁰⁸	116 ¹²	3000	70	5.0x10 ⁻² ADI	9.2x10 ⁻³	4.5x10 ⁻²	9.2x10 ⁻²
Alprazolam	Anxiolytics	2.2	4.9 ⁵	9.9x10 ⁻⁰⁷	75 ¹³	1	11	8.3x10 ⁻⁶ S-TDI	5.1x10 ⁻⁴	8.8x10 ⁻¹	5.1x10 ⁻³
Amoxicillin	Antibiotic	0.9	2.9 ⁵	2.5x10 ⁻¹⁶	0.3 ²⁹	1000	80	2.0x10 ⁻¹ 24 ADI	7.8x10 ⁻⁵	1.2x10 ⁻³	5.0x10 ¹
Azithromycin	Antibiotic	4.0	4.8 ⁶	5.4x10 ⁻²⁴	360 ¹³	300	6	1.1x10 ⁻² ADI	9.4x10 ⁻⁶	9.9x10 ⁻³	4.4x10 ⁻⁴
Carbamazepine	Antiepileptic	2.3	2.7 ⁷	1.1x10 ⁻⁰⁵	Persistent ¹⁴	1000	15	3.3x10 ⁻³ S-TDI	1.0x10 ⁻⁴	9.3x10 ⁻⁴	2.5x10 ⁻³
Celecoxib	Anti-inflammatory	4.0 ²	3.3 ²	7.9x10 ⁻⁰⁸	191 ²	200	3	3.3x10 ⁻³ S-TDI ²⁶	7.5x10 ⁻³	2.8x10 ⁻¹	1.7x10 ⁻²
Chloroquine	Antimalarials	4.6	5.3 ⁵	1.1x10 ⁻⁰⁷	120 ¹³	500	59	5.0x10 ⁻³ S-TDI ²⁶	4.4x10 ⁻³	1.5x10 ¹	1.8x10 ⁻¹
Ciprofloxacin	Antibiotic	-1.1	4.8 ⁸	5.2x10 ⁻¹⁴	120 ¹³	1000	50	1.5x10 ⁻⁴ 25 ADI	5.0x10 ⁻⁶	5.4x10 ⁻³	6.0x10 ⁻¹
Codeine	Antibiotic	1.1	2.8 ⁵	1.1x10 ⁻⁰⁷	120 ¹³	100	10	1.7x10 ⁻³ S-TDI	5.8x10 ⁻²	7.2x10 ⁻¹	9.4x10 ⁰
Diazepam	Psycholeptics	2.8	2.9 ⁹	3.7x10 ⁻⁰⁴	Persistent ¹⁵	10	1	8.3x10 ⁻⁵ S-TDI	1.0x10 ⁻³	1.4x10 ⁻²	9.1x10 ⁻²
Diclofenac	Anti-inflammatory	4.4	3.4 ⁷	4.8x10 ⁻⁰⁷	75 ¹³	100	41	5.0x10 ⁻⁴ ADI	1.0x10 ⁻⁴	4.1x10 ⁻³	1.0x10 ⁻¹
Erythromycin	Antibiotic	2.5	3.3 ⁹	5.5x10 ⁻²⁴	20 ¹⁶	1000	5	5.0x10 ⁻³ ADI	4.0x10 ⁻⁵	1.3x10 ⁻³	2.2x10 ⁻³
Fluoxetine	Psychoanaleptics	4.5	4.9 ⁴	9.0x10 ⁻⁰³	Persistent ^{14,15}	20	30	3.3x10 ⁻⁴ S-TDI	1.0x10 ⁻⁵	1.3x10 ⁻²	6.0x10 ⁻⁴
Gemfibrozil	Lipid modifying agents	4.2 ³	2.6 ⁵	1.2x10 ⁻⁰³	75 ¹³	1200	30	2.0x10 ⁻² S-TDI	1.5x10 ⁻⁴	1.2x10 ⁻³	7.8x10 ⁻³
Hydrochlorothiazide	Diuretics	0.0	1.1 ⁵	4.4x10 ⁻⁰⁷	120 ¹³	25	90	2.0x10 ⁻⁴ S-TDI	1.0x10 ⁻¹	3.3x10 ⁻²	1.0x10 ⁰
Ibuprofen	Anti-inflammatory	3.5	1.3 ⁴	1.5x10 ⁻⁰²	40 ¹²	1200	21	1.3x10 ⁻² S-TDI	1.0x10 ⁻⁶	4.5x10 ⁻⁷	3.0x10 ⁻¹
Isoniazid	Antimycobacterials	-0.7	1.0 ⁵	1.2x10 ⁻⁰⁹	75 ¹³	300	25	5.0x10 ⁻³ S-TDI ²⁶	2.4x10 ⁻²	7.1x10 ⁻³	1.2x10 ⁰
Metronidazole	Antibiotic	0.0	1.7 ⁸	1.7x10 ⁻⁰⁶	27 ¹⁷	2000	20	4.2x10 ⁻³ S-TDI ²⁶	4.1x10 ⁻²	4.5x10 ⁻²	2.5x10 ¹
Naproxen	Anti-inflammatory	3.2	2.5 ⁹	3.4x10 ⁻⁰⁵	7 ¹⁴	500	66	7.3x10 ⁻³ S-TDI	6.4x10 ⁻⁴	3.5x10 ⁻³	3.2x10 ⁻³
Ofloxacin	Antibiotic	-0.4	4.7 ⁷	5.0x10 ⁻¹⁵	360 ¹³	400	80	6.7x10 ⁻³ S-TDI ²⁶	5.0x10 ⁻⁴	4.4x10 ⁻¹	1.0x10 ⁰
Penicillin G	Antibiotic	1.8	1.9 ⁵	1.2x10 ⁻⁰⁹	75 ¹³	600	90	4.3x10 ⁻⁴ ADI	6.0x10 ⁻⁶	9.4x10 ⁻⁶	1.0x10 ¹
Propranolol	Beta blocker	3.1	3.4 ⁷	8.1x10 ⁻⁰⁸	52 ¹²	160	14	1.3x10 ⁻³ S-TDI	5.0x10 ⁻⁶	2.5x10 ⁻⁴	9.0x10 ⁻⁴
Salbutamol	Airway diseases	-0.9	2.9 ⁹	6.5x10 ⁻¹¹	30 ¹³	0.8	45	1.0x10 ⁻⁴ S-TDI	1.0x10 ⁻¹	1.3x10 ⁰	1.0x10 ¹
Sulfamethoxazole	Antibiotic	0.9	2.7 ⁷	9.7x10 ⁻⁰⁸	1 ¹⁸	2000	40	1.0x10 ⁻² ADI	5.9x10 ⁻⁴	5.6x10 ⁻³	1.0x10 ⁻³
Tetracycline	Antibiotic	-0.2	3.8 ¹⁰	4.7x10 ⁻¹⁹	120 ¹³	1000	60	3.0x10 ⁻² ADI	2.0x10 ⁻⁵	2.1x10 ⁻³	2.9x10 ⁰

Notes: $t_{1/2}$ = Half-life in soil; ADI = Acceptable daily intake; DDD = Defined daily dose; F_{exc} = Fraction excreted in urine—parent compound plus conjugates of parent compound; K_H = Henry's law constant; K_{OC} = Soil organic carbon-water partitioning coefficient; P = Octanol-water partition coefficient; $PNEC_{aquatic}$ = Toxicity endpoint for aquatic species (algae, daphnia and fish); $PNEC_{daphnia}$ = Toxicity endpoint for daphnia; $PNEC_{soil}$ = Toxicity endpoint for the terrestrial environment; S-TDI Surrogate tolerable daily intake.

References: (1) Experimental data from Sangster Research Laboratories (2009); (2) Pfizer (2006); (3) Pfizer (2008); (4) Yamamoto et al. (2005); (5) Calculated using KOCWIN (supplied with EPI Suite V4.0); (6) Ericson 2007; (7) Drillia et al. (2005); (8) Thiele-Bruhn (2003); (9) Barron et al. (2009); (10) Grung et al. (2008); (11) Estimated using HENRYWIN (supplied with EPI Suite V4.0); (12) Estimated as 2X the half-life in water (based on Boethling & Mackay's (2000) suggestion), half-lives in water from Yamamoto et al. (2009); (13) Estimated using LEV3EPI (supplied with EPI Suite V4.0); (14) Xu et al. (2009); (15) Redshaw et al. (2008); (16) Schlüesener & Bester (2006); (17) Ingerslev & Halling-Sørensen (2001); (18) Hoeltge & Kreuzig (2007); (19) WHO (2009); (20) Dollery (1998); (21) Moffatt et al. (2004); (22) McEvoy et al. (2008); (23) NEPC (2008) (24) ADI List (2008); (25) Jeong et al. (2009); (26) Calculated by dividing the lowest daily therapeutic dose from McEvoy et al. (2009) by a safety factor of a 1000 as suggested by NEPC (2008) and assuming the body weight of an adult as 60 kg; (27) From data compilation in Khan & Nicell (in preparation); (28) Conservatively estimated using the equilibrium partitioning model as presented in van Leeuwen (2003) since toxicity data from a primary soil producer and a consumer or a decomposer was not available; (29) Boxall et al. (2005); (30) Monteiro & Boxall (in press); (31) Most conservative value was used when more than one value was available

Table 3.3 Cu_c and Fpen_c values for various exposure pathways as well as the results of the two-tier evaluation process.

PhACs	Eco-toxicological exposure						Human-health exposure						"Tier A" assessment	"TierB" assessment		
	Terrestrial environment		Groundwater environment		Surfacewater environment		Food-chain transfer		Groundwater intake		Surfacewater intake		Fpen _c based risk judgment ¹	Canadian population penetration	Risk index	Final judgment
	Cu _c	Fpen _c	Cu _c	Fpen _c	Cu _c	Fpen _c	Cu _c	Fpen _c	Cu _c	Fpen _c	Cu _c	Fpen _c		Fpen _{local} ²	Fpen _{local} /Fpen _c	
	mg/L	%	mg/L	%	mg/L	%	mg/L	%	mg/L	%	mg/L	%		%		
Acetaminophen	8.0x10 ⁻¹	5.7x10⁻²	8.0x10 ⁰	5.7x10 ⁻¹	8.0x10 ⁰	5.7x10 ⁻¹	4.6x10 ⁰	3.3x10 ⁻¹	1.0x10 ²	7.4x10 ⁰	3.1x10 ²	2.2x10 ¹	Possible risk	6.71	117.5	Likely Risk
Alprazolam	1.7x10 ¹	2.3x10 ⁴	1.7x10 ²	2.3x10 ⁵	1.7x10 ²	2.3x10 ⁵	9.5x10 ⁻³	1.3x10⁻¹	7.5x10 ⁰	1.0x10 ⁴	2.2x10 ¹	3.1x10 ⁴	Minimal risk	<u>0.30</u>	<u>0.02</u>	Minimal risk
Amoxicillin	1.5x10 ⁰	2.8x10⁻¹	9.6x10 ⁵	1.8x10 ⁵	1.5x10 ¹	2.8x10 ⁰	8.3x10 ³	1.6x10 ³	3.4x10 ⁵	6.5x10 ⁴	1.0x10 ⁶	1.9x10 ⁵	Possible risk	0.95	3.4	Likely Risk
Azithromycin	8.9x10 ⁻²	7.4x10⁻¹	4.2x10 ⁰	3.5x10 ¹	8.9x10 ⁻¹	7.4x10 ⁰	4.2x10 ¹	3.5x10 ²	1.8x10 ³	1.5x10 ⁴	5.4x10 ³	4.5x10 ⁴	Possible risk	0.13	0.2	Minimal risk
Carbamazepine	3.6x10 ⁻³	3.6x10⁻³	9.1x10 ⁻²	9.1x10 ⁻²	3.6x10 ⁻²	3.6x10 ⁻²	5.1x10 ⁻¹	5.1x10 ⁻¹	1.9x10 ⁰	1.9x10 ⁰	5.7x10 ⁰	5.7x10 ⁰	Possible risk	0.20	55.0	Likely Risk
Celecoxib	3.9x10 ⁰	9.7x10¹	8.8x10 ⁰	2.2x10 ²	3.9x10 ¹	9.7x10 ²	2.1x10 ¹	5.3x10 ²	3.4x10 ¹	8.5x10 ²	1.0x10 ²	2.5x10 ³	Minimal risk	<u>0.80</u>	<u>0.008</u>	Minimal risk
Chloroquine	2.5x10 ²	1.3x10 ²	1.0x10 ⁴	5.3x10 ³	2.5x10 ³	1.3x10 ³	1.0x10 ²	5.2x10⁻¹	6.4x10 ³	3.2x10 ³	1.9x10 ⁴	9.7x10 ³	Minimal risk	<u>0.008</u>	<u>0.0002</u>	Minimal risk
Ciprofloxacin	8.9x10 ⁻²	2.7x10 ⁻²	1.1x10 ⁴	3.2x10 ³	8.9x10 ⁻¹	2.7x10 ⁻¹	1.5x10 ⁻³	4.6x10⁻⁴	5.9x10 ¹	1.8x10 ¹	1.8x10 ²	5.3x10 ¹	Possible risk	0.13	283.9	Likely Risk
Codeine	1.2x10 ¹	1.8x10 ²	2.0x10 ³	3.0x10 ⁴	1.2x10 ²	1.8x10 ³	3.4x10 ⁻¹	5.2x10⁰	8.1x10 ⁰	1.2x10 ²	2.4x10 ¹	3.6x10 ²	Minimal risk	<u>1.30</u>	<u>0.3</u>	Minimal risk
Diazepam	4.4x10 ⁻²	1.3x10 ²	4.0x10 ⁰	1.2x10 ⁴	4.4x10 ⁻¹	1.3x10 ³	2.0x10 ⁻²	5.9x10⁻¹	5.7x10 ⁻²	1.7x10 ²	1.7x10 ⁻¹	5.1x10 ²	Minimal risk	<u>0.24</u>	<u>0.004</u>	Minimal risk
Diclofenac	7.9x10 ⁻²	2.9x10⁻¹	7.9x10 ¹	2.9x10 ²	7.9x10 ⁻¹	2.9x10 ⁰	1.1x10 ¹	3.9x10 ¹	1.1x10 ¹	3.9x10 ¹	3.2x10 ¹	1.2x10 ²	Possible risk	0.80	2.8	Likely Risk
Erythromycin	3.7x10 ⁻²	1.1x10⁻¹	2.0x10 ⁰	6.1x10 ⁰	3.7x10 ⁻¹	1.1x10 ⁰	2.8x10 ¹	8.4x10 ¹	2.7x10 ²	8.1x10 ²	8.1x10 ²	2.4x10 ³	Possible risk	0.05	0.5	Minimal risk
Fluoxetine	2.3x10 ⁻²	5.7x10⁻¹	1.4x10 ⁰	3.4x10 ¹	2.3x10 ⁻¹	5.7x10 ⁰	4.1x10 ⁻¹	1.0x10 ¹	1.1x10 ¹	2.9x10 ²	3.4x10 ¹	8.6x10 ²	Possible risk	0.53	0.9	Likely Risk
Gemfibrozil	2.3x10 ⁻²	9.5x10⁻³	1.2x10 ⁰	4.9x10 ⁻¹	2.3x10 ⁻¹	9.5x10 ⁻²	3.3x10 ²	1.4x10 ²	8.5x10 ¹	3.5x10 ¹	2.5x10 ²	1.1x10 ²	Possible risk	0.03	3.2	Likely Risk
Hydrochlorothiazide	7.9x10 ⁻¹	5.3x10 ⁰	7.9x10 ⁰	5.3x10 ¹	7.9x10 ⁰	5.3x10 ¹	2.6x10 ⁻²	1.8x10⁻¹	7.5x10 ⁻²	5.0x10 ⁻¹	2.2x10 ⁻¹	1.5x10 ⁰	Possible risk	4.60	26.0	Likely Risk
Ibuprofen	1.2x10 ⁻⁵	7.1x10⁻⁶	3.6x10 ⁰	2.1x10 ⁰	1.2x10 ⁻⁴	7.1x10 ⁻⁵	2.3x10 ²	1.4x10 ²	8.5x10 ⁰	5.0x10 ⁰	2.5x10 ¹	1.5x10 ¹	Possible risk	3.20	450,702	Likely Risk
Isoniazid	1.8x10 ⁻¹	3.6x10⁻¹	9.4x10 ⁰	1.9x10 ¹	1.8x10 ⁰	3.6x10 ⁰	3.1x10 ⁻¹	6.1x10 ⁻¹	2.0x10 ⁰	3.9x10 ⁰	5.9x10 ⁰	1.2x10 ¹	Possible risk	0.02	0.1	Minimal risk
Metronidazole	1.2x10 ⁰	4.5x10 ⁻¹	7.4x10 ²	2.8x10 ²	1.2x10 ¹	4.5x10 ⁰	7.2x10 ⁻¹	2.7x10⁻¹	6.7x10 ⁰	2.5x10 ⁰	2.0x10 ¹	7.5x10 ⁰	Possible risk	0.06	0.2	Minimal risk
Naproxen	1.9x10 ⁻¹	8.8x10⁻²	9.7x10 ⁻¹	4.4x10 ⁻¹	1.9x10 ⁰	8.8x10 ⁻¹	2.8x10 ²	1.3x10 ²	1.9x10 ²	8.6x10 ¹	5.7x10 ²	2.6x10 ²	Possible risk	0.88	10.0	Likely Risk
Ofloxacin	4.0x10 ⁰	1.9x10 ⁰	8.0x10 ³	3.7x10 ³	4.0x10 ¹	1.9x10 ¹	7.2x10 ⁻²	3.4x10⁻²	9.2x10 ²	4.3x10 ²	2.8x10 ³	1.3x10 ³	Possible risk	0.01	0.2	Minimal risk
Penicillin G	2.0x10 ⁻⁴	5.4x10⁻⁵	3.3x10 ²	9.1x10 ¹	2.0x10 ⁻³	5.4x10 ⁻⁴	3.8x10 ⁻¹	1.0x10 ⁻¹	4.5x10 ⁻¹	1.2x10 ⁻¹	1.3x10 ⁰	3.7x10 ⁻¹	Possible risk	0.03	555.6	Likely Risk
Propranolol	5.2x10 ⁻³	3.5x10⁻²	9.3x10 ⁻¹	6.3x10 ⁰	5.2x10 ⁻²	3.5x10 ⁻¹	6.5x10 ⁰	4.4x10 ¹	4.6x10 ¹	3.1x10 ²	1.4x10 ²	9.2x10 ²	Possible risk	0.12	3.4	Likely Risk
Salbutamol	3.1x10 ¹	1.3x10 ⁴	3.1x10 ³	1.3x10 ⁶	3.1x10 ²	1.3x10 ⁴	3.9x10 ⁻³	1.6x10⁰	1.4x10 ⁰	6.0x10 ²	4.3x10 ⁰	1.8x10 ³	Possible risk	3.30	2.0	Likely Risk
Sulfamethoxazole	2.0x10 ⁰	3.8x10⁻¹	3.4x10 ⁰	6.4x10 ⁻¹	2.0x10 ¹	3.8x10 ⁰	1.2x10 ²	2.3x10 ¹	3.1x10 ³	5.8x10 ²	9.2x10 ³	1.7x10 ³	Possible risk	0.09	0.2	Minimal risk
Tetracycline	3.6x10 ⁻²	8.9x10⁻³	5.2x10 ³	1.3x10 ³	3.6x10 ⁻¹	8.9x10 ⁻²	9.9x10 ⁻¹	2.5x10 ⁻¹	1.2x10 ³	3.0x10 ²	3.6x10 ³	8.9x10 ²	Possible risk	0.06	6.7	Likely Risk

Most sensitive Fpen_c of all the pathways considered.

Bold: identified to be risky; Underlined: characterized as minimal risk after Tier A assessment.

(1) Upon comparison to the suggested Fpen_c cut-off of 5%.

(2) From Khan and Nicell (in prep).

national Canadian penetration factors, exposure to the terrestrial environment was found to be the most sensitive endpoint for 11 PhACs, while for the remaining 3 there exists a possible risk to human health through food-chain transfer. Only one drug, acetaminophen, had the potential to be disruptive both to human-health as well as the terrestrial environment. Based on the outcome of this analysis, it is recommended that the 14 compounds of significant risk listed in Table 3 should be subjected to further risk assessment and should either be carefully monitored in land-applied urine or should be removed from the urine prior to land application using a pre-treatment step. It should be noted that it is not surprising that such a high proportion of the PhACs included in Table 3 were deemed to have significant potential for risk given that the selection of these compounds for the purpose of this study, as explained above, was focused on compounds with characteristics that would be expected to contribute to elevated risk. A broader application of the method, which is now being undertaken, is not expected to lead to such a high proportion of risky compounds.

That being said, it is important to highlight the limitations of the current assessment. Firstly, even though the conceptual development of the F_{pen_c} and Cu_c factors is theoretically robust, the availability of experimental data for certain parameters required for their evaluation is quite limited. In particular, very limited or no terrestrial eco-toxicological data were available for the 25 PhACs considered here and therefore an equilibrium partitioning model (as suggested by van Leeuwen, 2003) was used to predict $PNEC_{soil}$ values from previously developed PNEC values for aquatic systems ($PNEC_{aquatic}$). Secondly, a recent study also brings into question experimental data from soil fate studies, suggesting that the persistence and leaching rates of PhACs in soil fate studies maybe significantly enhanced if the PhACs are applied to soil in urine as opposed to the conventional experimental protocol of applying them in distilled water (Lucas and Jones, 2009). Additionally, it is known that a large fraction of the PhACs considered here are potentially ionizable and, therefore, the use of plant uptake models that consider ionization may be more appropriate in describing their soil-to-plant partitioning rather than the quantitative structure-activity relationship (QSAR) approach used here, which was based on an octanol-water partition coefficient (P). However, at present it remains unclear what the likely pH of soil will be after it has been fertilized with urine. Furthermore, the most refined plant uptake model for ionized chemicals (Tapp, 2009) still needs to be experimentally validated before it can be used for screening purposes. Thus, until these limitations are addressed, the use of a P -based QSAR may suffice since it is likely to yield conservative estimates for the partitioning of PhACs from soil to plant matter. Thus, in some instances, further data would be required to refine the assessment inputs shown in Table 2. Beyond aforementioned limitations, it must be acknowledged that the current approach focuses on the risk posed by individual PhACs, the issues of mixtures and transformation products (i.e. metabolic or degradation

products) have not been addressed. This is largely a consequence of the lack of scientific understanding of these factors at present. However as the science of these aspects emerges out of infancy such factors could be readily incorporated into the equations developed here.

3.4 CONCLUSIONS

The application of human urine to land has an important benefit as a means of providing a sustainable source of fertilizer. In order to address growing concerns about the potential impacts associated with pharmaceutically active compounds (PhACs) in the environment, a prioritization/screening approach was proposed herein to assess their potential impacts of their presence in land-applied urine in terms of ecotoxicological and human-health endpoints. The method was applied to 25 selected PhACs and it was demonstrated that a two-tier approach can be used to identify exposure routes and toxicological endpoints that are of greatest concern and a priority list of PhACs whose presence in collected urine could possibly require pretreatment of urine before it is applied on land.

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Chapter 4: Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water

PREFACE

This chapter addresses the objectives of the thesis related to developing a better understanding of the sources through which PhACs are released to the environment and the evaluation of their human health relevance with respect to their potential presence in Canadian drinking waters.

Through the application of a set of selection criteria established as part of this study, 335 PhACs were selected for evaluation, making it one of the largest studies of its kind and the first to be performed for Canada. In order to estimate environmental loads of PhACs, source models were developed and parameterized for each compound. This included the extension of the models developed in Chapter 2 for the endogenous release of androgens and thyroids to these compounds in the Canadian context. An evaluation was also performed to estimate the significance of the various sources that could lead to the release of each PhAC. Among the sources evaluated was the clinical use of PhACs in hospitals. A comprehensive approach was also developed to produce estimates of acceptable daily intake (*ADI*) values for the potential human-health exposure to each PhAC of the evaluation set. *ADI* values were used along with respective environmental loading estimates to screen each of the PhACs of the evaluation set for possible risks to human-health. The chapter also furnishes an estimate of the relative importance of the various uses of antibiotics within Canada with respect to the overall load. Finally, the work also systematically evaluates whether existing monitoring data for PhACs in Canadian drinking water is sufficient.

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Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water

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ABSTRACT

In Canada, as many as twenty pharmaceutically active compounds (PhACs) have been detected in samples of treated drinking water. The presence of these PhACs in drinking water raises important questions as to the human-health risk posed by their aquatic release and, ultimately, their potential appearance in drinking water supplies. Therefore, the goal of the current investigation was to conduct a screening-level assessment of the human-health risks posed by the aquatic release of an evaluation set of 335 selected PhACs. Predicted and measured exposure concentrations were used to estimate the exposure of Canadians to each PhAC in the evaluation set. Acceptable daily intake levels for each PhAC were estimated by considering their respective tolerable daily intake values, acceptable daily intake values derived from the veterinary use of the PhAC, occupational exposure limits developed for their manufacture, and their lowest oral therapeutic doses. For PhACs that are genotoxic carcinogens, additional protective benchmarks based on a lifetime cancer risk were also considered. Derived acceptable daily intake values were compared to predicted and measured exposure concentrations to estimate a margin-of-exposure for each PhAC of the evaluation set. The results of the screening and prioritization exercise suggested that 322 PhACs of the 335 in the evaluation set are unlikely to pose human health risk. However, the analysis indicated that the following 14 PhACs should be prioritized for further investigation: triiodothyronine, thyroxine, ramipril and its metabolite ramiprilat, candesartan, lisinopril, atorvastatin, lorazepam, fentanyl, atenolol, metformin, enalaprilat, morphine and irbesartan.

KEYWORDS: Pharmaceuticals, Illicit Drugs, Environment, Drinking Water, Human-health, Risk Assessment, Hospitals

4.1 INTRODUCTION

The presence of a number of pharmaceutically active compounds (PhACs) has been confirmed in treated drinking waters (1). This typically raises concern since, due to their very nature, PhACs are expected to be pharmacologically active upon human exposure. These concerns are further heightened by the fact that drinking waters standards have been developed for only a handful of PhACs (2, 3) and, thus, they are not being regularly monitored in drinking waters nor are their human health impacts widely understood by most water utilities and the general public.

The presence of PhACs in drinking water supplies largely results from aquatic releases of wastewaters from sewage treatment plants (4). However, veterinary use and endogenous excretion of these compounds by animals could also be an important source (11). PhACs that result from veterinary sources are not necessarily routed directly to the environment, but are more likely to be released in a diffuse and attenuated manner either through the losses of animal manure during storage or through application to agricultural land.

PhACs in sewage treatment plant influents, and hence effluents, originate from a number of human sources, including, among others: the endogenous excretion of the PhAC (5); the PhAC's release from facilities where it is manufactured (6); its clinical use within the community (7,8) and within hospitals (9); the PhAC's disposal into landfills and its resulting presence in landfill leachates (10); the illicit use of the PhAC (12,13); and the clinical and/or illicit use of other drugs/chemicals that are metabolized to the PhAC upon consumption by humans (12-14).

To-date, only a handful of studies have been performed to evaluate the human-health relevance of the aquatic release of PhACs (4, 15-25) and these were primarily focused on the situation in the USA (4, 15-22) and Europe (4, 17, 23-25). As a result, to-date, the human-health relevance of PhACs releases to Canadian surface waters and, in turn, their potential presence in treated Canadian drinking waters, remains to be evaluated. Besides this obvious knowledge gap, a number of other considerations also drive the need for a Canadian specific human-health risk assessment and prioritization study. For instance, among OECD countries, the per capita drug expenditure of the Canadian population is second only to that of the USA (26). In addition, the use, and by extension the aquatic release, of certain PhACs is known to vary significantly from one national population to another. For example, consider that the per capita consumption of codeine in Canada is orders of magnitude higher than the levels with which the drug is used by certain European populations (12). Or, consider that the use of rabeprazole in Canada is nearly

500 times greater than the level with which it is used in Sweden (8, 28, 29). A comparison with the situation in the USA also reveals some noteworthy differences. For example, meprobamate, which is a PhAC that was found at the highest level in finished USA drinking waters (27), is only used in negligible quantities in Canada. Consider that, in 2006, the per capita Canadian consumption of meprobamate only amounted to 1.5 ng/cap·d (28, 29) and, furthermore, the drug carisoprodol, which is metabolized by humans to meprobamate, has been discontinued in Canada since 2003 (30). Therefore, an evaluation performed for one national population may not directly translate well to another unstudied national population.

The exposure of Canadians to PhACs was evaluated in this study through the use of predicted and, where available, measured data. When estimating the predicted exposure concentrations of selected PhACs, an attempt was made to account for a number of anthropogenic sources that could lead to the release of these compounds to the environment. In total, for each PhAC studied, up to seven contributions were considered, as follows: (i) the use of the PhAC in the general population; (ii) the use of the PhAC in hospitals; (iii) the general population's use of other drugs/chemicals that are metabolized by humans to the PhAC; (iv) the hospital-based use of other drugs/chemicals that are metabolized by humans to the PhAC; (v) the endogenous excretion of the PhAC; (vi) the illicit use of the PhAC; and (vii) the illicit use of other drugs/chemicals that are metabolized by humans to the PhAC. A number of previous studies only accounted for the release of a given PhAC due to its particular use in the general population (e.g., 15, 21). Consequently, in these earlier studies, the actual environmental load of a number of PhACs is unlikely to have been fully quantified. As an illustrative example, consider that no human-health risk assessment study to date has considered that morphine can be released to the aquatic environment through all of the following sources: its endogenous excretion, its clinical use in the general population, its use in hospitals, the use of a number of precursors (i.e., codeine, ethylmorphine, nicomorphine and pholcodine) in the general population and in hospitals, the illicit use of heroin, and, finally, the general population's consumption of poppy seeds (12). Furthermore, such broad source considerations can become important when conducting an assessment for a specific geographic region, as is demonstrated by the fact that almost the entire environmental load of morphine results from the use of heroin in a number of European countries, while in North America the predominant sources are the clinical use of morphine and its precursors (12).

With respect to determining the environmental levels of a PhAC that may trigger a human health effect, in the absence of established acceptable daily intake values (*ADIs*), most previous studies have resorted to

using the lowest oral therapeutic dose (*LOTD*) as the point of departure to arrive at screening-level ADIs for the PhAC under consideration (3, 4, 15, 18, 20, 23). Even though this is a fairly pragmatic approach (15), alternative points of departure have been suggested. For example, occupational exposure limits (*OELs*) developed by pharmaceutical manufacturers to protect their workforce, may represent a more suitable point of departure to arrive at screening-level *ADIs* for a given PhAC (31). Such an assertion stems from the recognition that *OELs* are limits that have specifically been developed to protect human health. In contrast, by definition, *LOTD* is a point of departure that is known to elicit varied responses in humans and not necessarily a health impact (15, 18). To-date, a broad scale evaluation using *OELs* and other points of departure to arrive at screening level *ADI* values has yet to be performed. Furthermore, no approach has been used that integrates these various methods to identify screening level acceptable daily intake *ADIs* for individual PhACs.

Therefore, given the above, the objectives of the current work were to:

- Develop a priority list of PhACs whose human-health relevance were to be evaluated;
- Estimate the environmental loading of each selected PhAC by considering all seven of the potential sources described above;
- Evaluate the importance of hospitals as a source of PhACs;
- Translate the estimated environmental loading of each of the PhACs into corresponding estimates of predicted exposure concentrations;
- Compile measured data from all literature sources reporting on the presence of PhACs in finished (i.e., treated) Canadian drinking waters and use the data to evaluate whether predicted concentrations can be used as conservative estimates for measured data when such data is not currently available;
- Develop an approach that integrates the various points of departure to estimate a conservative screening level acceptable daily intake (*ADI*) for each selected PhAC;
- Evaluate human health relevance of each selected PhAC by consider both predicted and measured exposure concentrations; and
- Develop a prioritized sub-set of PhACs that warrant further evaluation with respect to their human-health relevance.

In carrying out the health risk assessment of PhACs in the Canadian context, as described above, the intent was to develop a comprehensive approach that can be generally applied to any geographic region and updated over time as additional information becomes available.

4.2 MATERIALS AND METHODS

4.2.1 Selection of PhACs for Evaluation

In total, 335 PhACs were selected for evaluation. PhACs were specifically selected if:

- They were amongst the top 100 dispensed drugs (units/yr) in Canada (28,29), however natural salts and metals among this list were not considered further;
- Their presence had been confirmed in finished Canadian drinking waters (32-38);
- Their presence had been reported in Canadian surface waters (Note: See Appendix A for a full list of 34 references used to perform an evaluation with this criteria);
- They had been prioritized or studied in previous comparable studies from geographical locations other than Canada (4,15-20, 23-25);
- They were reported to have been illicitly used in Canada (39,40);
- They are an antibiotic that is used in Canada;
- They are amongst antineoplastic drugs that are widely used (e.g., fluorouracil); and/or
- They are amongst hormonal drugs that are widely used (e.g., cyproterone, tamoxifen).

The selected evaluation set is listed in its entirety in Appendix B.

To facilitate analysis and discussion, the evaluation set was classified according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System (60). When a given PhAC was determined to be prescribed under more than one ATC code, the code associated with the predominant use of that PhAC was assumed. Following a classification according to the ATC system the evaluation set was composed of the following: 26 Class A (Alimentary tract and metabolism) drugs; 4 Class B (Blood and blood forming organs) drugs; 55 Class C (Cardiovascular system); 10 Class D (Dermatologicals) drugs; 17 Class G (Genito-urinary system and sex hormones) drugs; 7 Class H (Systemic hormonal preparations, excluding sex hormones and insulins) drugs; 52 Class J (Anti-infectives for systemic use) drugs; 31 Class L (Antineoplastic and immunomodulating agents) drugs; 21 Class M (Musculo-skeletal system) drugs; 75 Class N (Nervous system) drugs; 4 Class P (Antiparasitic products,

insecticides and repellents) drugs; 17 Class R (Respiratory system) drugs; 5 Class S (Sensory organs) drugs and 4 Class V (Various) drugs. The remaining 7 PhACs did not belong to any ATC classification code. These PhACs included 2 endogenous hormones: androstenedione and dihydrotestosterone and 5 illicit drugs: cocaine, heroin, methamphetamine, 3,4-methylenedioxy-N-methylamphetamine (commonly known as ecstasy) and tetrahydrocannabinol. Overall, PhACs considered for evaluation covered a very broad range of pharmacological activities.

4.2.2 Exposure Assessment

Exposure of the population to each of the compounds in the evaluation set via drinking water was estimated by considering both predicted and measured exposure concentrations. In order to arrive at predicted exposure concentrations for each PhAC, it was also necessary to estimate the total environmental loading for each. When doing so, only anthropogenic sources were considered and, therefore, the potential veterinary contributions to the environmental load of a PhAC were not considered. The implications of this are discussed below. Further, only exposure through drinking water was considered, while exposure through food (e.g., fish, agricultural produce and breast milk) was not. The reason for this was that the PhACs under consideration were found to cover a large range of ionic states and for most such states models for their transfer into food are currently not available (68, 69).

4.2.2.1 Total Environmental Load

The total environmental load, M_T , for each PhAC was estimated using the following equation, in which the seven possible contributing sources for a PhAC of interest are summed:

$$M_T = M_{CG} + M_{CH} + M_{OC} + M_{OH} + M_{endo} + M_{IDU} + M_{OID} \quad (1)$$

where: M_{CG} is the clinical use of the PhAC in the general population; M_{CH} is the clinical use of the PhAC in hospitals; M_{OC} is the clinical use among the general population of drugs/chemicals that are metabolized to the PhAC; M_{OH} is the clinical use in hospitals of other drugs/chemical that are metabolized to the PhAC; M_{endo} is the endogenous production and excretion of the PhAC; M_{IDU} is the illicit use of the PhAC; and M_{OID} is the use of other drugs/chemicals that are metabolized to the PhAC. The manner in which each of these contributions was quantified for a given PhAC is described below.

The clinical use of the PhAC, M_{CG} , was estimated using the following equation:

$$M_{CG} = \sum_{i=1}^I N_{i,c} \cdot S_{i,c} \cdot (U_{ex,i} + F_{ex,i}) \quad (1a)$$

where: I is the total number of individual routes of administration of clinical preparations, i , with which the PhAC is administered when dispensed by community pharmacies; $N_{i,c}$ is the total number of prescriptions dispensed of the PhAC via community pharmacies for a given route of administration i ; $S_{i,c}$ are the prescription strengths for $N_{i,c}$; $U_{ex,i}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the urinary route for a given route of administration I ; and $F_{ex,i}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the fecal route for a given route of administration i . With the exception of acetaminophen, acetylsalicylic acid, clotrimazole and ibuprofen, the $N_{i,c}$ values used were those reported in the Canadian Compuscript Audit database (28) of IMS Brogan. Similarly, with the exception of acetaminophen, acetylsalicylic acid, clotrimazole and ibuprofen, $S_{i,c}$ values were also reported in the same database but, in certain instances, a cross reference to the Health Canada DPD database (30) was required to arrive at accurate estimates for $S_{i,c}$. To estimate $N_{i,c} \cdot S_{i,c}$ values for acetaminophen, acetylsalicylic acid, clotrimazole and ibuprofen methods and data sources detailed in Appendix C were utilized. As discussed in Appendix C, $N_{i,c} \cdot S_{i,c}$ estimates for acetaminophen and acetylsalicylic acid were derived from market data and therefore are likely to be conservative estimates. A database of $U_{ex,i} + F_{ex,i}$ values for each of the PhACs in the evaluation set was developed by compiling information from more than 500 literature sources. The database is presented in its entirety in Appendix D. In this database, primary literature references are used to estimate reliable excretion factors for each PhAC that also account for the effect of route of administration on the metabolic disposition of a given PhAC.

The clinical use of each PhAC in hospital, M_{CH} , was estimated using the following equation:

$$M_{CH} = \sum_{j=1}^J N_{j,H} \cdot S_{j,H} \cdot (U_{ex,j} + F_{ex,j}) \quad (1b)$$

where: J is the total number of individual routes of administration, j , with which a PhAC is administered when dispensed by and/or at hospital; $N_{j,H}$ is the total number of prescriptions dispensed of a given a PhAC via hospitals for a given route of administration j ; $S_{j,H}$ are the prescription strengths for $N_{j,H}$; $U_{ex,j}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the urinary route for a given route of administration j ; and $F_{ex,j}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the fecal route for a given route of administration j . The $N_{j,H}$ values used were those reported in the Canadian Drug Store and Hospital Purchases Audit database (29). $S_{j,H}$ values were also drawn from the same database but, in certain instances, a cross reference to the Health Canada DPD database (30) was required to arrive at accurate

estimates for $S_{j,H}$. $U_{ex,j} + F_{ex,j}$ values were estimated from the database described above and are presented in Appendix D.

The clinical use among the general population of drugs/chemicals that are metabolized to the PhAC, M_{OC} , was estimated using the following equation:

$$M_{OC} = \sum_{l=1}^L \sum_{k=1}^K N_{l,k,c} \cdot S_{l,k,c} \cdot (U_{ex,l,k} + F_{ex,l,k}) \cdot \frac{Mw_{PhAC}}{Mw_l} \quad (1c)$$

where: L is the total number of community pharmacy-dispensed drugs, l , that are metabolized to the PhAC upon human consumption; K is the total number of individual routes of administration, k , with which drug l is administered; $N_{l,k,c}$ is the total number of prescriptions dispensed of drug l for a given route of administration k ; $S_{l,k,c}$ are the prescription strengths for $N_{l,k,c}$; $U_{ex,l,k}$ is the fraction of drug l that is excreted via the urinary route as the PhAC for a given route of administration k ; $F_{ex,l,k}$ is the fraction of the drug l that is excreted via the fecal route as the PhAC when administered via the route of administration k ; Mw_{PhAC} is the molecular weight of the PhAC; and Mw_l is the molecular weight of the drug l . L was established by developing source models for all PhACs of the evaluation set that result from the metabolism of other drugs dispensed at community pharmacies. All source models developed are presented in Appendix E. The $N_{ex,l,k}$ values used were those reported in the Canadian Compuscript Audit database (28). $S_{ex,l,k}$ values were also reported in this same database but, in certain instances, a cross reference to the Health Canada DPD database (30) was required to arrive at accurate estimates for $S_{ex,l,k}$. $U_{ex,l,k} + F_{ex,l,k}$ were estimated by compiling data from relevant literature sources, as presented in Appendix E.

The clinical use in hospitals of other drugs/chemical that are metabolized to the PhAC, M_{OH} , was estimated using the following equation:

$$M_{OH} = \sum_{m=1}^M \sum_{o=1}^O N_{m,o,h} \cdot S_{m,o,h} \cdot (U_{ex,m,o} + F_{ex,m,o}) \cdot \frac{Mw_{PhAC}}{Mw_m} \quad (1d)$$

where: M is the total number of other hospital-dispensed drugs, m , that are metabolized to the PhAC upon human consumption; O is the total number of individual routes of administration, o , with which drug m is administered; $N_{m,o,h}$ is the total number of prescriptions dispensed of drug m for a given route of administration o ; $S_{m,o,h}$ are the prescription strengths for $N_{m,o,h}$; $U_{ex,m,o}$ is the fraction of drug m that is excreted via the urinary route as the PhAC for a given route of administration o ; $F_{ex,m,o}$ is the fraction of

the drug m that is excreted via the fecal route as the PhAC for a given route of administration o ; M_{wPHAC} is the molecular weight of the PhAC; and M_{w_m} is the molecular weight of the drug m . M was established by developing source models for all PhACs of the evaluation set that result from the metabolism of other hospital dispensed drugs. All source models are presented in Appendix E. The $N_{m,o,h}$ values used were those reported in the Canadian Drug Store and Hospital Purchases Audit database (29). $S_{m,o,h}$ values were also reported in the same database but, in certain instances, a cross reference to Health Canada DPD database (30) was required to arrive at accurate estimates for $S_{m,o,h}$. $U_{ex,m,o} + F_{ex,m,o}$ were estimated by compiling data from relevant literature sources, as presented in Appendix E.

The endogenous excretion of the PhAC, M_{endo} , was estimated using the following equation:

$$M_{endo} = P_T \cdot E_{endo} \quad (1e)$$

where P_T is total population and E_{endo} is the daily per capita endogenous release of a PhAC. Canadian population data circa 2006 was used in all calculations. P_T was estimated using data from Statistics Canada (40). E_{endo} was estimated using various methods and models presented in Appendix F.

The illicit use of the PhAC, M_{IDU} , was estimated using the following equation:

$$M_{IDU} = C_{IDU} \cdot \sum_{p=1}^P f_p (U_{ex,i,p} + F_{ex,i,p}) \quad (1f)$$

where: C_{IDU} is the net mass of the PhAC that is illicitly used; P is the total number of individual routes of administration, p , with the PhAC is illicitly administered; f_p is the fraction of C_{IDU} that is administered via route p ; $U_{ex,i,p}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the urinary route when illicitly administered via route p ; and $F_{ex,i,p}$ is the fraction of the PhAC that is excreted unchanged and as its glucuronide and sulphate conjugates via the fecal route when illicitly administered via route p . C_{IDU} was estimated using methods and models presented in Appendix G. f_p values were estimated using trends reported in CCSA (42), Khan and Nicell (11,12) and RCMP (43). $U_{ex,i,p} + F_{ex,i,p}$ values were estimated from the database described earlier and presented in Appendix D.

The illicit use of other drugs/chemicals that are metabolized to the PhAC, M_{OID} , was estimated using the following equation:

$$M_{OID} = \sum_{r=1}^R \sum_{q=1}^Q C_{OID,r,q} \cdot f_{q,r} (U_{ex,r,q} + F_{ex,r,q}) \cdot \frac{MW_{PhAC}}{MW_r} \quad (1g)$$

where: R is the total number of illicit drugs, r , that are metabolized to the PhAC upon human consumption; Q is the total number of individual routes of administration, q , via which drug r is administered; $C_{OID,r,q}$ is the net mass of drug r which is administered via route q ; $f_{q,r}$ is the fraction of $C_{OID,r,q}$ that is administered via route q ; $U_{ex,r,q}$ is the fraction of drug r that is excreted via the urinary route as the PhAC for route of administration q ; and $F_{ex,r,q}$ is the fraction of the drug r that is excreted via the fecal route as the PhAC for route of administration q ; $M_{W_{PHAC}}$ is the molecular weight of the PhAC; and M_{W_r} is the molecular weight of the drug r . R was established by developing source models for all PhACs of the evaluation set that result from the metabolism of other illicit drugs. All source models developed are presented in Appendix E. $C_{OID,r,q}$ was estimated using methods and models summarized in Appendix G. $f_{q,r}$ were estimated using trends reported in CCSA (42), Khan and Nicell (12,13) and RCMP (43). $U_{ex,r,q} + F_{ex,r,q}$ were estimated by compiling data from relevant literature sources, as presented in Appendix E.

When estimating values of M_{CG} , M_{CH} , M_{OC} , M_{OH} , M_{IDU} and M_{OID} , it was conservatively assumed that the total mass dispensed of a PhAC/drug and the mass demand for an illicit drug end up being used. Therefore, for each source chemical, the mass that is purchased/acquired but then not used was unaccounted for.

4.2.2.2 Predicted Exposure Concentrations (PEC)

The predicted exposure concentrations (PEC) for each PhAC of the evaluation set were estimated using the following equation:

$$PEC = \frac{M_T}{Q_{ww} \cdot DF} \cdot [(f_0) + f_1 \cdot (1 - R_1) + f_{1,2} \cdot (1 - R_{1,2})] \quad (2)$$

where: M_T is total load of the PhAC to the environment, Q_{ww} is median level of wastewater generated on a per capita basis; DF is a conservative level of dilution of a wastewater upon its immediate release to the environment; f_0 , f_1 and $f_{1,2}$ are the fractions of wastewaters that undergo no treatment, primary treatment, and a secondary level of treatment, respectively; and R_1 and $R_{1,2}$ are the levels with which the PhAC is removed in primary and secondary treatment plants, respectively. M_T was estimated using Eq. 1. Q_{ww} was estimated to be 504 L/cap·d by analyzing data reported for nearly a 1,000 sewage treatment plants in Environment Canada's MWWDB database (44) (see Appendix H). DF was conservatively assumed to be 10 based on a recent report co-authored by the authors of this study to Health Canada (45), in which immediate dilution factors for nearly nine hundred Canadian sewage treatment plants were estimated for

average and low flow conditions. f_o , f_1 and $f_{1,2}$ values were as those suggested by Environment Canada (46). R_1 and $R_{1,2}$ were those compiled in an in-house database of removal rates reported in the literature for PhACs in sewage treatment plants. For cases where literature data was not available, the Simple Treat model (47) was used along with appropriate quantitative structure–activity relationship models (48, 49) to estimate removal rates. Overall, the database aimed to conservatively account for the removal of PhACs in sewage treatment plants. The database can be found in Appendices I and J.

Eq. 2 was used to calculate three estimates for the predicted exposure concentrations, ranging from the most to least conservative; namely, PEC_1 , PEC_2 and PEC_3 . PEC_1 values were estimated assuming no metabolism or removal in treatment plants of the PhACs. PEC_2 estimates accounted for some metabolism of the PhACs, but it was assumed that the PhACs were not removed in sewage treatment plants. Estimates for PEC_3 accounted both for metabolism and for removal in sewage treatment plants. Note that PEC_3 , even though it is the least conservative of the three estimates furnished, still represents a highly conservative estimate for the concentration at which the population could be exposed to individual PhACs via drinking water. Consider that PEC_3 is akin to the population continuously drinking treated wastewaters that had been minimally diluted. Therefore, estimates for PEC_3 as furnished here, do not account for the added attenuation (dilution, degradation, photolysis or sorption) of the minimally diluted load before its arrival at the intake of a drinking water treatment plant and any subsequent removal in the plant before supply to the community. Nevertheless, PEC_1 and PEC_2 are also of value since a risk evaluation with these concentrations, as opposed to PEC_3 , reveals those PhACs for which the risk outcome resides in assumptions made about metabolic loss and removal via sewage treatment plants. Overall, an evaluation performed with any of the three PEC estimates is expected to be highly conservative and perhaps most importantly for the overall objective of the current study ensures that false negative (i.e. suggesting lack of risk where some risk might actually exist) classifications are minimized.

4.2.2.3 Measured Exposure Concentrations (MEC)

Measured exposure concentrations (MEC) for the evaluation set were compiled from literature sources reporting on the presence of PhACs in finished (i.e., treated) drinking waters in Canada. In total, 5,813 $MECs$ were compiled from all relevant literature sources (32-38).

4.2.3 Estimation of Acceptable Daily Intake (ADI)

The Acceptable Daily Intake (*ADI*) of a substance is defined as the maximum quantity that can be ingested on a daily basis and not result in undesirable effects on human health (18). Here, consistent with previous work (4), any effect is considered undesirable. Since *ADIs* for most PhACs have not been established by regulatory bodies, multiple lines of evidence were considered to arrive at a conservative estimate of the *ADI* for each PhAC of the evaluation set. The overall approach taken is summarized in Figure 4.1 and discussed below.

When available, tolerable daily intake (*TDI*) values, as derived by Health Canada, were directly adopted as the *ADI* for the compound of interest. In the absence of such data, *ADIs* derived for the potential veterinary use of the PhAC by such agencies as Joint FAO/WHO Expert Committee on Food Additives and European Medicines Agency Veterinary Medicines and Inspections were used. However, for the vast majority of the PhACs in the evaluation set, *TDI* values were not available; furthermore, these compounds have not been used for veterinary medicine purposes. Therefore, *ADI* values for most PhACs of the evaluation set remain to be established. In the absence of government/international agency-derived benchmarks for a PhAC, a number of approaches were considered to estimate a variety of provisional *ADIs* (*p-ADIs*) for each PhAC of the evaluation set. Following such evaluations, the lowest of the derived *p-ADIs* was selected as the *ADI* for the PhAC under consideration (see Figure 4.1).

One point of departure typically used to derive a *p-ADI* for a PhAC is its lowest oral therapeutic dose, *LOTD* (15, 23). In recognition of this, the following equation was used to estimate the *p-ADI* for a PhAC from its *LOTD*, when available:

$$p-ADI_{LOTD} = \frac{LOTD}{SF} \quad (3a)$$

where *LOTD* is the lowest oral therapeutic dose of the PhAC in adults and *SF* is a safety factor, the purpose of which is to extrapolate *LOTD* to levels that can be considered safe for continuous human

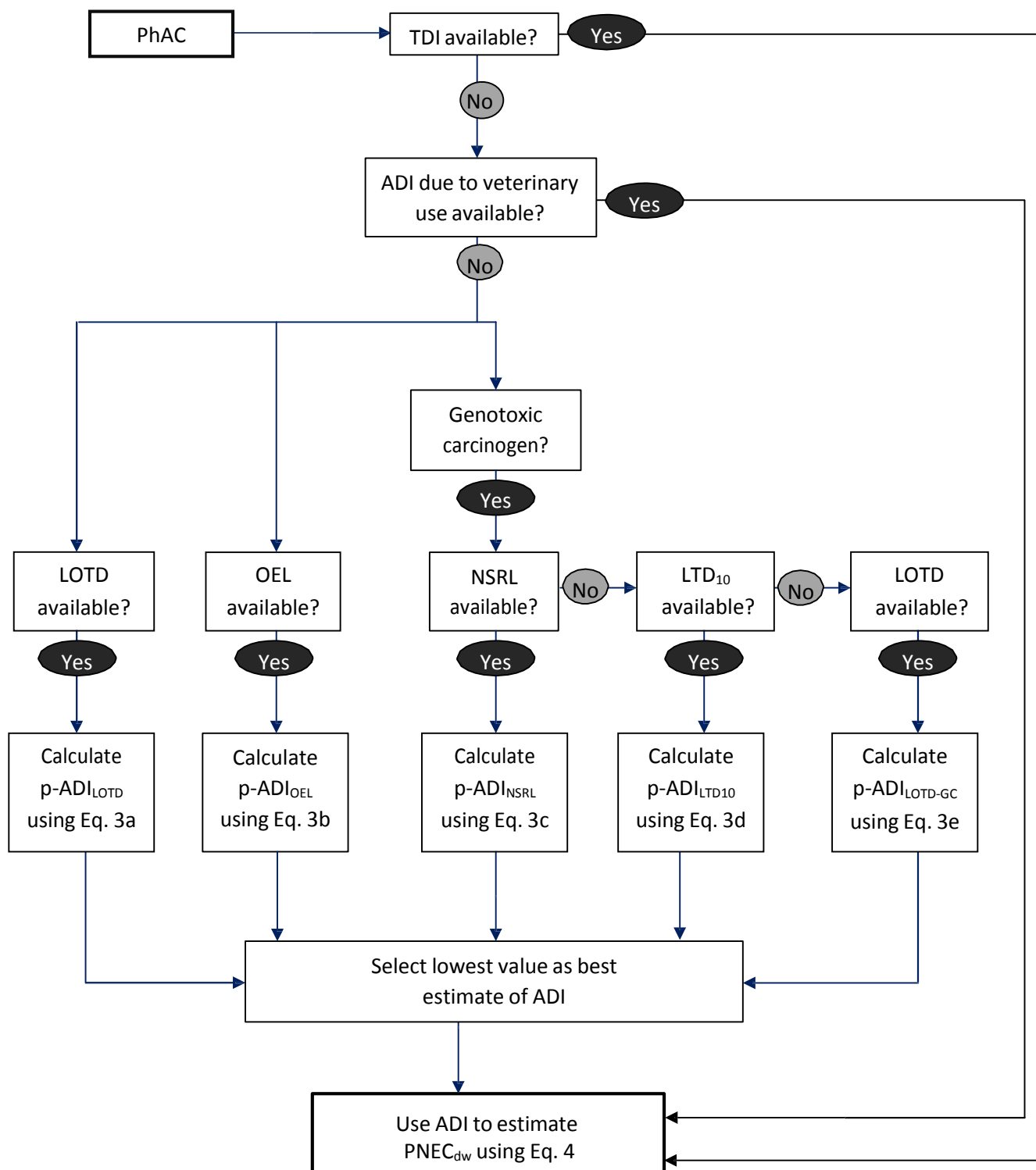


Figure 4.1: Approach used to estimate the acceptable daily intake for each PhAC of the evaluation set.

Abbreviations: ADI = acceptable daily intake; TDI = tolerable daily intake; LOTD = lowest oral therapeutic dose, LTD₁₀ = lower 95% confidence limit of the dose required to induce tumors in 105 of exposed animals; NSRL = no significant risk level and is the daily intake as estimated by the California EPA to pose an added lifetime cancer risk of 10⁻⁵; OEL = occupational exposure limit.

exposure. *LOTDs* were estimated from drug monographs available through Health Canada's Drug Product Database (30) and by consulting dosage schedules presented in Lexi-Comp's Drug Information Handbook (50) and those presented through UptoDate.com (58). *LOTD* values for adults were used here, since not all drugs of the evaluation set are used pediatrically. A *SF* of 10,000 was used if the PhAC possesses at least one of the following attributes: it is a cytotoxic drug, it is a hormone, it is a pregnancy Class D or Class X drug, or it has been categorized as a hazardous drug by National Institute for Occupational Safety and Health (51). For all other cases a default *SF* of 1,000 was used (15).

An alternative to the *LOTD* approach described above has been suggested by Straub & Flückiger (31). Specifically, Straub & Flückiger (31) suggested that occupational exposure limits derived by pharmaceutical manufacturers for their workers can be used with appropriate extrapolation factors to arrive at a *p-ADI* for a given PhAC. Their proposed approach can be expressed as follows:

$$p-ADI_{OEL} = \frac{OEL \cdot Q_{air}}{EF} \quad (3b)$$

where: *OEL* is the 8-hr time-weighted average occupational exposure limit derived by pharmaceutical manufacturers to protect their workers; *Q_{air}* is the volume of air breathed by a worker over duration of 8 hrs; and *EF* is extrapolation factor used to extrapolate a human-health benchmark derived for those who work in pharmaceutical manufacturing operations to the general population. *OELs* are typically reported in material safety data sheets (MSDS) developed for each PhAC by its various manufacturers. Therefore, *OELs* were compiled from MSDS from various manufacturers of pharmaceuticals. In the cases where multiple *OELs* were available for a given PhAC, the lowest was adopted. For *Q_{air}* the default value of 10 m³ was used (52). *EF* was assumed to be 100 following the work of Straub & Flückiger (31).

For genotoxic carcinogenic PhACs, additional benchmarks that reflect protection from an added lifetime cancer risk must also be considered. Conservatively, the “one hit” model was assumed (55).

When available, No Significant Risk Levels (*NSRL*) as derived by California EPA (53) were used to estimate a *p-ADI* for a genotoxic carcinogenic PhAC of the evaluation set, as follows:

$$p-ADI_{NSRL} = \frac{NSRL}{BW_{NSRL-adult}} \quad (3c)$$

where $NSRL$ is the daily intake as estimated by California EPA and BW is the average weight of an adult. The $NSRL$ values used here were those reported in a California EPA compilation (53) and the value of $BW_{NSRL-adult}$ used was the average weight of an adult assumed by California EPA in their estimations of $NSRL$ levels.

In the event a $NSRL$ level of a given genotoxic carcinogen PhAC of the evaluation set was not available, the following approach was used:

$$p - ADI_{LTD} = \frac{LTD_{10}}{10^5} \quad (3d)$$

where: LTD_{10} is the lower 95% confidence limit of the dose required to induce tumors in 10% of exposed animals and 10^5 is the factor that linearly, and therefore conservatively, extrapolates LTD_{10} to an acceptable added lifetime cancer risk of 10^{-6} . The LTD_{10} values used here were those reported in the Carcinogenic Potency Database (54).

In cases where neither a $NSRL$ nor a LTD_{10} were available for a genotoxic carcinogen, the following equation used:

$$p - ADI_{LOTD-GC} = \frac{LOTD}{10^5} \quad (3e)$$

where, as before, $LOTD$ is the lowest oral therapeutic dose for an adult and 10^5 is the factor that linearly, and therefore conservatively, extrapolates $LOTD$ to an acceptable added lifetime cancer risk of 10^{-6} .

4.2.4 Predicted No Effect Concentration for Exposure of Humans via Drinking Water

Predicted no effect concentrations ($PNEC$) for the exposure of humans to each PhAC via drinking water ($PNEC_{dw}$) were estimated using the following equation:

$$PNEC_{dw} = \frac{ADI \times BW}{IR_{d.w.}} \quad (4)$$

where: ADI is the acceptable daily intake for the PhAC; BW is the body weight for the most sensitive human receptor; and $IR_{d.w.}$ is the average daily ingestion rate of drinking water by the most sensitive human receptor. ADI was estimated using the methods described in “Development of Acceptable Daily

Intakes (ADI)” section and summarized in Figure 4.1. Of the 5 receptors considered by Health Canada - infants (0 to 6 months), toddlers (7 months to 4 years), children (5 to 11 years), adolescents (12 to 19 years) and adults (20 years+) – the combination of the BW and IR_{dw} of infants is such that they are determined to be the most sensitive receptor to contaminants in drinking water. Therefore, BW and IR_{dw} values were assumed to be those of a Canadian infant as defined by Health Canada (56).

4.2.5 Risk Assessment

The risk associated with each PhAC of the evaluation set was quantified by calculating margins of exposure (MOE) for each. The lower the magnitude of MOE the higher the risk to human-health. The $MOEs$ were estimated using both predicted (PEC) and, where available, measured exposure concentrations ($MECs$). It is important to recognize that $MECs$, though often considered to be a gold standard, may have been deduced from samples that have not have been collected under reasonably anticipated worst-case exposure conditions (e.g., low flow conditions). Therefore, even for PhACs for which $MECs$ were available, concurrent evaluations using their respective $PECs$ were also performed.

The predicted margins of exposure (MOE_p) for each PhAC of the evaluation set were estimated using the following equation:

$$MOE_p = \frac{PNEC_{dw}}{PEC} \quad (5)$$

Where possible, the MOE_M for a PhAC of the evaluation set was estimated in highly conservative manner using the following equation:

$$MOE_M = \frac{PNEC_{dw}}{MEC} \quad (6)$$

Typically, a MOE of less than 1.0 is considered to be indicative of a possible human-health risk. Recognizing the highly conservative nature with which $PNEC_{dw}$ and PEC values were estimated here, a MOE_p of less than 1.0 was interpreted as an indicator of possible risk. However, an MOE of >1 and <10 was used for the added goal of developing a list of priority PhACs for further evaluation. A $MOE > 10$ was interpreted as suggesting negligible risk.

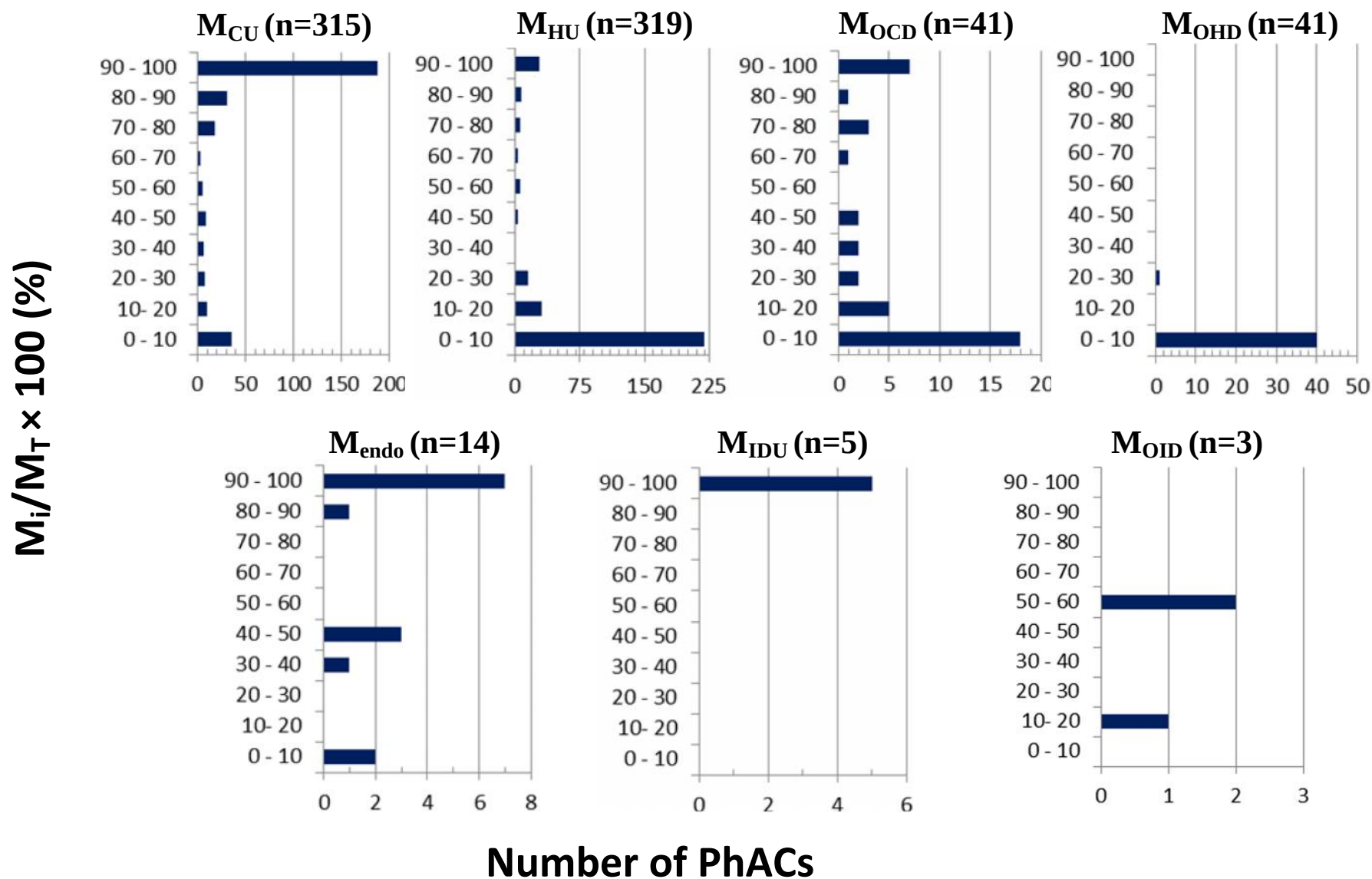


Figure 4.2: Significance of each source term M_i (i.e., M_{CU} , M_{HU} , M_{OCD} , M_{OHD} , M_{endo} , M_{IDU} , or M_{OID}) with respect to the net load of each PhAC (M_T) of the evaluation set of 335 PhACs. n is the total number of PhACs for which a given source term was found to be relevant.

Abbreviations: M_{CU} = mass load due to the use of the PhAC in the general population; M_{HU} = mass load due to the use of the PhAC in hospitals; M_{OCD} = mass load due to the use of other PhACs in the general population; M_{OHD} = mass load due to the use of other PhACs in hospitals; M_{endo} = endogenous excretion of the PhAC; M_{IDU} = illicit use of the PhAC; M_{OID} = illicit use of other PhACs.

Note that, while the evaluation of mixtures represents a very important issue that must eventually be addressed, this was beyond the scope of the current investigation.

4.3 RESULTS AND DISCUSSION

4.3.1 Sources of PhACs to the Environment

As discussed above, seven distinct source terms were considered when estimating the total environmental load (M_T) of each PhAC. Figure 4.2 summarizes the relevance and the significance of each source term in terms of their contribution to the net environmental load of the 335 PhACs selected for analysis. Appendix K further elaborates on the data summarized in Figure 4.2 by listing the details of these source terms for each PhAC.

The overall relevance of each source term for the entire evaluation set is indicated in Figure 4.2 by the variable n . The use of a PhAC in the general population (M_{CU}) and in hospitals (M_{HU}) was found to be relevant for 315 and 319 PhACs, respectively. The reason that the relevance number for M_{HU} was higher than that for M_{CU} was that certain cytotoxic drugs such as cytarabine, daunorubicin, ifosfamide, cisplatin and idarubicin are only clinically used in hospitals and, as such, are not dispensed in the general public. For 41 PhACs, the use of other drugs/chemicals in the general population (M_{OCD}) and in hospitals (M_{OHD}) was found to be relevant sources of these specific compounds. Another 14 PhACs were established to be endogenously excreted (M_{endo}), whereas a handful of PhACs were either illicitly used (M_{IDU}) or resulted from the illicit use of other drugs (M_{OID}).

Figure 4.2 further suggests that, depending on the PhAC being considered, each of the source terms could account for, at the very least, a significant fraction of a PhACs net environmental load. For example, consider that the data summarized in Figure 4.2 suggests that the individual source terms M_{CU} , M_{HU} , M_{OCD} , M_{endo} and M_{IDU} account for greater than 90% of the net environmental load for 188, 28, 7, 7 and 5 PhACs, respectively. The two other contributions, M_{OHD} and M_{OID} , were found to be significant for a select few cases. From the perspective of the entire evaluation set, not surprisingly, the use of the PhAC in the general population (M_{CU}) was found to be the single most importance source, followed by the use of the PhACs in hospitals (M_{HU}). Overall, since each of the seven contributions can be significant for the release of a given PhAC, it is suggested that all seven source terms must be considered when estimating the net environmental loading of a PhAC. To neglect some of these source terms might result in a significant underestimation of the environmental burden of a given PhAC.

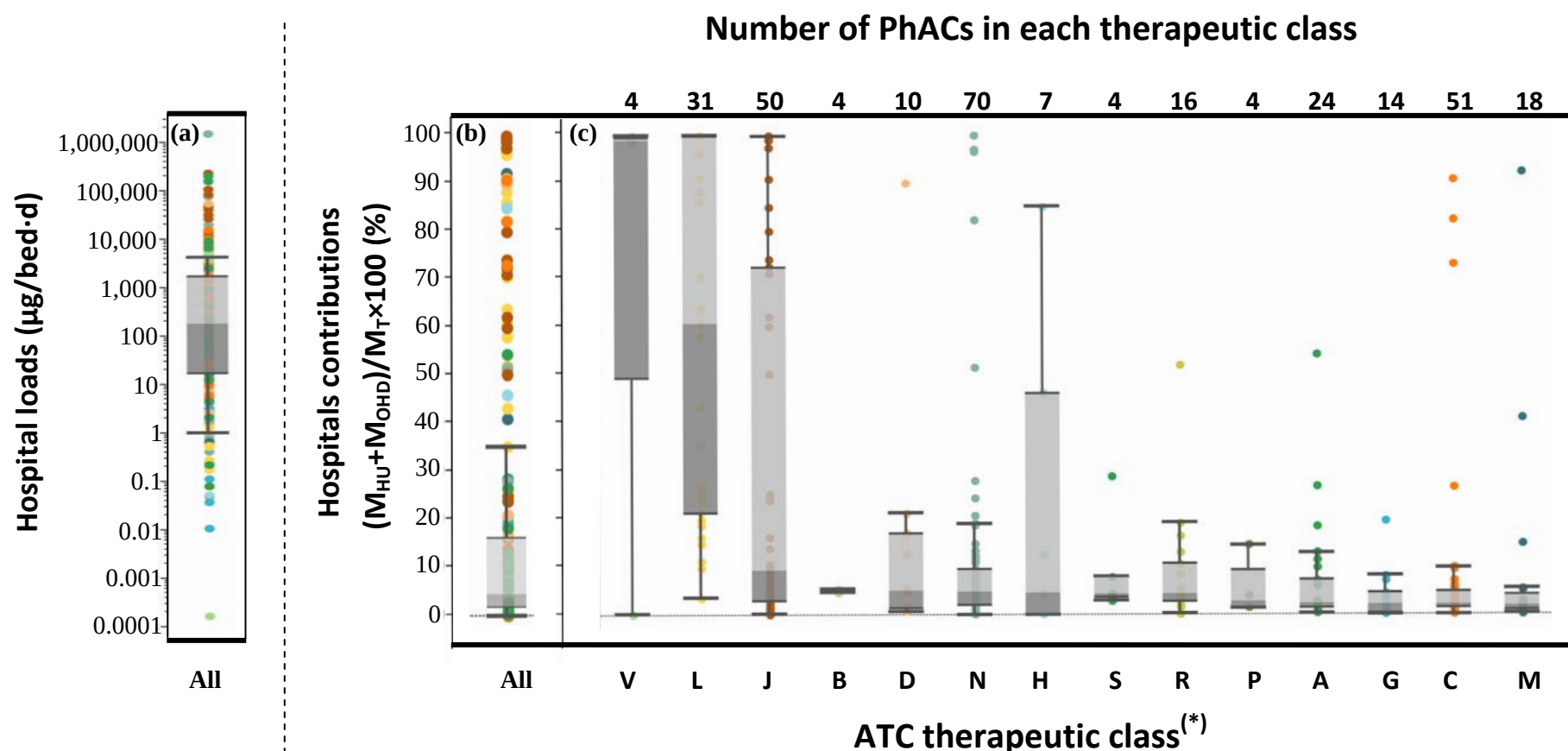


Figure 4.3: Hospitals as a source of PhACs: (a) Net load of all 320 PhACs for which hospitals are significant sources; (b) Overall significance of hospitals as a source ($M_{HU}+M_{OHD}$) relative to the net environmental load (M_T) of each PhAC for the 320 PhACs; (c) Significance of hospitals as a source of PhACs grouped according to therapeutic classes as defined by the Anatomical Therapeutic Chemical (ATC) Classification System. Colors are coordinated across all the three graphs and are indicative of therapeutic classes shown in (c).

Notes: (*) Classifications according to the World Health Organization ATC classification system (60) where abbreviations used on the y-axis represent the following classes of drugs: A = Alimentary tract and metabolism; B = Blood and blood forming organs; C = Cardiovascular system; D = Dermatologicals; G = Genito-urinary system and sex hormones; H = Systemic hormonal preparations; J = Anti-infectives; L = Antineoplastic and immunomodulating agents; M = Musculo-skeletal system; N = Nervous system; P = Antiparasitic products; R = Respiratory system; S = Sensory Organs; and V = Various.

Due to particular concerns associated with hospitals that can serve as potential “hotspots” for the use and the release of certain PhACs (61), the contributions of hospitals is evaluated further in Figure 4.3. Overall, hospitals were found to be a relevant source for 320 PhACs (i.e., $M_{HU} + M_{OHD}$) of the evaluation set (see Appendix K). Figure 4.3(a) suggests that hospitals loads of the PhACs of the evaluation set can vary over several orders of magnitude. The median hospital load for the 320 PhACs was established to be 180 $\mu\text{g}/\text{bed}\cdot\text{d}$. Figure 4.3(b) suggests that when the evaluation set is considered in its entirety drugs dispensed through hospitals account for less than 10% of the environment load of most PhACs. However, there are a significant number of PhACs that appear to be predominantly or almost entirely sourced through hospitals. Consider that for 41 PhACs more than 70% of their net environmental load was sourced through hospitals (see Appendix K). Overall, the hospital contribution to the net environmental load of PhAC can vary significantly from one case to another. Note that the overall trend suggested by Figure 4.3(b) is not entirely unexpected since a dominant selection criterion for the PhACs in the evaluation set was the inclusion of the top 100 highly dispensed drugs in Canada and the vast majority of these are community-based drugs.

To better grasp which types of PhACs are predominantly used in hospitals and which are not, Figure 4.3(c) segregates that data presented in Figure 4.3(b) by the broad therapeutic classes defined by the World Health Organization (60). From this, trends begin to emerge. Figure 4.3(c) suggests that PhACs belonging to most drug classes are only used at relatively minor level in hospitals, however exceptions were found to exist for most such drug classes. The two drugs classes that were found to be primarily used in hospitals were drug Class L (Antineoplastic and immunomodulating agents) and Class V (Various). Thirty-one PhACs of the evaluation set were Class L drugs and, of these, 19 were cytotoxic drugs that are primarily administered in and/or made available through hospitals (61, 62). The median hospital contribution for all Class L drugs was 61%, with estimates for this class of drugs ranging from 3.6% for azathioprine to 100% for a number of cytotoxic drugs. Only 4 PhACs of the evaluation set were Class V drugs; therefore the sample size upon which a judgment is being made is rather small. Nevertheless, Class V contains diagnostic agents and contrast media and these drugs are also known to be primarily administered in hospitals (62).

Hospitals were also found to be a minor but still significant source for Class J (Antiinfectives) drugs. Of the 50 Class J drugs for which hospital contributions were found to be relevant, 44 were antibiotics. The median hospital contribution for all Class J drugs was 9.3% (see Figure 4.3c), with values ranging from 0.1% for spiramycin to 99.8% for penicillin G. Hospitals accounted for greater than 95% of the net

environmental load of 8 Class J drugs, all of which were antibiotics. Specifically, these were: cefazolin, ceftriaxone, piperacillin, tazobactam, cefuroxime, ceftazidime, ticarcillin and penicillin G. All eight aforementioned PhACs are administered in Canada through injections, which might be a reason for their predominant use in hospitals. Overall, hospitals appear to be a major source for only some antibiotics.

It is worth noting that the values reflected in Figure 4.3 do not account for the fact that a fraction of these hospital-dispensed drugs are issued and administered to outpatients and are, therefore, in actual fact excreted in the general population. For example, Weissbrodt et al. (62) reported that, at a Swiss hospital, 70% of the studied cytotoxics and 50% of the studied iodinated contrast media were administered to outpatients and were therefore destined to be excreted in the general population rather than in hospital. Therefore, the fractions plotted in Figure 4.3 likely overestimate the significance of hospitals as a specific geographical source of PhACs into the environment but can be considered accurate representations of the proportion of PhACs that are sourced through hospitals. Overall, trends observed here for the contribution of Canadian hospitals to the net environmental loads of PhACs agree with trends reported for Dutch and Danish hospitals (63, 64) in that hospitals appear to be a minor source for most PhACs but in certain specific instances can be a significant or dominant source of the environmental load of a given PhAC. The broader implications of this observation is that, even if PhACs in the wastewaters of hospitals are successfully treated before capture by municipal sewer systems, the majority of the mass load of most PhACs will still be released into sewer systems for subsequent treatment and/or disposal in the environment.

The discussion above has focused on the significance of the various source terms to the overall selected set of 335 PhACs. An equally valuable discussion is to evaluate how many source terms are relevant for a given PhAC. The number of source terms that are relevant for individual PhACs ranged from 0 to 6 (see Appendix K). Specifically, none of the seven sources accounted for 1 PhAC (as explained below), a single source accounted for 11 PhACs, 2 sources accounted for 280 PhACs, and 3, 4, 5 and 6 source terms lead to the release of 12, 25, 5 and 1 PhACs, respectively. The data suggests that the vast majority of the environmental loads of PhACs in the evaluation set resulted from 2 source terms. Not unexpectedly, the reason for this was that most of the PhACs were only clinically used within the general population and in hospitals (see Appendix K). However, for 43 PhACs, more than 2 source terms were found to be relevant (see Appendix K). In the case of morphine, as many as 6 source terms (and 7 contributions) had to be considered in order to arrive at an estimate for its load to the Canadian

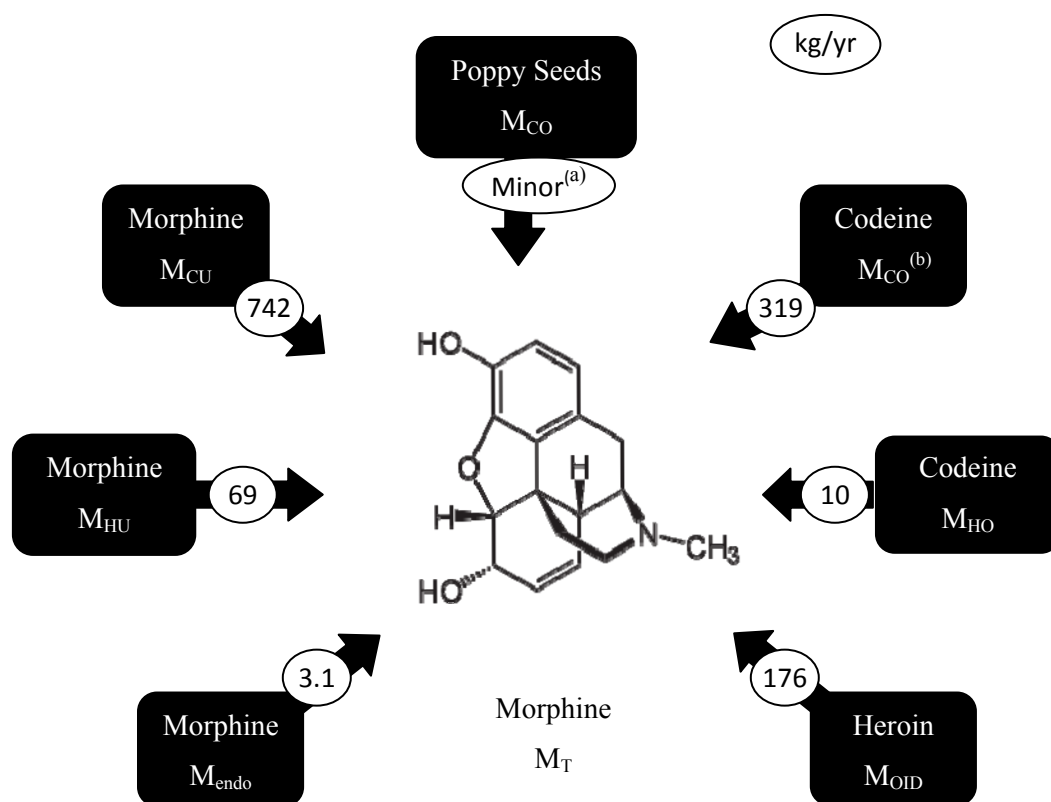


Figure 4.4: Source model for the release of morphine to the Canadian environment.

Notes: (a) Expected to be of minor importance based on the work of Khan and Nicell (11). (b) Other precursors of morphine, ethylmorphine, nicomorphine and pholcodine are not used in Canada (30).

environment (see Figure 4.4). The single PhAC for which none of the seven source terms was found to be relevant was roxithromycin, since this PhAC has yet to be approved for sale in Canada or in the USA (30, 67). Despite this, roxithromycin has been detected in Canadian surface waters and treated drinking waters (35). At present, the origin of this PhAC in Canadian waters remains uncertain but it is possible that the detected roxithromycin is a residue arising from the degradation of another chemical. Note that the latter point highlights a potential limitation of the present analysis in that the possible environmental generation of a PhAC has not been accounted for since such information is typically not available.

It is also of interest to examine the importance of the net environmental load of a PhAC that results from endogenous excretion. Fourteen PhACs of the evaluation set were found to be released via endogenous excretions (see Table 4.1). As expected, most of the PhACs for which endogenous excretion was found to be significant are naturally-produced hormones. For example, similar to estimates furnished for the USA (65, 66), the hormones estrone, estradiol and estriol were found to predominantly or almost entirely result from endogenous excretions. However, it was surprising to note that other compounds that are usually associated with clinical use such as morphine and codeine can also be endogenously produced. Overall, more than 90% of the environmental loads for eight of the PhACs were found to result from endogenous excretions (Table 4.1). A consequence of this is that if these PhACs are found to pose a human-health and/or eco-toxicological risk then one has no choice but to facilitate their removal from sewage and drinking water through process upgrades in treatment plants. Conversely, if a PhAC almost entirely results from the exogenous use of relevant pharmaceutical preparations (e.g., codeine) and is found to pose unacceptable human-health and/or eco-toxicological risk, the possibility of managing the risk through limiting or substituting the use of this PhAC with alternative pharmaceutical preparations remains available.

Similar to the interest in the fraction of the environmental load that results from endogenous excretions, there is also interest in the fraction that results from illicit sources. Again, this interest arises from the consideration that should a PhAC that predominantly results from illicit sources pose an unacceptable human-health and/or eco-toxicological risk one may have no choice but to facilitate its removal in sewage and/or drinking water treatment plants. Illicit contributions were found to be relevant for the following six PhACs: amphetamine, cocaine, heroin, methamphetamine, MDMA and morphine. Of these, MDMA and heroin are not clinically used in Canada (30) and, therefore, they are only released to Canadian aquatic environment through the illicit use of these drugs. In contrast, amphetamine, cocaine, methamphetamine

Table 4.1 Contribution of endogenous excretions to the net release of individual PhACs.

PhAC	Endogenous contribution to net loads
	$[M_{\text{endo}}/M_T \times 100]$
	(%)
Androstenedione	100
Triiodothyronine	Almost 100
Acetylcysteine	>99
Cortisone	>99
Dihydrotestosterone	>99
Estriol	99
Thyroxine	94
Estrone	91
Estradiol	60-77
Testosterone	59
Cortisol	53
Levodopa	39
Morphine	0.2
Codeine	0.03

and morphine, can all be released to the Canadian aquatic environment through licit and illicit sources. As shown in Figure 4.4, a model accounting for the numerous sources of morphine is quite complex, with nearly 13.5% of its net environmental load resulting from the population's use of illicit heroin. Cocaine, in addition to being an important illicit drug, is also used clinically in Canada (30); however only 0.3% of its environmental load is estimated to result from its clinical use in hospitals (see Appendix K). In addition to its clinical sources, amphetamine can also result from the illicit use of methamphetamine (see Appendix E); with as much as 56% of its environmental load accounted for by the illicit use of methamphetamine (see Appendix K). Note that methamphetamine itself can result from the clinical use of the precursor drug selegiline and its own illicit use (see Appendix E). More specifically, the illicit use of methamphetamine accounts for 99.7% of the PhAC's load to the Canadian aquatic environment (see Appendix K). Overall, of the six PhACs for which illicit contributions were found to be relevant, five were established to largely or almost entirely result from illicit sources. Therefore, if these five PhACs are found to pose an unacceptable human-health or eco-toxicological risk, one would have little choice but to consider process modifications to facilitate their removal in wastewater and/or drinking water treatment plants.

4.3.2 Predicted Exposure Concentrations

Three successively less conservative values for the predicted exposure concentrations, denoted as PEC_1 , PEC_2 and PEC_3 as described above, are plotted in Figure 4.5 for the set of selected PhACs. Individual PEC estimates for each PhAC are tabulated in Appendix L. PEC_3 estimates have also been plotted in Figure 4.6 where the data has been categorized by ATC classes to facilitate interpretation and discussion. Since three PhACs of the evaluation set were not in use in Canada for the study year of 2006, PEC estimates could only be furnished for 332 PhACs of the 335 in the evaluation set. The three exceptions are fenoprofen which was discontinued from use in Canada circa 2002, roxithromycin which has yet to be approved for use in Canada, and buprenorphine which was only approved for sale in Canada in 2007 (30).

Overall, when the metabolic losses of individual compounds are accounted for (i.e., estimates of PEC_2 relative to PEC_1), an estimated median reduction of 56% of the environmental load is predicted. When accounting for their removal in sewage treatment plants over and above metabolism (i.e., estimated of PEC_3 relative to PEC_2), an additional 22% median reduction in environmental load is predicted (see Figure J.1 in Appendix L).

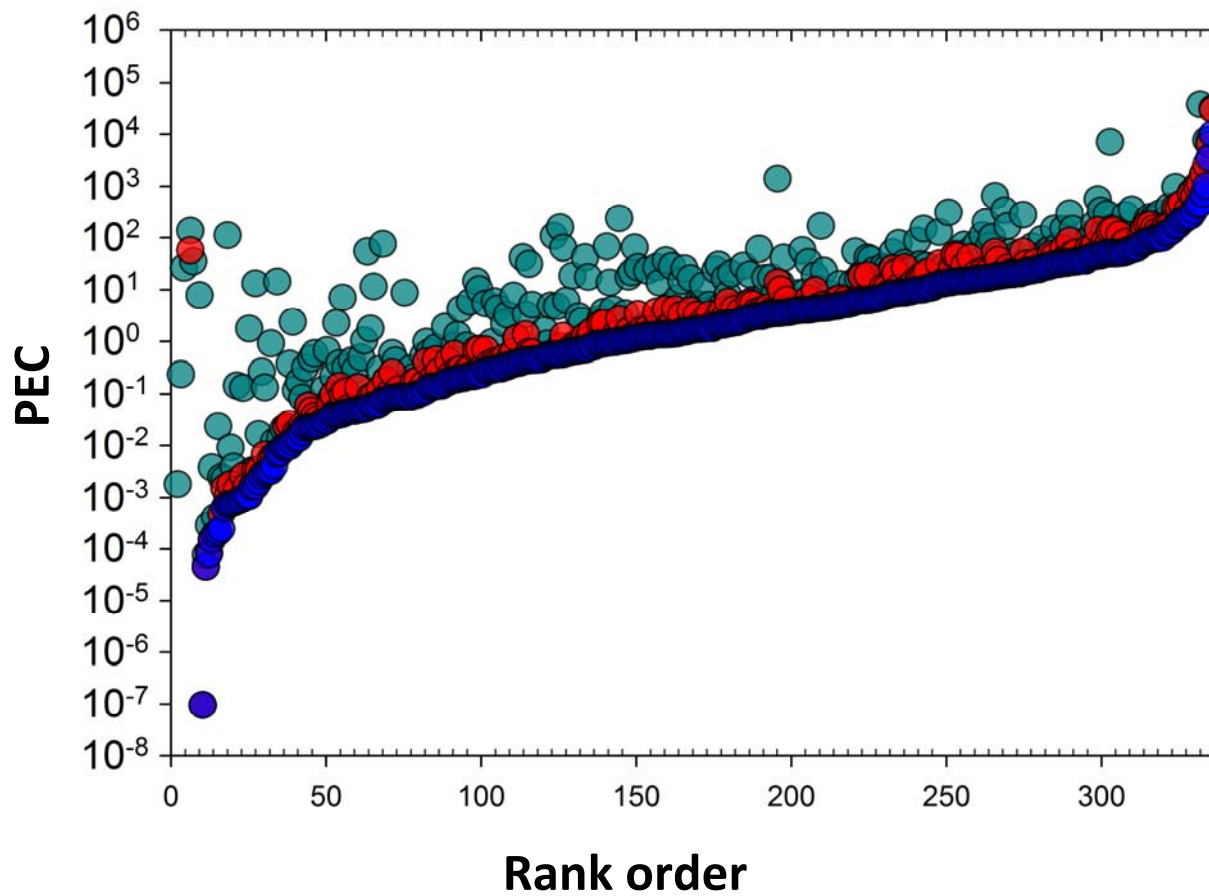


Figure 4.5: Frequency plots of the predicted environmental concentrations PEC_1 (●), PEC_2 (●) and PEC_3 (●) where data is sorted by rank order of PEC_3 values. Individual PEC estimates for each PhAC are listed in Appendix L.

Table 4.2: Fifty top ranked PhACs according to estimates of predicted environmental concentrations (PEC₃) and the reported number of Canadian drinking water and surface water samples that have been analyzed for their presence.

PhAC	ATC Class	PEC ₃	Number of samples that have been analyzed for their presence	
			Surface Water ^(a)	Treated Drinking Water ^(b)
Acetaminophen	N	10,000	212	176
Metformin	A	3,500	-(c)	-
Ibuprofen	M	1,000	496	219
Acetylcysteine	V	714	-	-
Theophylline	R	459	-	-
Amoxicillin	J	424	-	-
Naproxen	M	333	514	219
Gabapentin	N	270	-	-
Docusate	A	255	-	-
Hydrochlorothiazide	C	229	9	-
Etidronic Acid	M	219	-	-
Cephalexin	J	178	-	-
Aminosalicylic Acid	A	169	-	-
Penicillin G	J	140	26	32
Irbesartan	C	126	-	-
Atenolol	C	122	19	-
Sulfasalazine	A	101	-	-
Clarithromycin	J	98	12	3
Codeine	N	96	9	-
Penicillin V	J	96	-	-
Ciprofloxacin	J	91	160	159
Valsartan	C	85	-	-
Atorvastatin	C	81	27	-
Furosemide	C	76	-	-
Cefazolin	J	67	-	-
Piperacillin	J	63	-	-
Carbamazepine	N	61	453	221
Hydroxychloroquine	P	58	-	-
Sulfamethoxazole	J	54	364	221
Cefprozil	J	52	-	-
Tetracycline	J	52	214	214
Acetylsalicylic Acid	N	51	-	-
Acyclovir	J	51	-	-
Ceftazidime	J	51	-	-
Diltiazem	C	50	-	-
Cimetidine	A	49	-	-
Metoprolol	C	46	16	-
Valproic Acid	N	46	-	-
Acebutolol	C	45	-	-
Clopidogrel	B	43	-	-
Losartan	N	41	-	-
Metronidazole	P	41	-	-
Trimethoprim	J	38	369	221
Chlorhexidine	D	37	-	-
Methyldopa	C	37	-	-
Lamotrigine	N	36	-	-
Eprosartan	C	35	-	-
Phenytoin	N	35	-	-
Allopurinol	M	34	-	-
Sotalol	C	33	7	-

Notes:(a) Surface water counts based on data compiled from all 34 references listed in Appendix A; (b) Based on data compiled from all studies reporting on the presence of PhACs in finished Canadian drinking waters (32-38); (c) not measured.

The top 50 PhACs ranked according to their estimate PEC_3 values are tabulated in Table 4.2. PEC_3 values ranged from 33 ng/L for sotalol to approximately 10,000 ng/L for acetaminophen. Class J (Anti-infectives for systemic use) drugs were particularly well represented with 14 of the 52 drugs from this class in this list and, of these, 13 were antibiotics. The median PEC_3 for all 52 Class J drugs was 12 ng/L, with estimates ranging from 0.03 ng/L for spiramycin to 424 ng/L for amoxicillin (see Figure 4.6). Of all classes, the median PEC_3 for Class J drugs was the second highest and lower only than that of Class P drugs, for which only 4 drugs were included in the evaluation set. Class C (Cardiovascular) drugs were also well represented in the top 50 list with 12 of the 55 evaluation set drugs from this class making the list (Table 4.2). The median PEC_3 for Class C drugs was the third highest at 9 ng/L, with specific estimates for this class of drugs varying from 0.8 pg/L for nimodipine to 229 ng/L for hydrochlorothiazide (see Figure 4.6). Even though 31 Class L (Antineoplastic and immunomodulating) drugs were included in the evaluation set, not one was amongst the top 50 list (Table 4.2). The highest PEC_3 for a Class L drug was estimated to be 3.4 ng/L for azathioprine, an immunosuppressant drug, and the highest estimated PEC_3 for a cytotoxic drug was estimated to be 2.1 ng/L for fluorouracil. The median level PEC_3 for all 31 Class L drugs was estimated to be 0.03 ng/L, with estimates ranging from 0.05 pg/L for dactinomycin to 3.4 ng/L for azathioprine (see Figure 4.6). Furthermore, the median PEC_3 of 0.03 ng/L for all Class L drugs was the lowest all of all drug classes considered (see Figure 4.6). The second and third lowest median PEC_3 values were for Class S and Class R drugs. Most Class S and Class R drugs included in the evaluation set are administered locally into the eye, the ear, the nose or the throat and this is the likely reason for the low median PEC_3 estimated for these drug classes. Not one of the Class S drugs and only acetylcysteine of the 17 Class R drugs were in the top 50 list. However, clinical use in the general population and in hospitals is a minor contributor to the net environmental load of acetylcysteine, since its load to Canadian environment almost entirely results from endogenous excretions (see Table 4.1). Similar to Class L drugs, not one of the 17 Class G (Genito-urinary system and sex hormones) drugs included in the evaluation set was in the top 50. PEC_3 estimates for Class G drugs ranged from 1 pg/L for desogestrel to 6.2 ng/L for estriol and the median level PEC_3 for all 16 Class G drug was estimated to be 0.1 ng/L. Even though it is clear that most Class L and Class G drugs are only expected to be present in the Canadian aquatic environments at low ng/L to sub ng/L levels, these levels by themselves cannot be taken to be indicative of the lack of risk posed by such drugs since Class L and G drugs are expected to be highly potent in their action (15).

As expected, amongst the top 10 PhACs were acetaminophen and ibuprofen, two pain killers that are available over-the-counter and are widely used in Canada and elsewhere (23). The prescription pain killer

Number of PhACs in each therapeutic class

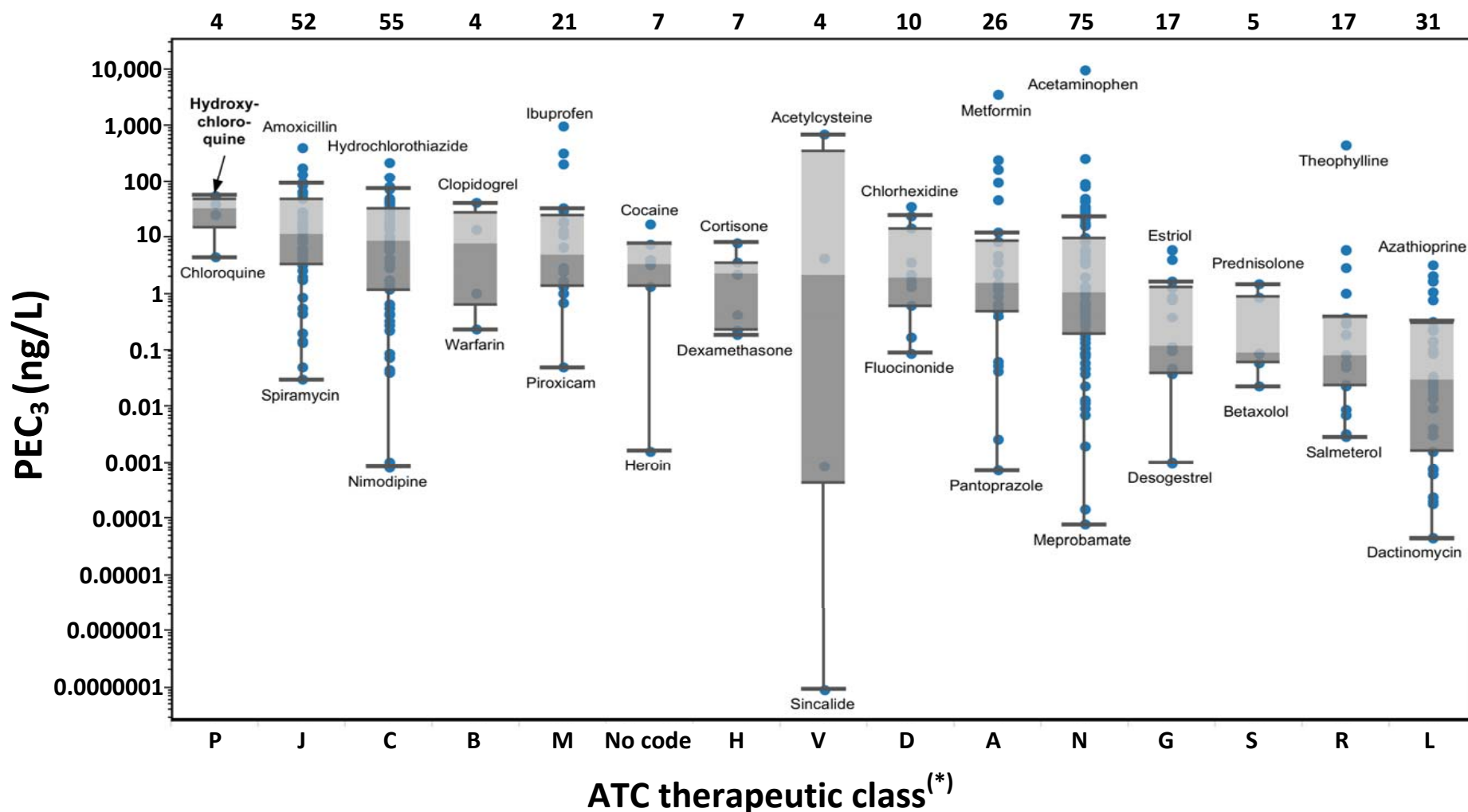


Figure 4.6: PEC₃ estimates grouped according to therapeutic classes as defined by the Anatomical Therapeutic Chemical (ATC) Classification System.

Note: (*) Classifications according to the World Health Organization ATC classification system (WHO, 2013) where abbreviations used on the y-axis represent the following classes of drugs: A = Alimentary tract and metabolism; B = Blood and blood forming organs; C = Cardiovascular system; D = Dermatologicals; G = Genito-urinary system and sex hormones; H = Systemic hormonal preparations; J = Antiinfectives; L = Antineoplastic and immunomodulating agents; M = Musculo-skeletal system; N = Nervous system; P = Antiparasitic products; R = Respiratory system; S = Sensory Organs; and V = Various.

naproxen was also amongst the top 10 PhACs. Amoxicillin, a widely used antibiotic, was estimated to have the fifth highest PEC_3 . Also amongst the top 10 were acetylcysteine and theophylline, two PhACs that are almost entirely released to Canadian surface waters due to sources other than their clinical use (Table 4.1). Almost 99% of theophylline's environmental load results from the Canadian population's ingestion of caffeine; since theophylline, in addition to being a clinical drug itself, is also a metabolite of caffeine (see Appendix E). Metformin, gabapentin and hydrochlorothiazide ranked 2nd, 8th and 10th, respectively, and despite their high use in Canada and elsewhere these drugs are only occasionally studied for their aquatic presence and relevance (70). The PEC_3 for docusate was likely an underestimate since this PhAC, in addition to be a common excipient in pharmaceutical preparations, is also available over-the-counter in Canada for use as a laxative (30).

4.3.3 Compilation of Measured Exposure Concentrations (MEC)

In total, 5813 measurements of exposure concentrations were compiled from studies (32-38) reporting on the presence of PhACs in finished (i.e. treated) Canadian drinking waters. Of the 5813 analyses performed, 170 yielded a positive detection for a PhAC. Therefore, to date PhACs have been detected within finished Canadian drinking water with an overall detection frequency of 2.9% in samples taken. Despite the fact that PhACs are only rarely detected in finished Canadian drinking waters, concentrations as high as 601 and 155 ng/L have been reported for carbamazepine and erythromycin, respectively (see Table 4.3).

The compiled data covers the analysis of only 47 PhACs and of those 20 have been detected in at least one finished Canadian drinking water sample (Table 4.3). The number of samples analysed for each PhAC ranged from 1 for a number of antidepressants (bupropion, citalopram, paroxetine, sertraline and venlafaxine) to 237 for the estrogens estradiol and estrone. Of the 47 PhACs monitored, extensive data ($n > 100$) was available for 26 of them. Of these, ibuprofen and carbamazepine are the two that are most commonly detected, with overall detection frequencies of 22 and 19%, respectively. In contrast, extensive monitoring data in Canada for the presence of estradiol ($n=237$), estriol ($n=236$), ethinylestradiol ($n=236$), indomethacin ($n=218$), chloramphenicol ($n=155$), doxycycline ($n=155$), progesterone ($n=155$) and warfarin ($n=155$) are still to yield a single positive detection. If the list of PhACs monitored is analysed by therapeutic classes, it is clear that antibiotics are well represented and typically well monitored, while only limited to no monitoring data is available for some other classes. For example, Class L drugs are only covered by two drugs (cyclophosphamide and methotrexate) and even then, for these two drugs only 10 analyses have been reported.

Table 4.3: PhACs monitored and detected in Canadian drinking water samples following treatment and their predicted environmental concentrations based on three levels of conservative assumptions.

PhAC	ATC Class	Measured ^(a)					Predicted ^(b)		
		n ^(c)	detects	FOD ^(d)	MEC _{max}	Reference for MEC _{max}	PEC ₁	PEC ₂	PEC ₃
				%	ng/L		ng/L		
Ofloxacin	J	4	2	50	1.6	(33)	5	4	2
Ibuprofen	N	219	47	22	75	(36)	7,702	2,619	1,030
Carbamazepine	N	221	42	19	601	(35)	357	89	89
Gemfibrozil	C	218	26	12	4	(35)	73	29	15
Erythromycin	J	214	13	6.1	155	(35)	75	21	16.3
Roxithromycin	J	214	10	4.7	41	(35)	— ^(f)		
Acetaminophen	N	176	6	3.4	29	(36)	32,642	30,357	10,117
Tetracycline	J	214	5	2.3	15	(35)	116	116	52
Fluoxetine	N	65	1	1.5	6	(36)	20	7	6
Bezafibrate	C	218	3	1.4	2.9	(38)	29	22	11
Ketoprofen	M	218	3	1.4	1	(38)	6	5	3
Sulfamethoxazole	J	221	3	1.4	2	(35)	280	84	54
Clofibric Acid	C	219	2	0.9	1.1	(33)	— ^(g)		
Ciprofloxacin	J	159	1	0.6	7	(38)	65	32	32
Equilin		159	1	0.6	n.r. ^(d)	(35)	— ^(h)		
Norfloxacin	J	159	1	0.6	n.r.	(35)	23	9	9
Diclofenac	M	186	1	0.5	n.r.	(35)	151	44	31
Naproxen	M	219	1	0.5	26	(36)	878	659	333
Trimethoprim	J	221	1	0.5	15	(35)	61	48	38
Estrone	G	237	1	0.4	1	(38)	5	3	2

Additional PhACs monitored but not detected in Canadian drinking water samples: estradiol (n=237), estriol (n=236), ethinylestradiol (n=236), indomethacin (n=218), chloramphenicol (n=155), doxycycline (n=155), progesterone (n=155), warfarin (n=155), testosterone (n=68), fenoprofen (n=63), pentoxifylline (n=63), fenofibrate (n=59), norethisterone (n=32), penicillin G (n=32), sulfadiazine (n=32), cyclophosphamide (n=7), sulfacetamide (n=4), sulfapyridine (n=4), sulfisoxazole (n=4), clarithromycin (n=3), enalapril (n=3), methotrexate (n=3), bupropion (n=1), citalopram (n=1), paroxetine (n=1), sertraline (n=1) and venlafaxine (n=1).^(a) Not included in the list above are PhACs that are only used veterinary purposes.

Notes: (a) Based on data compiled from the following sources: (32-38); (b) Estimated using Eq. 2; (c) n = number of samples analyzed; (d) FOD = frequency of detection; (e) n.r. = not reported by the reference in question; (f) Not approved for sale in Canada or the United States (30, 67) and, therefore the source of the PhAC to Canadian aquatic environment currently remains unclear; (g) Parent drug was discontinued in 2006 (30); (h) Knowledge gaps prevent the generation of reliable predictions for this PhAC (66).

It is worth noting that the *MECs* for enalapril, equilin, erythromycin, estradiol, estrone, estriol, ketoprofen, penicillin G, pentoxifylline, progesterone, testosterone, tetracycline and trimethoprim also result from the release of these drugs from veterinary sources since these PhACs are either endogenously excreted by animals (e.g., estrone) and/or are exogenously administered or fed to animals in Canada (e.g., erythromycin) (30).

4.3.4 PEC as a Conservative Estimate for MEC

As established in the preceding section, *MECs* are only available for a handful of PhACs. Therefore, for cases where such data was not available, it was of interest to establish whether *PEC₃* estimates can be used as conservative substitutes for measurements. The degree to which *PEC₃* estimates are conservative can be assessed by comparing *MEC* data and their respective *PEC₃* estimates for all PhACs that have been positively detected in finished Canadian drinking waters. However, the question remains as to which *MEC* value should the respective *PEC₃* estimate be compared to? Typical practice in risk assessment is to use 95th percentile *MEC* (*MEC₉₅*) value or, in other words, an *MEC* value that is only exceeded by 5% of the values in the data set (71). However, *MEC₉₅* values for 15 of the 20 detected PhACs were below the detection limit as their presence in drinking waters has only yielded positive detections in less than 5% of the samples analysed (Table 4.3). Because of this, a two-step approach was taken to evaluate the degree to which *PEC₃* estimates were conservative. Firstly, and in a more conservative fashion than typical risk assessment practice, *MEC_{max}* values for all detected PhACs were compared to their respective *PEC₃* estimates. Then only for those PhACs for which the *PEC₃* estimates were found to be lower than their respective *MEC_{max}* values was a second evaluation performed with *MEC₉₅* values.

Table 4.3 suggests that, with the exceptions of carbamazepine and erythromycin, *PEC₃* estimates are higher and hence more conservative than their respective *MEC_{max}* values. An evaluation for diclofenac, equilin and norfloxacin could not be performed since the study that reported the single positive detections for these PhACs (35) failed to report the levels at which they were detected. Nevertheless, 99.5% of the *MECs* for these PhAC were below the detection limit.

For the cases of carbamazepine and erythromycin, a more elaborate assessment using *MEC₉₅* values was necessary. The analysis summarized in Appendix M suggests that *MEC₉₅* for carbamazepine in finished Canadian drinking water samples was 9.8 ng/L, while the *PEC₃* was estimated to be 82 ng/L. Appendix M further suggests that the *PEC₃* estimate of 82 ng/L for carbamazepine was higher (i.e., more conservative) than 98% of *MECs* reported. The *MEC₉₅* for erythromycin was estimated to be between 3 to 10 ng/L (35,

36, 38), which was lower than the PEC_3 estimate furnished for this PhAC of 16 ng/L. Overall, it appears that a given the estimate of PEC_3 values as furnished here is more conservative than the vast majority of the $MECs$ measured for its presence in finished Canadian drinking waters. This is not entirely unexpected given the number of conservative assumptions made in estimating PEC_3 values.

4.3.5 Acceptable Daily Intakes Values

The approach summarized in Figure 4.1 was used to estimate the ADI for each PhAC of the evaluation set.

A TDI derived by Health Canada was only available for the PhAC chloral hydrate. For another 31 PhACs, $ADIs$ were available due to the veterinary use of these compounds in Canada and/or elsewhere. These 31 PhACs included 19 antibiotics, 5 glucocorticoid steroids, 4 painkillers, 1 androgen, 1 estrogen and 1 diuretic. For the remainder the 303 PhACs, provisional ADI ($p-ADI$) were developed following the procedure summarized in Figure 4.1.

$LOTDs$ were available for 289 of the 303 PhACs for which $p-ADIs$ were to be established. The remaining 14 PhACs were either not orally administered (e.g., levobunolol) or were not clinically used and, therefore, generally lacked a dosing schedule (e.g., clofibric acid). While performing $p-ADI$ evaluations with $LOTD$ as the point of departure, $LOTDs$ for adults were typically used. The reason this was done was that a large fraction of the PhACs being considered did not have an established pediatric use and therefore lacked corresponding dosing schedules. To assess the robustness of using adult $LOTDs$, an evaluation was performed for all 224 PhACs of the evaluation set for which adults as well as pediatric dosage regimens were both found to exist. The results of the evaluation, which are summarized in Appendix N, suggested that for 199 PhACs, or 88% of the cases, $LOTDs$ for adults were lower, and hence more conservative, than their pediatric counterparts. Without performing a comprehensive assessment as the one performed here, others (18) have also alluded to the fact that, for most PhACs, the $LOTD$ for adults are lower than their pediatric counterparts. Overall, for the 199 PhACs for which adults $LOTDs$ were found to be more conservative, adult $LOTDs$ were used. For the 25 exceptions for which pediatric $LOTDs$ were found to be lower, pediatric $LOTDs$ were used. For all remaining PhACs, which lacked pediatric dosing schedules, adult $LOTDs$ were used.

$OELs$ were available for 234 of the 303 PhACs for which $p-ADIs$ were to be estimated. For the remaining compounds, either $OELs$ had not been developed by the respective manufacturers or, despite an extensive

data search conducted during this study; no suitable material safety data sheets containing such information could be located. *NSRL* and *LT_{D10}* as shown in Figure 4.1 were only relevant for genotoxic carcinogenic PhACs of the evaluation set.

Ultimately, following the procedure in Figure 4.1, estimated *ADI* values for 133, 164, 3 and 3 PhACs were based on *LOT_D*, *OEL*, *NSRL* and *LT_{D10}* values, respectively. Appendix O presents a summary for each PhAC of the data inputs that were available and, of these, which one was ultimately selected following the procedure of Figure 4.1 to arrive at an *ADI* for each of the 335 PhAC of the evaluation set.

For 220 of the PhACs, both *OEL* and *LOT_D* values were available and in 70% of these cases, or 149 PhACs, *p-ADIs* derived from the *OEL* point of departure were more conservative than those derived using the *LOT_D* approach. To date, *OEL* limits have only been used in the development of *ADI* for only 4 PhACs (16, 31)

4.3.6 Predicted No Effect Concentrations for Exposure via Drinking Water

Predicted no effect concentrations for exposure via drinking water (*PNEC_{dw}*) were estimated for each PhAC from their respective *ADI* values using Eq. 4. Of the receptors defined by Health Canada, infants were selected since they are the most sensitive to drinking water contaminants given that it has been reported that infants in Canada drink more water on a per weight basis than toddlers, children, teens and adults (56). Therefore, conservatively, *PNEC_{dw}* estimates furnished and discussed here are specific for exposure of infants. Note that Canadian exposure factors (56) are such that the respective *PNEC_{dw}* for teens, adults, children and toddlers were found to be 2.2, 1.7, 1.5 and 1.01 times higher than those derived for infants.

PNEC_{dw} values for the entire evaluation set are plotted in Figure 4.7 where the data has been categorized by ATC classes to facilitate interpretation. The estimated *PNEC_{dw}* values ranged from a minimum of 30 pg/L for the anticancer drug dactinomycin (a Class L drug) to a maximum of nearly 9 mg/L for the contrast media diatrizoate (a Class V drug). Amongst the most potent (i.e. lowest median *PNEC_{dw}*) drug classes were Class G, Class L, those for which an ATC class code has not been assigned (i.e., “No Code”), and Class H (see Figure 4.6). These classes cover such sub-classes as anti-cancer drugs, sex hormones and other hormones, drugs used for endocrine therapy, illicit drugs and immunosuppressants, all of which are sub classes of drugs that would be expected to be highly potent in their potential to yield effects on human health.

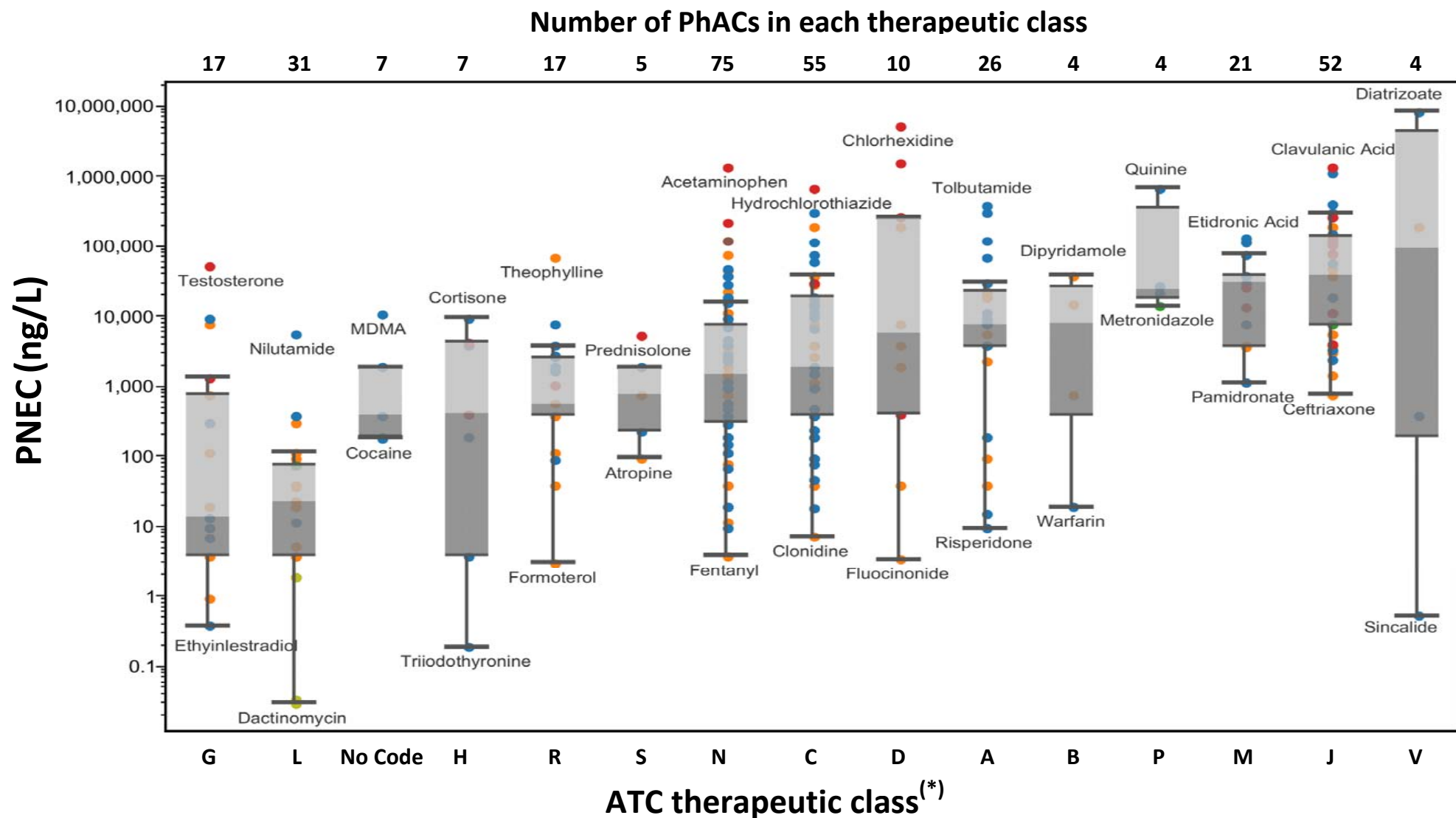


Figure 4.7: PNEC estimates grouped according to therapeutic classes as defined by the Anatomical Therapeutic Chemical (ATC) Classification System. PNEC estimates have been color coded according to the data input ultimately used in the derivation of ADIs following the procedure of Figure 4.1 as follows: ADI_{vet} (■), LOTD (■), LTD₁₀ (■), NSRL (■), OEL (■), TDI (■).

Note: (*) Classifications according to the World Health Organization ATC classification system (WHO, 2013) where abbreviations used on the y-axis represent the following classes of drugs: A = Alimentary tract and metabolism; B = Blood and blood forming organs; C = Cardiovascular system; D = Dermatologicals, G = Genito-urinary system and sex hormones; H = Systemic hormonal preparations; J = Antiinfectives; L = Antineoplastic and immunomodulating agents; M = Musculo-skeletal system; N = Nervous system; P = Antiparasitic products; R = Respiratory system; S = Sensory Organs; and V = Various.

The most potent drug class was Class G with a median $PNEC_{dw}$ of 14 ng/L. Class L drugs were also found to be particularly potent in terms of their potential to cause human-health effects where the median $PNEC_{dw}$ for this class of drugs was estimated to be 23 ng/L. Of the 31 Class L drugs, 19 were anti-cancer drugs and another 11 were endocrine therapy drugs. The median $PNEC_{dw}$ for all 19 anti-cancer drugs was 12 ng/L with individual estimates ranging from 0.03 ng/L for dactinomycin to 390 ng/L for capecitabine. The median $PNEC_{dw}$ for all 11 endocrine therapy drugs was 39 ng/L with individual estimates ranging from 2 ng/L for leuprolide to 6 µg/L for nilutamide. The PhACs classified as “No-Code” included five illicit drugs and two endogenous androgens. The $PNEC_{dw}$ for the 5 illicit drugs ranged from 187 ng/L for cocaine to nearly 11 µg/L for MDMA. The $PNEC_{dw}$ for the two androgens included in the “No-Code” class were 390 ng/L for dihydrotestosterone and approximately 2 µg/L for androstenedione. Particularly potent among the Class H drugs were the thyroid hormones triiodothyronine and thyroxine with $PNEC_{dw}$ values of 0.2 and 3.9 ng/L, respectively. Triiodothyronine and thyroxine are almost entirely released to the Canadian environment due to their endogenous excretion (see Table 4.1).

Drug classes that were found to lack potency in potentially affecting human health included Class J and Class M drugs. Consider that median $PNEC_{dw}$ for all 52 Class J drugs, of which 43 were antibiotics, was approximately 39 µg/L. The $PNEC_{dw}$ estimates for class J drugs ranged from nearly 800 ng/L for ceftriaxone to 1.4 mg/L for clavulanic acid (see Figure 4.7). The median $PNEC_{dw}$ for all 21 Class M drugs, of which 14 were anti-inflammatory drugs, was 31 µg/L. Specific estimates for Class M drugs ranged from 1.2 µg/L for pamidronate to 137 µg/L for etidronic Acid (Figure 4.7). For the 14 anti-inflammatory drugs, the median $PNEC_{dw}$ was estimated to be 35 µg/L with individual estimates ranging from 4 µg/L for indomethacin to 117 µg/L for mefenamic acid. Included amongst the 14 anti-inflammatory drugs was ibuprofen, the one PhAC that is most commonly detected in finished Canadian drinking water (see Table 4.3). The $PNEC_{dw}$ for Ibuprofen was estimated to be nearly 8 µg/L.

4.3.7 Risk Assessment Using Measured Exposure Concentrations (MEC)

A risk assessment using measured exposure concentrations was performed in highly conservative manner by estimating the margin of exposure (MOE) for the highest MEC (MEC_{max}) reported for each PhAC that has been detected in at least one finished Canadian drinking water sample (see Table 4.4). The resulting MOE_{m-max} estimates ranged from 4 for estrone to 137,500 for sulfamethoxazole. Therefore, not a single MOE_{m-max} was estimated to be below the risk trigger limit of 1.0. MOE_{m-max} values below 100 were only observed for 2 PhACs; namely, estrone and carbamazepine. The MOE_{m-max} for estrone was estimated to be 4 based a single positive detection reported by Tabe et al. (38). However, to date 237 drinking water

Table 4.4: Risk assessment of PhACs using maximum environmental concentrations, MEC_{max} , reported in finished Canadian drinking water samples.

PhAC	n	FOD ^(a)	MEC _{max}	Reference for MEC _{max}	PNEC _{dw} ^(b)	MOE _{m-max} = MEC _{max} /PNEC
		%	ng/L		ng/L	
Estrone	237	0.4	1	(38)	4	4
Carbamazepine	221	19	601	(35)	7,860	13
Ibuprofen	219	22	75	(36)	7,860	105
Fluoxetine	65	1.5	6	(36)	1,960	327
Ciprofloxacin	159	0.6	7	(38)	4,130	590
Erythromycin	214	6.1	155	(35)	138,000	890
Roxithromycin	214	4.7	41	(35)	58,900	1,437
Naproxen	219	0.5	26	(36)	39,300	1,512
Tetracycline	214	2.3	15	(35)	82,500	5,500
Trimethoprim	221	0.5	15	(35)	110,000	7,333
Gemfibrozil	218	12	4	(35)	39,300	9,825
Bezafibrate	218	1.4	2.9	(38)	39,300	13,552
Ketoprofen	218	1.4	1	(38)	27,500	27,500
Clofibric Acid	219	0.9	1.1	(33)	31,400	28,545
Acetaminophen	176	3.4	29	(36)	1,375,000	47,414
Ofloxacin	4	50	1.6	(33)	157,000	98,125
Sulfamethoxazole	221	1.4	2	(35)	275,000	137,500

Notes: (a) FOD = frequency of detection; (b) Estimated using Eq. 4 with ADI as listed in Appendix O.

samples have been analysed in Canada for the presence of estrone and only 1 of these samples has yielded a positive detection. Therefore, 99.6% of the *MECs* for estrone in finished Canadian drinking water were below detection limits. In contrast, carbamazepine is one of the most commonly detected PhACs in finished Canadian drinking waters (see Table 4.4). The MOE_{m-max} for carbamazepine was estimated to be 13. However, if the evaluation is performed with MEC_{95} instead, which is in line with typical risk assessment practice, the *MOE* for exposure to carbamazepine increases to 802 ($PNEC_{dw}$ of 7,860 ng/L divided by MEC_{95} of 9.8 ng/L). Overall, a risk assessment with *MECs* reported thus-far for PhACs in finished Canadian drinking waters suggest that they pose a negligible risk to human-health.

4.3.8 Risk Assessment Using Predicted Exposure Concentrations (PEC)

Since extensive monitoring data of finished Canadian drinking waters was only available for 27 PhACs ($n > 100$; see Table 4.3), a conservative risk assessment of the evaluation set with *PEC* estimates was also performed. An estimated MOE_p of less than 1.0 was taken to be indicative of “possible risk” and that the PhAC in question should be considered for further study and prioritization. A value of greater than 1.0 but less than 10 was taken to suggest that the PhAC in question represented a “low risk” but still required further consideration for prioritization, and a value greater than 10 was taken to indicate “negligible risk”.

Margins of exposure based on PEC_3 estimates (MOE_{p3}) are plotted by ATC Classes in Figure 4.8. Specific MOE_{p3} estimates for each PhAC are listed in Appendix P with individual values ranging from 205×10^6 for meprobamate to 0.08 for triiodothyronine. Of the entire evaluation set only two PhACs, estriol (a Class G drug) and triiodothyronine (a Class H drug), were predicted to have MOE_{p3} values below the trigger limit for possible risk of 1.0. MOE_{p3} estimates for an additional 14 PhACs were predicted to fall between 1 and 10 (Figure 4.8 and 9). The remaining 319 PhACs were found to pose a negligible risk since their respective MOE_{p3} estimates were found to be greater than 10 (Figure 4.8). Specifically for these 319 PhACs; 44, 95, 93, 47 and 40 PhACs were estimated to have a MOE_{p3} of greater than 10 but less than 100, greater than 100 but less than 1000, greater than 1000 but less than 10,000, greater than 10,000 but less than 100,000, and greater than 100,000, respectively (Figure 4.9).

If MOE_{p3} estimates are evaluated according to therapeutic class, Class L drugs were found to present the highest level of relative risk with a median MOE_{p3} of 330, with specific estimates for this class of drugs ranging from 621×10^3 for buserelin to 34 for azathioprine. Therefore, every one of the 31 Class L drugs evaluated was found to pose a negligible risk to human-health (see Figure 4.8). Similar to Class L drugs, all drugs of the evaluation set belonging to ATC Classes B, D, R, S, P, J and V were found to pose a

Number of PhACs evaluated	31	17	7	55	75	7	4	10	21	17	5	4	52	26	4
Number of PhaCs with $MOE_{p3} < 10$	0	2	0	6	5	2	0	0	1	0	0	0	0	1	0
Number of PhaCs with $MOE_{p3} < 1$	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0

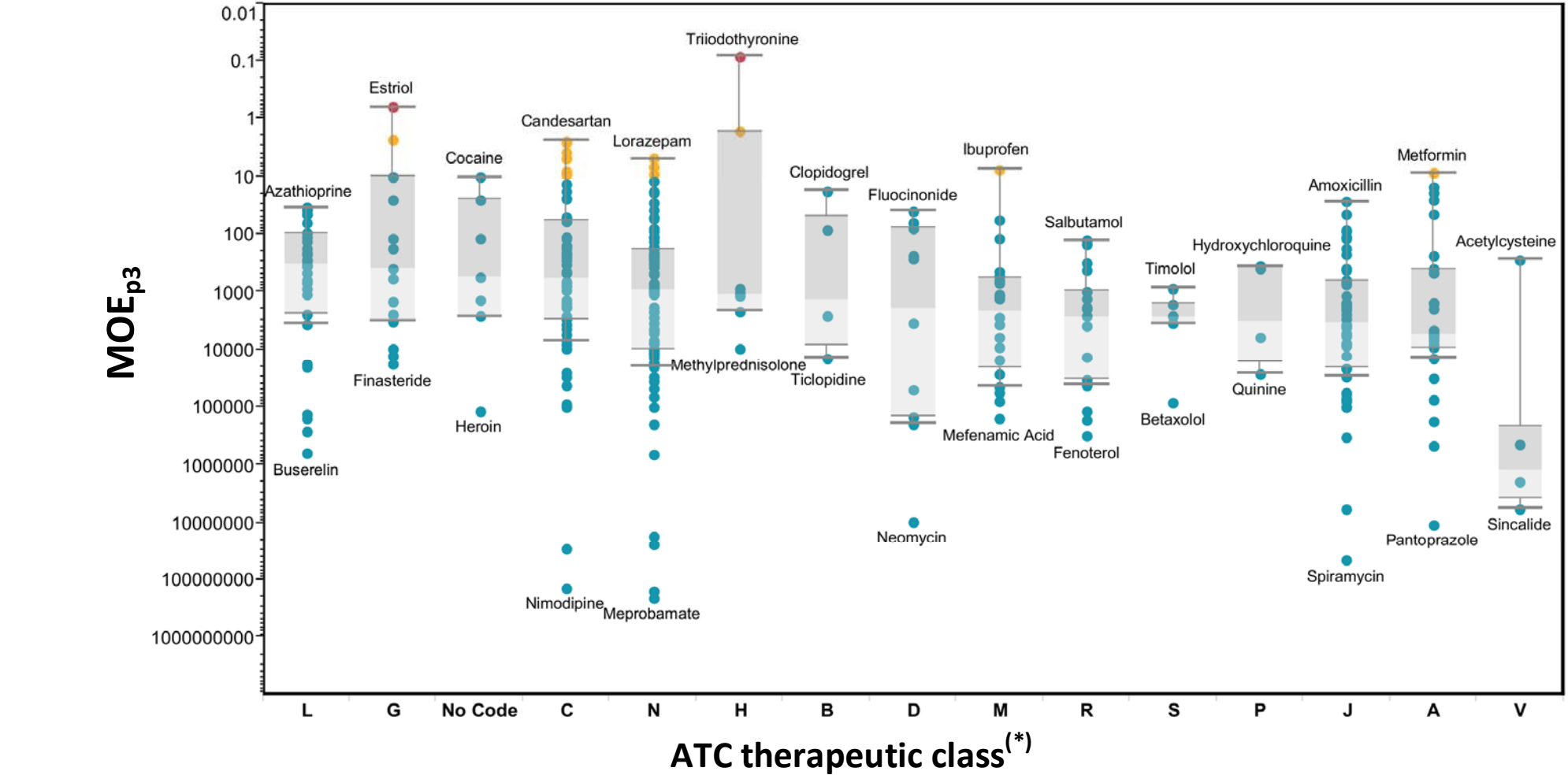


Figure 4.8: Margin of exposure, MOE_{p3} (PNEC_{dw} divided by PEC₃), estimates grouped according to therapeutic classes as defined by the Anatomical Therapeutic Chemical (ATC) Classification System. MOE_{p3} estimates have been color coded with respect to their estimated risk to human-health as follows: Possible risk (■); Low risk, but should be considered for further prioritization (■); Negligible risk (■).

Note: (*) Classifications according to the World Health Organization ATC classification system (WHO, 2013) where abbreviations used on the y-axis represent the following classes of drugs: A = Alimentary tract and metabolism; B = Blood and blood forming organs; C = Cardiovascular system; D = Dermatologicals; G = Genito-urinary system and sex hormones; H = Systemic hormonal preparations; J = Anti-infectives; L = Antineoplastic and immunomodulating agents; M = Musculo-skeletal system; N = Nervous system; P = Antiparasitic products; R = Respiratory system; S = Sensory Organs; and V = Various.

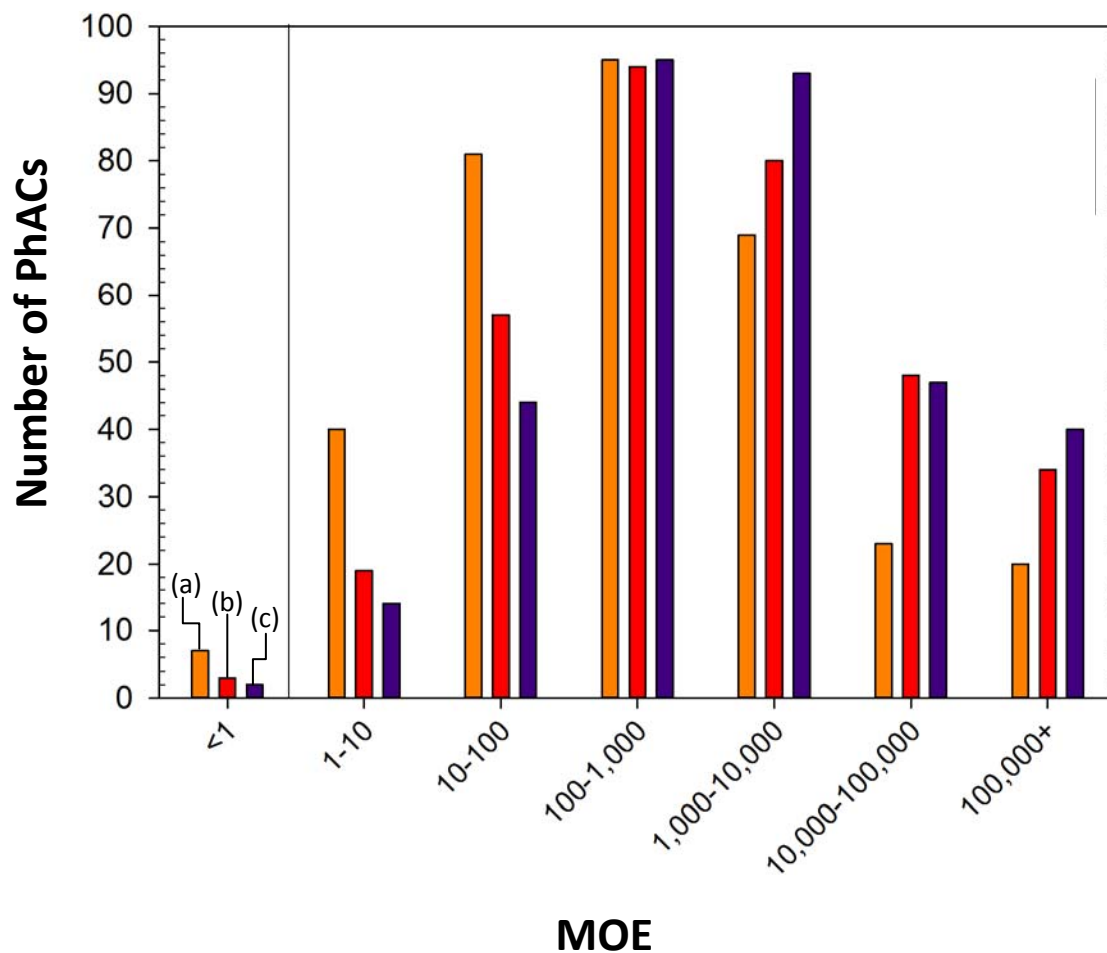


Figure 4.9: Margin of exposure, MOE, distribution when evaluated with PEC₁ (MOE_{p1} █), PEC₂ (MOE_{p2}, █) and PEC₃ (MOE_{p3}, █) estimates.

Notes: (a) includes: triiodothyronine, estriol, cocaine, morphine, estrone, thyroxine, ramipril; (b) includes: triiodothyronine, estriol, thyroxine; (c) includes: triiodothyronine, estriol.

negligible risk to human-health. All PhACs for which an ATC class could not be assigned (represented by “No Code”) were also found to pose a negligible risk to human-health. After Class L drugs, Class G drugs were found to have the second lowest median MOE_{p3} of 395, with specific estimates for this class of drugs ranging from nearly 18,000 for finasteride to 0.63 for estriol. In addition to estriol, estrone was the other Class G drug for which a MOE_{p3} of < 10 was predicted, all 15 other Class G drugs were found to pose a negligible risk. Also noteworthy was the fact that as many as 7 and 4 PhACs belonging to Classes C and N, respectively, were predicted to have MOE_{p3} values between 1 and 10 (see Figure 4.8 and Table 4.5). Of the seven Class H drugs evaluated only the two thyroid hormones were found to have MOE_{p3} estimates of less than 10 (see Figure 4.8 and Table 4.5). Specifically, a MOE_{p3} of 1.7 was estimated for thyroxine and 0.08 for triiodothyronine. Of all 21 Class M drugs evaluated, only ibuprofen was predicted to have a MOE_{p3} estimate of less than 10 (see Figure 4.8). Similarly, of all 26 Class A drugs evaluated only metformin was predicted to have a MOE_{p3} estimate of less than 10 (see Figure 4.8). All genotoxic carcinogenic PhACs of the evaluation set were also predicted to present a negligible risk.

Considering the highly conservative nature of PEC_3 estimates, and hence, estimates of MOE_{p3} , a prioritization evaluation was performed for all 15 PhACs for which a MOE_{p3} of less than 10 was estimated. The goal of this evaluation was to develop from the list of 15 PhACs, a sub-list of priority PhACs for which development of comprehensive ADI values, extensive monitoring in Canadian drinking waters and geo-spatially explicit contaminant fate modelling would be recommended. The results of the prioritisation evaluation are summarized in Table 4.5. Overall, each of the 15 PhACs were prioritized unless there was extensive MEC data ($n > 100$) in finished drinking waters suggesting negligible risk or, in the absence of extensive MECs, there was compelling evidence to suggest that the PhAC being considered was highly unlikely to reach drinking water intakes due to a high sorption and/or degradation potential.

Of the 15 PhACs, MECs in finished drinking water were only available for three: ibuprofen, estrone and estriol. MEC data for ibuprofen suggested that it poses negligible risk to human-health and therefore can be considered to not be a priority compound. However, given the fact that ibuprofen is the one PhAC that is detected with the highest frequency in finished Canadian drinking waters (see Table 4.3), it carries the potential to be used as an indicator compound for the contamination of Canadian drinking waters with PhACs. Extensive monitoring data ($n=236$) for estriol and estrone in Canada has only yielded zero and one positive detections, respectively. Therefore, these PhACs are essentially undetected in finished Canadian drinking water samples. This is to be expected as both estriol and estrone are known to degrade

Table 4.5: Prioritization of PhACs for future monitoring studies based on predicted and measured environmental concentrations.

PhAC	Predicted		Measured in drinking water		Potential to transport to drinking water intakes		Prioritize?
	PEC ₃ ^(a) ng/L	MOE _{p3} ^(b)	Detects/ Analyzed ^(c)	MOE _{m-max} = PNEC ^(d) /MEC _{max} ^(c)	Sorption ^(e)	Degradation ^(e)	
Triiodothyronine	2.4	0.08	n.m.		Sorption could not be modelled. Log D (@ pH 7.4) = 2.50	t _{1/2} = 60 d est.	Yes
Estriol	6.2	0.64	0/236	n.d.	Log K _{oc-sediment} = 2.99	t _{1/2} = 0.12 d	No. Extensive Canadian monitoring data is available without a single positive detection. Rapidly degrades once released into the aquatic environment.
Thyroxine	2.3	1.7	n.m.		Sorption could not be modelled. Log D (@ pH 7.4) = 2.89	t _{1/2} = 180 d est.	Yes
Estrone	1.7	2.3	1/237	4	Log K _{oc-sediment} = 3.44	t _{1/2} = 2.3 d	No. Extensive Canadian monitoring data is available with only a single positive detection. A photolysis product, lumiestrone, warrants further monitoring since it has been suggested that it is both estrogenic and persistent (73).
Ramipril	20	2.4	n.m.		Sorption could not be modelled. Log D (@ pH 7) = -0.16	t _{1/2} = 38 d est. 20-50% degradation of the compound seen after 28 days in an OECD 301 test.	Yes
Candesartan	15	2.6	n.m.		K _{d-sediment} = 2-4 L/kg	t _{1/2} = 95-222 d	Yes
Lisinopril	25	3.9	n.m.		Sorption could not be modelled. Log D (@ pH 7.4) = -1.81	t _{1/2} = 15 d est. 0% degradation of the compound seen after 28 days in an OECD 301 test.	Yes
Atorvastatin	81	4.8	n.m.		Log K _{oc-sediment} = 3.20	t _{1/2} = 6.6 d (Half-life observed in a microcosm)	Yes
Lorazepam	3.9	5.0	n.m.		Sorption could not be modelled. Log D (@ pH 7.4) = -1.81	t _{1/2} = < 1 d (Photolysis half-lives)	Yes
Fentanyl	0.6	7.0	n.m.		Log K _{oc} = 3.20 (est.)	t _{1/2} = 15 d est. Unstable in raw sewage.	Yes

Ibuprofen	1030	7.6	47/227	105	Log $K_{oc-sediment} = 2.08$	$t_{1/2} = 2.5 - 5$ d	No, extensive Canadian monitoring for the PhAC suggests negligible risk to human-health.
Atenolol	122	8.0	n.m.		Log $K_{oc-sediment} = 1.9 - 2.1$	$t_{1/2} = 2.3 - 30$ d	Yes
Metformin	3540	8.8	n.m.		Log $K_{oc} = 1.5$	$t_{1/2} = 8 - 9$ d	Yes
Enalaprilat	11	8.9	n.m.		Sorption could not be modelled. Log D (@ pH 7) = 2.50	$t_{1/2} \leq 1$ d (Photolysis half-lives)	Yes
Morphine	22	9.0	n.m.		Log $K_{oc-sediment} = 2.6 - 2.7$	$t_{1/2} = 0.3$ d	Yes
Irbesartan	126	9.3	n.m.		Log $K_{oc} = 2-3$	$t_{1/2} = 0.3 - 24$ d (Photolysis half-lives)	Yes

Notes: (a) Estimated using Eq. 2; (b) Estimated using Eq. 5; (c) Compilation of data from (32-38); (d) Estimated using Eq.4 with ADIs as those listed in Appendix O; (e) Refer to Appendix Q for the sources of the listed data; (f) n.m. not measured.

in the environment (16). In conjunction with the lack of detection of these PhACs, one must also recognize that the *p-ADI* developed in the current assessment for estrone and estriol of 0.00014 µg/kg·d is highly conservative (see Appendix O). Consider that the *ADI* for estradiol, due to its veterinary uses, has been estimated by the Joint FAO/WHO Expert Committee on Food Additives to be 0.050 µg/kg·d (see Appendix O), a level that is 360 times higher than the conservative *p-ADI* developed for estriol and estrone in the current assessment. Yet estrone and estriol have been suggested to be 10 and 27 times less potent than estradiol in binding to the alpha estrogen receptor (16). Overall, it is concluded that estrone and estriol should not be considered as compounds of concern for priority follow-up. However, a photolysis product of estrone, lumiestrone, has been shown to be estrogenic and persistent (73) and therefore warrants further consideration.

For the remaining 12 PhACs, no monitoring data was available in finished Canadian drinking waters and, further, there was no compelling evidence to suggest that their respective sorption and/or degradation potentials would prevent their loads from being transmitted to drinking water intakes (see Table 4.5). Therefore, it is concluded that they should be prioritized for further studies. Each of the 12 prioritized PhACs are briefly discussed below.

A MOE_{p3} of 0.08 was estimated for triiodothyronine, which is a thyroid hormone that is almost entirely released to the Canadian aquatic environment due to endogenous excretions (see Table 4.1). Upon its release to the environment, triiodothyronine is expected to be mobile and persistent (see Table 4.5) but it has yet to be monitored in drinking waters from Canada or elsewhere. In fact, to-date there is only the report of a single influent and a single effluent sample from a Finnish sewage treatment plant that have been analysed for the environmental presence of this PhAC (76). In both samples analyzed, triiodothyronine was found to be below the detection limit of 2-4 ng/L (76).

The MOE_{p3} for the other thyroid hormone, thyroxine, was estimated to be 1.7. Almost 94% of the load of thyroxine to the Canadian environment results from endogenous excretions (see Table 1). Thyroxine is also predicted to be persistent and sufficiently mobile upon its release to the environment (see Table 4.5 and (77)). To date environmental monitoring of thyroxine within the Canadian environment has not been conducted. In fact, the measurement of thyroxine has only been reported in a single influent and a single effluent sample from a Finnish sewage treatment plant (76). Thyroxine was detected in both the influent and the effluent at respective levels of 64 and 22 ng/L. If this effluent level is divided by a commonly-used dilution factor of 10, a surface water concentration of 2.2 ng/L can conservatively be estimated. If

further this surface water concentration of 2.2 ng/L is used as an exposure concentration a MOE of 1.8 (3.9 ng/L ($PNEC_{dw}$ for thyroxine divided by 2.2 ng/L) can be predicted.

A MOE_{p3} of 2.4 was estimated for ramipril, which is used for the treatment of hypertension and congestive heart failure. Ramipril is expected to be released to the Canadian aquatic environment primarily through its direct use in the general population, as only a small fraction of the PhAC is sourced through hospitals (see Figure 4.10). Upon its release to the environment, ramipril is expected to be mobile and subject to some degradation (see Table 4.5). Ramipril remains to be monitored in Canadian drinking or surface waters. However, an extensive monitoring campaign in France (78), failed to yield a single positive detection for Ramipril in 285 finished drinking water samples for a limit of detection of 5 ng/L. The PEC_3 estimated here for ramipril of 20 ng/L may have been overestimated due to an assumption made about the metabolism of the PhAC; that is, based on metabolic disposition data available for ramipril; it was unclear what fraction of the PhAC is excreted unchanged via the fecal route (see Appendix D). Therefore, it was conservatively assumed that the net fecal elimination of the PhAC of approximately 40% was in the form of unchanged ramipril. If this assumption had not been made, the PEC_3 estimate for ramipril would have only been 0.5 ng/L and, consequently, its MOE_{p3} would have been estimated at the negligible risk level of 98.

A MOE_{p3} of 2.6 was estimated for candesartan, which is typically used for the treatment of hypertension. Candesartan is primarily released to the Canadian aquatic environment through its use in the general population, with hospital use accounting for less than 1% of its environmental load (see Figure 4.10). Upon its release to the environment, candesartan is expected to be highly mobile and persistent (see Table 4.5 and (80)). Candesartan is yet to be monitored in Canadian environmental matrices. . Outside of Canada, only limited environmental occurrence data for this PhAC have been reported (79) but concentrations as high as 1,100 ng/L for candesartan have been reported in German surface waters (79). If this surface water maximum is conservatively taken as a reasonable estimate of exposure concentration, a MOE of 0.04 is calculated, which is well below the risk trigger level of 1.0 and, thus, could be of concern. Note that, on a per capita basis, the use of candesartan in Germany is nearly twice the level with which the drug is used in Canada (29, 30, 79).

Lisinopril is an angiotensin-converting enzyme-inhibiting PhAC that is typically used for the treatment of hypertension. A MOE_{p3} of 3.9 was estimated for lisinopril. Lisinopril is primarily released to the Canadian aquatic environment through its use in the general population, with only 2% of the environmental load coming from hospitals, (see Figure 4.10). Lisinopril is expected to be highly mobile

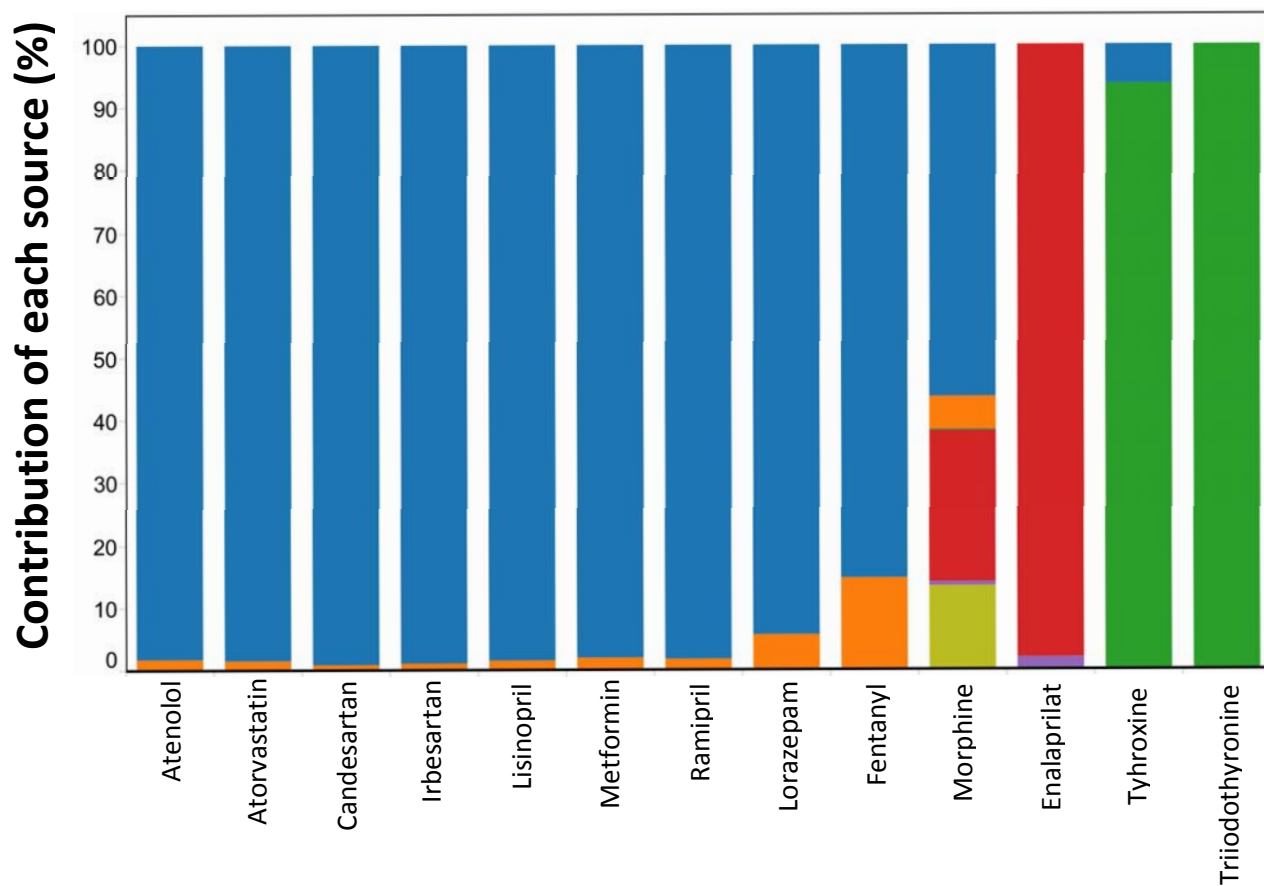


Figure 4.10: Sources of prioritized PhACs: M_{CG} (■); M_{CH} (■); M_{endo} (■); M_{OC} (■); M_{OH} (■); M_{OID} (■).

and persistent upon its release to environment (see Table 4.5). Canadian environmental matrices have yet to be monitored for the presence of lisinopril. Furthermore, no drinking water monitoring data for this PhAC even from locations outside Canada could be located in the literature. However, levels as high as 3,300 ng/L have been reported for this PhAC in effluents from sewage treatment plants in the USA (81). If this measured maximum is divided by a conservative dilution factor of 10, a highly conservative surface water concentration of 330 ng/L can be predicted. Further, if this surface water concentration is used as an estimate of the exposure concentration, a *MOE* of 0.3 (98 ng/L (*PNEC_{dw}* for Lisinopril) divided by 330 ng/L) can be predicted, which is below the trigger threshold of 1.0 and, therefore, could be of concern. That being said, the above evaluation is highly conservative.

Atorvastatin is a PhAC that is used to lower blood cholesterol. A *MOE_{p3}* of 4.8 was estimated for this compound. Atorvastatin is almost entirely released to the Canadian aquatic environment due to its use in the general population, with less than 1% of the PhAC being sourced through Canadian hospitals (see Figure 4.10). Upon its release to the environment, the environmental load of atorvastatin load would be expected to be somewhat attenuated due to sorption to sediments and degradation (see Table 4.5). Atorvastatin has yet to be monitored in Canadian drinking waters, but reports exist of it being monitored in Canadian surface waters. To date, 27 Canadian surface water samples have been analysed for the presence of atorvastatin (see Appendix P) in which atorvastatin was detected with a frequency of 33% and at a maximum concentration of 59 ng/L (see Appendix P). If this maximum concentration in surface waters is conservatively used as an estimate of exposure concentration, a *MOE* of 6.7 is calculated (390 ng/L (*PNEC_{dw}* for atorvastatin) divided by 59 ng/L). Analyses of eighteen American finished drinking water samples did not yield a single positive detection for atorvastatin (27). Furthermore, when the associated source waters were analyzed, atorvastatin was only detected in 2 of the 19 samples analyzed with a maximum of 2 ng/L (27). However, atorvastatin was reported to be present at a level of 1 ng/L in a finished drinking water sample from Spain (83). With a *MEC* of 1 ng/L, a *MOE* of 390 is calculated, thereby indicating negligible risk to human-health.

Lorazepam is a benzodiazepine that is used for the treatment of anxiety disorders. Lorazepam is predominantly expected to be released to the Canadian aquatic environment due to its use in the general population; however, as much as 6% of the PhAC is sourced through hospitals (see Figure 4.10). Upon its release to the environment, Lorazepam is expected to be mobile and subject to degradation (see Table 4.5). Canadian environmental matrices have yet to be monitored for the presence of lorazepam. However, lorazepam was not detected in finished French and Spanish drinking waters (82, 83). The per capita

consumption of lorazepam in France is similar to the level with which the PhAC is used in Canada (14, 28, 29).

Fentanyl is an opioid that is used as an anesthetic and to relieve pain. As much as 15% of the PhAC is sourced through Canadian hospitals, while the remainder is made available to the general population through pharmacies (see Figure 4.10). An environmental load of fentanyl would be expected to be attenuated due to sorption onto sediments and degradation (see Table 4.5). Fentanyl has yet to be monitored in Canadian surface or drinking waters. However, fentanyl was found to be below limits of quantification/detection in the influent and the effluent of a Canadian sewage treatment plant (84). Fentanyl was also not detected in finished Dutch and Spanish drinking waters (85, 86). However, an extensive survey of European effluents was able to detect fentanyl with a detection frequency of less than one percent and with a maximum concentration of 1.6 ng/L (90). It is also worth noting that, in the recent years, there has been a steady increase in the use of fentanyl in Canada (87), with an increase of 50% recorded over the period of 2005 to 2012 (87).

Atenolol is a beta blocker that is used for the treatment of cardiovascular diseases. It is primarily released to the Canadian environment through its use in the general population, with only 2% of the PhAC being sourced through hospitals (see Figure 4.10). Upon its release to the environment, atenolol is expected to be mobile and subject to degradation. Canadian drinking waters have yet to be monitored for the presence of atenolol. However, nineteen (19) Canadian surface water samples have been analysed for the presence of this PhAC (see Appendix P). In these samples, atenolol was detected with a frequency of 47% and at a measured maximum concentration of 53 ng/L (see Appendix P). If the measured maximum in surface water of 53 ng/L is conservatively taken as an exposure concentration, a *MOE* of 18 is calculated, indicating negligible risk. Atenolol has been detected in finished drinking waters in the USA with a maximum concentration of 26 ng/L (1). In contrast, atenolol was not detected in English and French finished drinking waters when analysed with detection limits of 2 and 25 ng/L, respectively (78, 88).

Metformin is an anti-diabetic drug for which a *MOE*_{p3} of 9.0 was estimated (see Table 4.5). Metformin is almost entirely released to the Canadian aquatic environment due to its use in the general population (see Figure 4.10). Upon its release to the environment, metformin is expected to be mobile and subject to some degradation (see Table 4.5). Metformin has yet to be monitored in Canadian drinking and surface waters, but it has been monitored in the influent and effluent of a Canadian sewage treatment plant equipped with a membrane bioreactor (89) and the discharges of untreated wastewater by the city of Victoria in the

Province of British Columbia (99). Metformin was measured in concentrations as high as 110,000 ng/L in one of the discharges of untreated wastewater from the city of Victoria (99). Outside Canada, metformin was not detected in finished Dutch drinking waters when sought using an analytical method with a detection limit of 50 ng/L (75).

Enalaprilat is an angiotensin-converting-enzyme (ACE) inhibitor that is typically used for the treatment of hypertension and certain types of chronic heart failures. Even though enalaprilat is clinically used in Canada (30), almost the entire load of the PhAC in the Canadian environment is expected to be due to the use of the precursor pro-drug enalapril (see Appendix K). Enalapril, and therefore enalaprilat, is primarily used in the general population with a relatively minor fraction of the PhAC being sourced through hospitals (see Figure 4.10). Upon its release to the environment, enalaprilat is expected to be mobile and subject to degradation (see Table 4.5). Canadian environmental matrices have yet to be monitored for the presence of enalaprilat. Further, no drinking water monitoring data for the PhAC from locations outside of Canada could be identified. However, levels as high as 150 ng/L have been reported for this compound in effluents from sewage treatment plants in the USA (81). If this measured maximum is divided by a dilution factor of 10, a highly conservative surface water concentration of 15 ng/L is predicted and, a *MOE* of 6.5. Note that enalaprilat is poorly bioavailable upon oral ingestion (58) and this is one of the reasons for why enalaprilat is clinically administered via intravenous injections.

Morphine is an opioid that is typically used as a painkiller. As discussed earlier and summarized in Figure 4.4, morphine in the Canadian environment arises from a number of sources. Of these, the single most important source is the use of morphine itself in the general population (Figure 4.4 and 10). However, other sources still account for an estimated 42% of the net environmental load (see Figure 4.10). Upon its release to the environment, morphine is expected to be mobile and liable to significant degradation (see Table 5). To-date, morphine has not been monitored in Canadian surface or drinking waters, however it has been measured in effluents from Canadian sewage treatment plants at levels as high as 69 ng/L (74). If this maximum concentration measurement is divided by a dilution factor of 10, a highly conservative surface water concentration of 6.9 ng/L is predicted along with an *MOE* of 28, indicating negligible risk. Outside Canada, morphine was not detected in finished Dutch and German drinking waters (72, 86).

Irbesartan is a drug that is used for the treatment of high blood pressure and certain kidney diseases. Irbesartan is primarily released to the Canadian aquatic environment due to its use in the general population, with hospitals being a minor source for the PhAC's environmental load. Upon its release to the environment, irbesartan would be expected to be mobile and possibly liable to degradation (see Table

4.5). Canadian environmental matrices have yet to be monitored for the presence of Irbesartan. Outside Canada, irbesartan could not be detected in finished Spanish drinking waters (59, 82). However, an extensive survey of European effluents was able to detect irbesartan with a 100% detection frequency and a maximum of 17,900 ng/L (90).

It is worth noting that of the 12 prioritized PhACs, $ADIs$ for 8 PhACs were ultimately estimated using respective $LOTD$ values and a highly conservative safety factor, SF , of 10,000. Specifically, these PhACs were: triiodothyronine, thyroxine, ramipril, lisinopril, atorvastatin, lorazepam, atenolol and enalaprilat (see Appendix O). A SF of 10,000 was used for triiodothyronine and thyroxine because they are endogenous thyroid hormones. For the other six PhACs a SF of 10,000 was used because they were either pregnancy class D or X drugs. However, had the default SF of a 1,000 been used instead, MOE_{p3} for 7 PhACs listed above would have been estimated at negligible risk levels (i.e., $MOE_{p3} > 10$), while the MOE_{p3} for triiodothyronine would have still remained below the trigger limit of 1.0 for possible risk. Nevertheless, since the goal here was to prioritize the human-health risk of PhACs in a manner that false negative classifications were minimized the use of highly conservative SF remains. That being said it is important to appreciate the conservative nature of our analysis, both in estimating exposure and accounting for effects on human-health.

Overall, our results are consistent with those reported by others (1, 4, 15-25) in that most PhACs, even when evaluated highly conservatively, are deemed unlikely to pose a human-health risk. Interestingly, lisinopril, atenolol and enalaprilat, three PhACs prioritized here, were also among the six shown to pose the highest relative, yet low, risk to the health of the population in the USA (81).

A limitation of evaluations performed with MOE_{p3} estimates, as has been the focus thus far, is that the risk outcome for a give PhAC could be highly sensitive to the assumptions made about its metabolic loss and removal in sewage treatment plants. Therefore, it is also of value to perform risk evaluations with PEC_1 estimates to see for which PhACs a risk outcome of “possible risk” resides in assumptions made about their metabolic loss and removal in sewage treatment plants. Such an evaluation, which is sometimes referred to as the total residue approach, conservatively assumes that a given PhAC’s metabolites and transformation products are as potent as the PhAC itself and further assumes that the total residue is not removed in sewage treatment plants.

The results of a risk evaluation based on PEC_1 estimates (MOE_{p1}) are summarized in Figure 4.9. The results show that if the total residue approach is assumed, only seven PhACs of the evaluation set would yield a MOE_{p1} value less than the trigger limit of 1.0 for “possible risk”. Specifically, these seven PhACs

were triiodothyronine, estriol, cocaine, morphine, estrone, thyroxine and ramipril (see Figure 4.9). As discussed earlier, triiodothyronine and estriol also trigger “possible risk” based on PEC_3 estimates (see Figure 4.9). An evaluation with PEC_2 estimates (i.e. considering metabolic losses but discounting removal in sewage treatment plants) triggers possible risk for thyroxine as well as triiodothyronine and estriol (see Figure 4.9). Therefore, the possible risk outcomes of cocaine, morphine, estrone and ramipril reside in assumption made about their metabolism, while that for thyroxine resides in assumptions made about its metabolism and subsequent removal in sewage treatment plants. Of the latter five PhACs, estrone likely poses a negligible risk to human-health, as discussed earlier.

Cocaine is extensively metabolized by humans with between less than 1% and 8% of the drug being excreted unchanged (12). Of the various metabolites of cocaine, only norcocaine and cocaethylene are active (94). Norcocaine is twice as potent as cocaine, while cocaethylene is equipotent (86, 94). However, only less than 0.1% and 0.7% of an administered dose of cocaine are excreted as norcocaine and cocaethylene, respectively (12). In a number of investigations, it has been shown that cocaine undergoes significant depletion in sewage treatment plants (84). Canadian surface or drinking waters have yet to be monitored for the presence of cocaine or its active metabolites. However, cocaine could not be detected in finished Dutch and English drinking waters (86, 88). In contrast, cocaine has been detected in tap waters in unidentified locations by Boleda et al. (92) to a maximum of 2.9 ng/L, which translates to an estimated *MOE* of 64 representing a negligible risk. Norcocaine could not be detected in finished Dutch and Spanish drinking waters (86, 92). Cocaethylene was detected to a level of 0.9 ng/L in Spanish tap waters and not detected in finished Dutch drinking waters (86, 92). An exposure concentration of 0.9 ng/L for cocaethylene translates to a negligible risk *MOE* of 192 (187 ng/L (i.e., the $PNEC_{dw}$ for cocaine - since cocaethylene is equipotent - divided by 0.9 ng/L). Overall, it appears that cocaine and its active metabolites are unlikely to be present in Canadian drinking waters at levels that results in risks to human health.

The remaining three PhACs, morphine, thyroxine and ramipril were already among the list of PhACs prioritized through a risk evaluation with MOE_{p3} values. Nevertheless, their metabolism and removal in sewage treatment plants warrants further discussion.

Morphine largely results from its direct clinical use and the clinical and illicit use of its precursors (see Figure 4.4). For the PEC_1 estimate for morphine, it was conservatively assumed that the entire mass of morphine itself and its clinical and illicit precursors end up in the environment as morphine. Therefore, the PEC_1 estimate for morphine not only accounts for the total residue of morphine, but also of its

precursors. This results in a highly artificial, yet conservative, estimate of PEC_1 for morphine. Morphine is primarily excreted by humans as its glucuronide conjugates (12). Since such conjugates are known to revert to the parent compound upon their release to the environment (12), they were considered as the parent compound when PEC_2 and PEC_3 estimates were calculated for morphine. The only other active metabolite of morphine is normorphine, which has been suggested to be one-fourth as potent as morphine (93). Additionally, less than 5% of an administered dose of morphine is excreted as normorphine (12). Normorphine is yet to be monitored in Canadian environmental matrices. However, it was not detected when sought for in tap waters from a number of countries (92).

Ramipril is in fact a pro-drug for the active metabolite ramiprilat (30). Approximately 9% of an administered dose of ramipril is eliminated via urine and bile as ramiprilat and its glucuronide conjugate (95). Much like ramipril, ramiprilat has not been monitored to-date in Canadian environmental matrices. However, an extensive monitoring campaign of finished drinking waters in France found ramiprilat in a single sample of the 285 samples analyzed. Specifically, the single positive detection was between the study's limit of detection (not reported) and the limit of quantification (5 ng/L). Ramiprilat was found in 2 of the 285 samples source water samples analyzed, again at levels between the limit of detection and the limit of quantification for the study. Other than this study, little monitoring data has been reported for the environmental occurrence of ramiprilat. Recognizing this, ramiprilat is included in the list of priority compounds that warrant further study.

Thyroxine is primarily released to the Canadian environment through endogenous excretions (see Table 1). Nevertheless, important uncertainties are present in arriving at the net environmental load for this PhAC (see Appendix F). In addition, the treatment plant removal rate used for this PhAC results from the analysis of a single sample (76). Therefore, these uncertainties with respect to the environmental fate and loading of thyroxine indicate that further study of this PhAC is warranted.

4.3.9 Veterinary Contributions

In Canada, the aquatic releases of 31 of the 335 PhACs in the evaluation set are also expected to result from veterinary sources since these compounds are either endogenously excreted by animals (e.g., estrone) and/or are exogenously administered or fed to animals (e.g., erythromycin) (see Table 4.6). Extensive *MEC* data for a PhAC, if available, can be taken to include veterinary sources, but such sources were not considered in the *PEC* estimates calculated here. Of the 31 PhACs for which veterinary contributions are expected, extensive *MEC* data was only available for six of them (see Table 4.6). For these six, an evaluation using *MEC* values has already suggested that they pose a negligible risk to

human-health (see Table 4.4 and 4.6). Therefore, the release of these PhACs from human and veterinary sources likely represents a negligible risk to human-health due to their potential presence in finished drinking waters.

Of the remaining 25 PhACs, limited ($n > 10$ and < 100) and scant ($n > 1$ and < 10) *MEC* data was available for 3 and 2 PhACs, respectively, while for 20 PhACs no *MEC* data was available at all (see Table 4.6). In the absence of sufficient *MEC* data, the potential for the unaccounted veterinary contributions to push the *MOE* values for these PhACs to “possible risk” levels can be evaluated by considering the magnitude of their respective *MOE_{p3}* values. With the exception of thyroxine and triiodothyronine, the respective *MOE_{p3}* values are such that it is highly unlikely that the unaccounted for veterinary contributions for a listed PhAC are such that they will increase the *MOE* estimate to significant risk levels (see Table 4.6). As an example of the logic used here, consider the PhAC amoxicillin, it is highly unlikely that the mass of amoxicillin administered for veterinary purposes (Note: amoxicillin is not used in feeds) in Canada is such that, upon its inclusion in calculations, it would decrease its *MOE* from the value of 28 to a level less than the trigger limit of 1.0. For the two thyroid hormones, thyroxine and triiodothyronine, it seems likely that veterinary contributions could significantly add to their risk levels, given that their respective *MOE* values based on human sources alone already are just above or and an order of magnitude below the risk trigger value of 1.0, respectively.

Even though, with the exception of the thyroid hormones, it is unlikely that the 31 PhACs listed in Table 4.6 will be used at such levels for veterinary purposes that they will end up posing human-health risks due to their potential presence in finished drinking waters, it is still worth highlighting that a significant fraction of several of the PhACs listed in Table 4.6 could result from veterinary sources.

Table 4.6: PhAC of the evaluation set that are also expected to be released to the Canadian aquatic environment through veterinary sources in addition to their human sources

PhAC	ATC Class	Veterinary Sources		Measured		Predicted
		Exogenous use	Endogenous excretion	n/p ^(c)	MOE _{m-max} ^(d)	MOE _{p3} ^(e)
Extensive MECs	Estrone	G	✓	237/1	4	2.3
	Estradiol	G	✓	237/0	Not detected	1,500
	Estriol	G	✓	236/0	Not detected	0.6
	Trimethoprim	J	✓	221/1	7,733	3,700
	Tetracycline	J	✓	214/5	5,500	1,600
	Erythromycin	J	✓✓	214/13	890	8,400
Limited MECs	Testosterone	G	✓	68/0	Not detected	13,000
	Pentoxifylline	C	✓	63/0	Not detected	101,000
	Penicillin G	J	✓✓ ^(b)	32/0	Not detected	84
Scant MECs	Sulfapyridine	J	✓	4/0	Not detected	113
	Enalapril	C	✓	3/0	Not detected	59
No MECs	Triiodothyronine	H	✓	-		0.1
	Thyroxine	H	✓	-		1.7
	Docusate	A	✓ ^(a)	-		15
	Amoxicillin	J	✓	-		28
	Levodopa	N	✓	-		38
	Dihydrotestosterone	No code	✓	-		120
	Hydrocortisone	D	✓	-		260
	Ampicillin	J	✓	-		640
	Androstenedione	No code	✓	-		1,400
	Atropine	S	✓	-		1,600
	Dexamethasone	H	✓	-		2,200
	Lidocaine	C	✓	-		3,000
	Prednisolone	S	✓	-		3,500
	Acetylsalicylic Acid	N	✓	-		4,500
	Ketoprofen	M	✓	-		9,100
	Methylprednisolone	H	✓	-		9,900
	Selegiline	N	✓	-		36,000
	Gentamicin	J	✓	-		60,300
	Omeprazole	A	✓	-		74,000
	Chlorhexidine	D	✓	-		148,000
	Neomycin	J	✓✓	-		9,540,000

Notes: (a) (✓) = is a source (30); (b) (✓✓) = expected to be a significant sources since the PhAC is authorized for use in animal feed (96); (c) Based on data compiled from the following sources: (32-38), n = number of samples analyzed, p = number of positive detections; (d) See Table 4.4 for further details; (e) Estimated using Eq. 5.

Anderson et al. (11) estimated that, depending on the assumptions made for what fractions of veterinary excretions are routed to surface waters, the mass of estrogens (i.e., estrone, estradiol and estriol) contributed by veterinary sources to surface waters in the USA could vary from as little as 29% to as much as 91% of the net load of such PhACs. An equivalent analysis for Canada remains to be performed. In addition to estrogens, a significant fraction of the surface water loads of a number of antibiotics may result from veterinary sources. In Canada, nine PhACs, share veterinary and human uses (see Table 4.6); however, it is only the antibiotics used in animal feeds that are expected to have a significant veterinary contribution. Of the nine, only neomycin, penicillin G and erythromycin are approved for use in animal feeds on Canadian farms (96). Due to the lack of input data, it is currently not possible to estimate for each of these three PhACs what fraction of their respective surface water loads arises from veterinary as opposed to human sources. However, the net mass of antibiotics used in Canada for veterinary purposes is available (59) and this can be used with the net mass of antibiotics used by humans (28, 29) to estimate, that during 2006, the staggering amount of nearly 2,000 tonnes of antibiotics were used in Canada (see Figure 4.11). Alarming, 88% of this mass was used for veterinary purposes, another 10% was used for clinical purposes in the general population, and the remaining 2% was sourced through hospitals. Due to an importation loophole in Canada (97), some estimate that the use of antibiotics for veterinary purposes may be 33% higher than 1,766 tonnes shown in Figure 4.11. If this is true, the total mass of antibiotics used in Canada could be 30% higher and the net veterinary contribution to the total load could be as high as 90%. This estimate clearly highlights the need to account for veterinary sources for certain compounds.

4.3.10 Sufficiency of Existing Monitoring Data

As indicated earlier, nearly 6,000 analyses covering 47 PhACs, have been performed in Canada to evaluate the presence of PhACs in Canadian drinking waters. This raises the question as to whether the existing monitoring data is sufficient. Specifically, it is worth asking the question, are we monitoring what needs to be monitored?

Ultimately, the need to monitor a PhAC should reside in the risk posed. Table 4.5 suggests that of the 15 PhACs found to have a MOE_{P3} evaluations less than 10, extensive monitoring data was only available for three (i.e., estriol, estrone and ibuprofen), whereas no monitoring data in Canadian drinking waters was available for the remaining 12. Further, of those 12, only atenolol and atorvastatin have been sought in a limited number of Canadian surface waters (See Appendix P). Therefore, most PhACs which pose a relatively high human-health risk have yet to be monitored in Canada drinking water supplies.

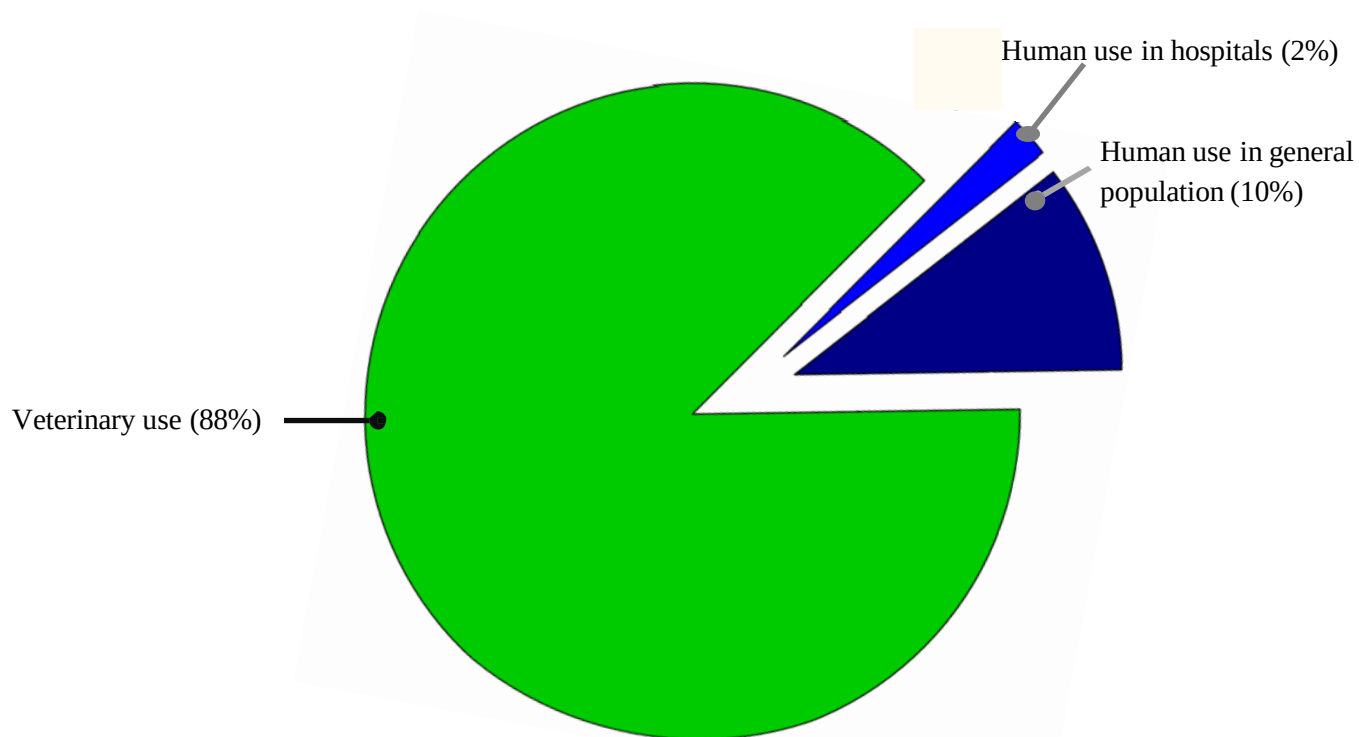


Figure 4.11: Distribution of antibiotics use in Canada. Total consumption was 2,000 tonnes in 2006.

Notes: Human use in the general population and hospitals was estimated from IMS Brogan Data (28, 29), veterinary use as that reported by Canadian Animal Health Institute (57).

A case can also be made to monitor those PhACs that are expected to be found at the highest concentrations in the environment and, therefore, carry a higher potential to end up in drinking waters (98). Again the existing monitoring data is found to be wanting (see Table 4.2) in that most PhACs predicted to occur in the Canadian environment at high concentration are yet to be monitored in Canadian surface and drinking waters while for others only limited data has been reported thus far. Consider that of the top 50 PhACs in terms of PEC_3 estimates only eight have been extensively monitored in Canadian surface and drinking waters (see Table 4.2). In fact, among this list of top 50 PhACs, no monitoring data is available for 34 and 40 PhACs in Canadian surface and drinking waters, respectively (see Table 4.2). Christian Daughton of the United States Environmental Protection Agency has also highlighted the limitations of the existing monitoring data for PhACs (98) in that most PhACs expected to be found in the environment at high levels have yet to be monitored or have only been analysed in a limited number of samples.

One could also make the case that the most potent PhACs (i.e., with lowest $PNEC_{dw}$ values) should be monitored. Of the 50 most potent PhACs of the evaluation set, only six and five of them have been monitored in Canadian surface and drinking waters, respectively.

Overall, it is clear that whether the evaluation is based on risk posed, predicted exposure concentrations or potency, the existing monitoring data is found wanting.

4.4 CONCLUSIONS

This research has focused on developing an understanding of the sources of PhACs to the environment and on evaluating their human-health relevance with respect to their potential presence in drinking water. The approaches and models developed in this study were applied to an evaluation set of 335 PhACs in the Canadian context to establish the following:

- Hospital contributions to the net load of individual PhACs were found to vary significantly from one case to another. For most PhACs, hospitals appeared to be a minor source. However, for 41 PhACs greater than 70% of their respective environmental loads was estimated to be sourced through hospitals. Class L and Class V drugs of the evaluation set were found to be sourced primarily through hospitals.
- Of the 14 PhACs for which endogenous contributions were found to be relevant, nine were established to predominately to almost entirely result from endogenous sources.

- Of the 6 PhACs for which illicit contributions were found to be relevant, five were established to predominately to almost entirely result from illicit sources.
- Class J and Class P drugs of the evaluation set were found to be the two drug classes with highest median predicted exposure concentrations when accounting for removal through removal through human metabolism and wastewater treatment. Therefore, on average, PhACs belonging to these drug classes are expected to be present in the environment in the highest concentrations. In contrast, Class L drugs were estimated to be the least abundant in the environment.
- Class L and Class G drugs of the evaluation set were established to be the most potent in their potential to cause human-health effects. Conversely, Class J and Class M drugs were established to be the least potent in their potential to yield human-health effects.
- A compilation of measurement data indicates that 20 PhACs have thus far been detected in Canadian finished drinking waters with an overall detection frequency of only 3%.
- *ADIs* or *TDIs* were only available for 31 PhACs and, thus, for the remaining 303 PhACs provisional *ADIs* were developed. Of these, *ADI* values for 133, 164, 3 and 3 of the PhACs were based on *LOTD*, *OEL*, *NSRL* and *LTD₁₀* values, respectively. For 220 PhACs, both *LOTD* and *OEL* values were available and in nearly 70% of these cases an *OEL*-based approach yielded the more conservative *p-ADI*.
- A risk evaluation based on measurements could only be performed for 17 PhACs and all of them were found to pose a negligible risk to human-health. The same risk evaluation but based on predictions, rather than measurements, suggested that 323 PhACs of the evaluation set are expected to pose a negligible risk to human-health due to their potential presence in drinking waters. However, the following 14 PhACs warrant prioritization for further study: triiodothyronine, thyroxine, ramipril and its metabolite ramiprilat, candesartan, lisinopril, atorvastatin, lorazepam, fentanyl, atenolol, metformin, enalaprilat, morphine and irbesartan.
- The currently available monitoring data for PhACs in Canadian surface and drinking waters was found to be wanting irrespective of whether their suitability was assessed based on risk posed, predicted exposure concentrations, or potency resulting in human-health effects.

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Chapter 5: Contraceptive Options and their Associated Estrogenic Environmental Loads: Relationships and Trade-offs

PREFACE

In Chapters 2 to 4, the use of a given PhAC, and hence its environmental release, was taken to result in some environmental and/or human-health risk. By logical extension, it can often be assumed that the elimination of the use of a PhAC would result in the negation of risk. Even though such an assertion largely holds true for many individual PhACs, it cannot be applied to a group of PhACs whose sources and environmental impacts are inter-related. This chapter demonstrates this by addressing the objective of the thesis related to developing and applying an approach to better understand and evaluate the relationships and trade-offs involved between a population's contraceptive choices and the respective loads of steroidal estrogens to the environment. Some of the questions explored to achieve this objective were as follows:

- Should estrogenic loads only be associated with the use of those contraceptive options that are themselves estrogen-based?
- Does the use of a given contraceptive option avert or lead to the release of estrogens to the environment?
- Does contraception, including the numerous approaches available for this purpose, collectively avert or lead to the release of estrogens to the environment?
- When current users of estrogen-based oral contraceptives discontinue the use of their option, should the resulting associated estrogenic load be expected to increase or decrease?
- Are there contraceptive options whose use can allow the population to simultaneously meet environmental, public health and family planning objectives?
- Should the issue of estrogenic loading to the environment be addressed by altering the contraceptive choices available to a population?

The appendices for this chapter can be found at the end of this thesis.

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Contraceptive Options and their Associated Estrogenic Environmental Loads: Relationships and Trade-offs

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ABSTRACT

This work explores the relationships between a user's choice of a given contraceptive option and the load of steroidal estrogens that can be associated with that choice. Family planning data for the USA served as a basis for the analysis. The results showed that collectively, the use of contraception in the USA conservatively averts the release of approximately 4.8 tonnes of estradiol equivalents to the environment. 35% of the estrogenic load released over the course of all experienced pregnancies events and 34% the estrogenic load represented by all resultant legacies are a result of contraception failure and the non-use of contraception. A scenario analysis conducted to explore the impacts of discontinuing the use of ethinylestradiol-based oral contraceptives revealed that this would not only result in a 1.7-fold increase in the estrogenic loading of the users, but the users would also be expected to experience undesired family planning outcomes at a rate that is 3.3 times higher. Additional scenario analyses in which ethinylestradiol-based oral contraceptive users were modeled as having switched entirely to the use of male condoms, diaphragms or copper IUDs suggested that whether a higher or lower estrogenic load can be associated with the switching population depends on the typical failure rates of the options adopted following discontinuation. And, finally, it was estimated that in the USA, at most, 13% of the annual estrogenic load can be averted by fully meeting the contraceptive needs of the population. Therefore, while the issue of estrogen impacts on the environment cannot be addressed solely by meeting the population's contraceptive needs, a significant fraction of the estrogenic mass released to environment can be averted by improving the level with which their contraceptive needs are met.

KEYWORDS: Contraception, Estrogen, Unintended pregnancy, Birth control pill, Wastewater

5.1 INTRODUCTION

The environmental release of natural and synthetic steroidal estrogens is of concern because it is suspected that these compounds are major causative agents of fish feminization and other associated environmental impacts [1-10]. Consequently, ethinylestradiol (EE_2), the synthetic estrogen used in birth control pills, and estradiol (E_2), the most potent natural estrogen, are being considered for regulation by the European Union with proposed Environmental Quality Standards of 35 and 400 pg/L, respectively [11], [12]. Proposed Swiss standards are very similar [13]. However, an industry led effort [14] proposed no-effect benchmarks for these estrogens at levels that are significantly higher than those proposed by the European Union and Switzerland.

EE_2 is primarily released due to its use in predominant oral contraceptives and, more recently, due to its use in transdermal patches and vaginal rings [15]. In addition to being endogenously produced, E_2 is released into the environment through the use of hormone replacement therapy (HRT) preparations and recently due to the use of NataziaTM, a one-of-a-kind combined oral contraceptive (OC) pill containing E_2 instead of EE_2 as the estrogen [15-21]. Two other steroidal estrogens, namely estrone (E_1) and estriol (E_3), have also recently drawn regulatory interest [22]. In addition to being endogenously produced, E_1 and E_3 are released into the environment due to their use in various HRT preparations [16-19].

Approximately 1,970 kg of estrogens, expressed as estradiol equivalents (E_{2-eq}), are released each year to sewage treatment plants in the United States of America (USA) for treatment (Figure 5.1). Of this mass, after undergoing wastewater treatment, an estimated 260 kg of E_{2-eq} are discharged to waterways in the USA. Forty days after release, which is a typical residence time of a wastewater parcel in rivers [23], only 3 kg of the original discharged E_{2-eq} load are expected to remain (Figure 5.1). Of particular note is the fact that the release of natural estrogens due to all pregnancy-related events accounts for 59% of the post-treatment load and an additional 16% of this load arises due to the direct release of EE_2 from the use of oral contraceptives (Figure 5.1). However, EE_2 is considerably more persistent than E_1 , E_2 and E_3 [17], [24], [25] and, hence, even though the net E_{2-eq} river laden load will decrease over time, the fraction of that load that is due to residual presence of EE_2 will steadily increase from 16%. For example, consider that after 40 days, it is estimated that only about 1% of the initially released load would remain, but almost 100% of this load would be due to the residual presence of EE_2 (Figure 5.1). Hence, the loads that arise from pregnancy-related events and those released due to the use of EE_2 are important.

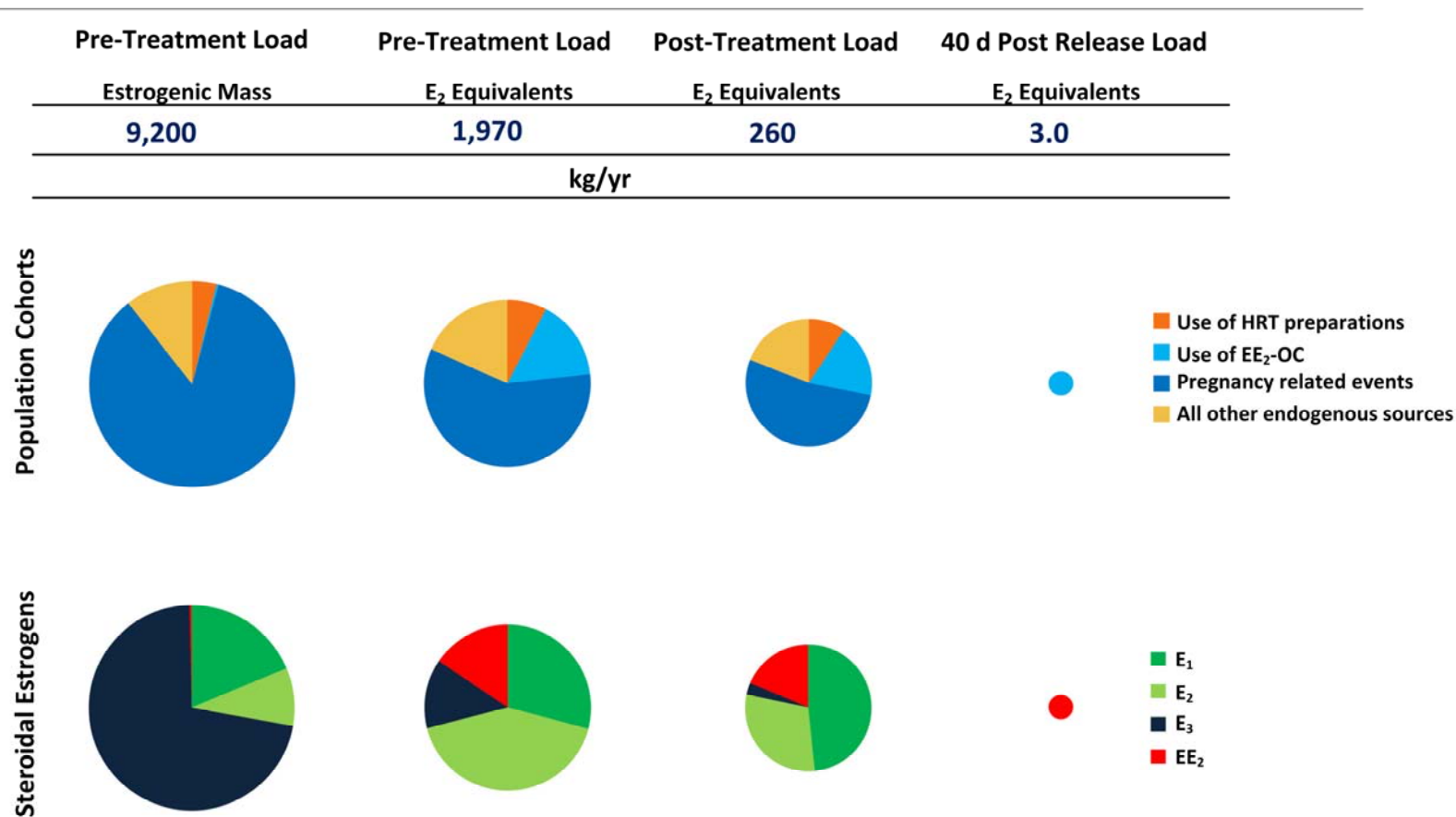


Figure 5.1: Estimated Steroidal Estrogen Loads in the USA circa 2002. The relative size of the pie charts is proportional to the logarithm of the estimated loads. Estrogen masses were estimated using the data compiled in Section SI-1. Estradiol (E₂) equivalents were estimated by summing the respective mass loads of each estrogen, weighted according to their estrogenic potencies relative to estradiol, as follows: $[E_1]/3 + [E_2] + [E_3]/2 + 10 \cdot [EE_2]$. The justifications for potencies weightings used in this equation are detailed in Section SI-2.

To-date, estrogen loads arising from all pregnancy-related events and those arising from the release of EE₂ due its use in oral contraceptives have been treated as mutually independent in literature [16], [26-28]. We contend that this is problematic since it leads to the misconception that the use of an ethinylestradiol-based oral contraceptive (EE₂-OC) is the only form of contraception that has an estrogenic load associated with its use and, by extension of this, other forms of contraception are presumed to not have any associated estrogenic loads. This misinterpretation largely arises from the belief that the use of a particular contraceptive option only results in an estrogenic load if the option itself is estrogen-based [26], [27]; however, this is not entirely true given that every contraceptive option fails to some extent [29]. Such failures lead to unintended pregnancies, the result of which is a temporary increase in the excretion of natural steroidal estrogens over the course of the pregnancy. Hence, at the very least, the choice to use each contraceptive option has a load of natural steroidal estrogens associated with its use. Therefore, it can be said that a fraction of the overall pregnancy load, which by far is the single most important contributor to the net estrogenic load (Figure 5.1), results from the failure of contraceptive choices made by the population. Consider that nearly half of the pregnancy events experienced in the USA are unintended [30], [31]. However, the fraction of the estrogenic load released over the course of all pregnancy events that are unintended (and, hence, are due to the failure and non-use of methods of contraception) remains to be quantified.

The recognition that each contraceptive option has an estrogenic load of natural hormones associated with its use leads to an important question: that is, how do the estrogenic loads associated with various contraceptive options compare? For example, consider the work of Wise et al. [26] who suggested that one way of reducing the EE₂ load on the environment would be for some EE₂-OC users to switch to non-hormonal methods of contraception such as copper intrauterine devices (copper IUD), diaphragms, or male condoms. As much as this suggestion holds true when considering the direct release of EE₂ alone, the recognition that each contraceptive option has an indirect estrogenic load associated with its use (i.e., due to the failure of the option) requires that suggestions such as those of Wise et al.'s be reevaluated with a renewed focus. That is, it should be asked how the total environmental load of steroidal estrogens would likely change if a given group of users switched from using EE₂-OC to such alternative methods. Moreover, the change in the overall load of steroidal estrogens should be estimated for those EE₂-OC users who discontinue the use of their current contraceptive option by switching to other methods or by abandoning the use of contraception altogether (Note: currently, one-third of the EE₂-OC users discontinue the use of their option within the first year [29]). The objective of such an evaluation would be to assess the change in the associated estrogenic loading of an EE₂-user when she chooses to

discontinue the use of her current option. The impacts of such decisions on estrogenic loading of an EE₂-user have yet to be conceptually recognized or mathematically modeled in literature.

Furthermore, not only does the use of each contraceptive option have an estrogenic load associated with its use, but the use of each also prevents an estrogenic load from being released to the environment. That is, given that the use of every contraceptive option, when compared to not using any method at all, averts a number of pregnancies [29], this prevents a load of natural estrogens from being released to the environment from the averted pregnancies and by subsequent generations of offspring. Therefore, it can be qualitatively stated that a population's use of each non-estrogen based contraceptive method on a net basis prevents the release of an estrogenic load to the environment. Such an assertion is not directly applicable for those contraceptive options that are themselves estrogen-based since the use of such estrogens-based options invariably involves estrogenic loading trade-offs. Consider that, on the one hand, the use of such options averts an estrogenic load from being released through the prevention of pregnancies and, on the other hand, their use leads to the direct release of estrogenic load via the excreta of respective users. Such considerations have largely remained unacknowledged in the literature to-date and, hence, no estimates, or models to arrive at them, are currently available to quantify the total estrogenic load that is averted through a population's collective use of contraception or specifically averted through the use of each given option.

The above discussion highlights why it is necessary that the relationships between the choice of using a given contraceptive option and the associated estrogenic load should be examined in more than a cursory fashion. This is especially important given that the regulation of steroidal estrogens, and most particularly that of EE₂, is likely to engender considerable public debate [27], [32-35], [65] with important implications for both the environment and human reproductive health. Thus, a better understanding of the relationships between contraceptive options and their associated loads of steroidal estrogens on the environment is required in order to fully inform this debate. This is the overall objective of the present study. Note that, in order to put the importance of the estrogen load for each contraceptive option into a proper perspective, other considerations with respect to parental planning and public health implications will be briefly discussed, where relevant.

5.2 METHODS AND MODELS

Unless otherwise indicated, all estrogenic loads discussed below are calculated on a pre-treatment basis; i.e., loads discharged by a population into the sewer system prior to their treatment and/or release into the

environment. While the models developed in this study were developed to be universally applicable, the parameterization of the models and their application were performed using data from the USA, for which extensive data sets were available. The reference year for most data is circa 2002.

5.2.1 Estrogenic Equivalents

Since estrogens act in an additive manner [36] and since the eco-toxicological potency of all estrogens is not equal [11], [12], [17], [18], [24], [36] there is a need to express the mass loads of the various estrogens on an equivalence basis. In the present study, the net estrogenic loads are expressed as equivalents of estradiol ($E_{2\text{-eq}}$), the most potent natural estrogen. Specifically, for this evaluation, EE_2 , E_1 and E_3 were assumed to be 10 [11], [12], 0.33 [24] and 0.04 [37], [38] times as potent as E_2 , respectively. For the rationale behind the selected potencies, see Section SI-2.

5.2.2 Net Estrogen Load Due to a Population's Use of a Given Contraceptive Option

The objective of this research is to examine the implications of the use of various forms of contraception by accounting for all estrogenic loads attributable to the use of a given contraceptive option. Conceptually, the net environmental estrogenic load associated with the use of a given option, n , is composed of three distinct contributions represented by the variables $J_{d,n}$, $J_{f,n}$, and $J_{L,n}$ (see Figure 5.2).

The most obvious of these and the only one directly acknowledged in the literature to-date is $J_{d,n}$, which is the contribution that is directly released upon use of a contraceptive option, n , via the excreta of respective users. This contribution is non-zero for estrogen-based contraceptive options only. More specifically, of the various contraceptive options considered here, the contribution $J_{d,n}$ is only relevant for EE_2 -based preparations (EE_2 -OC) and the recently authorized E_2 -based oral contraceptives (E_2 -OC). See Section SI-3 for a detailed discussion on the modelling of this contribution and the parameterization of the resulting model.

An additional contribution, $J_{f,n}$, arises from the recognition that all contraceptive options will occasionally fail (see Figure 5.2). Failure of a contraceptive option will often lead to an *unintended pregnancy*, which refers to a pregnancy that is undesired at the time of conception and occurs either through the failure of the contraceptive option being used or the non-use of contraception altogether [29]. A pregnancy leads to a significant increase in the endogenous excretion of E_1 , E_2 and E_3 . The magnitude of this increase is a function of the duration of the pregnancy [39], [40], which is directly related to its outcome (i.e., birth, induced abortion, spontaneous abortion, and ectopic pregnancy) [41]. It is important to note, however, that

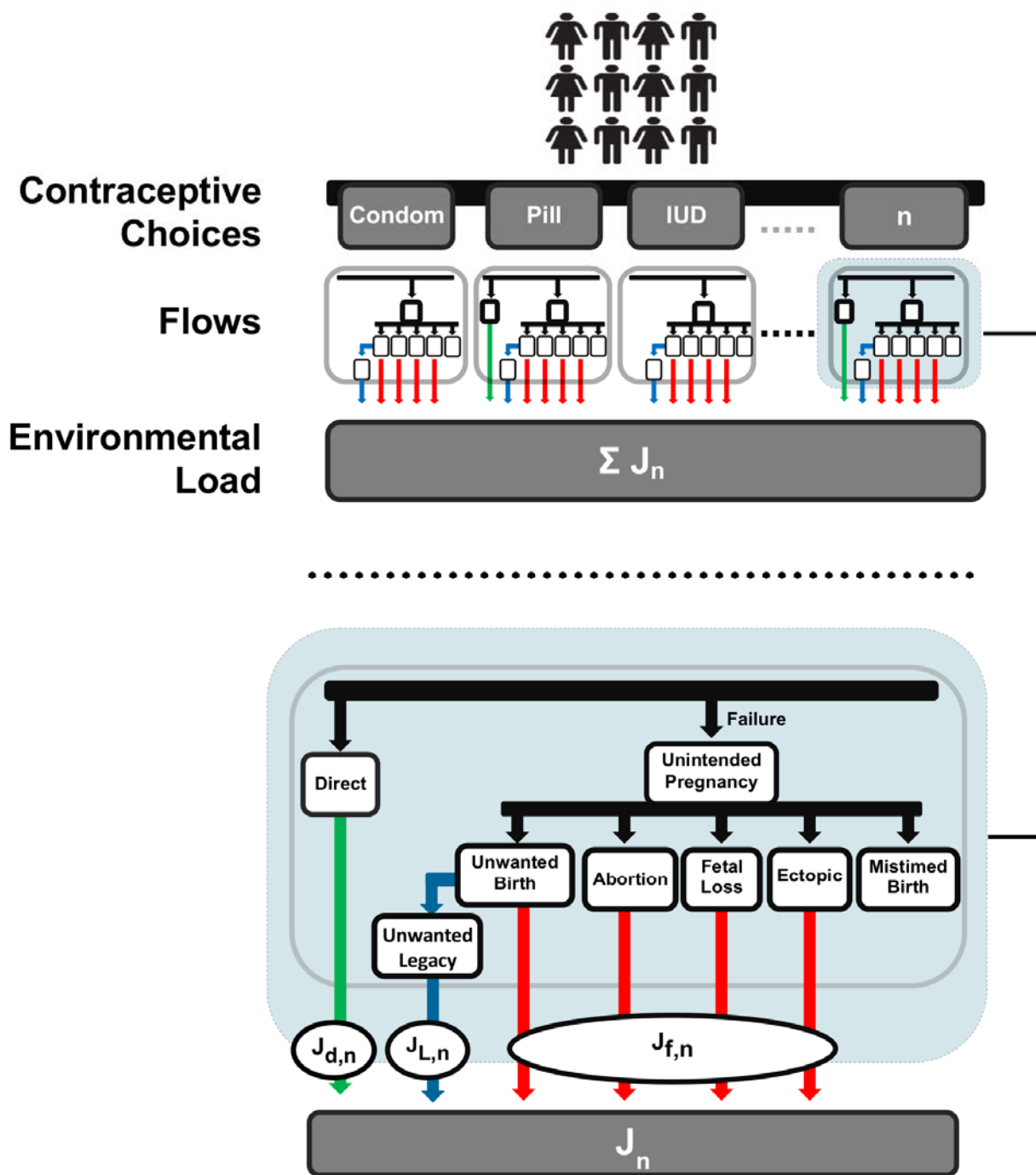


Figure 5.2: Relationship between contraceptive choices and the resultant flows of steroidal estrogens (i.e., through direct excretion and contraceptive failure) contributing to the net load of steroidal estrogens attributable to the use of a particular contraceptive option (J_n) or the total of all options (i.e., ΣJ_n). Note that since mistimed births only lead to time-displaced estrogenic flows such pregnancies are not identified as a source of steroidal estrogenic attributable to a user's choice of a particular contraceptive option.

the load of natural estrogens released over the course of an unintended pregnancy resulting in the outcome of birth, should not be fully attributed to the parents' choice of using a given contraceptive option. That is, consider that births that result from unintended pregnancies are classified in family planning literature as either being *mistimed* or *unwanted* [42-44]. A *mistimed* birth is a time-displaced birth in that it occurs earlier than desired [44]. Hence, the estrogenic load associated with such a birth can be considered to be simply displaced in time and, therefore, should not be attributed to the parents' choice of a given contraceptive option. In contrast, an *unwanted* birth can be viewed as an “extra” birth, since it occurs despite the couple's lack of intent at the time of conception to have a child in the future [44]. Since *unwanted* births are “extra” births that occur because the needs of the parents could not be fully met by their contraceptive method(s) of choice, the estrogenic load released over the course of the resultant unintended pregnancies should be attributed to the parents' contraceptive choices. This consideration does not apply to all other outcomes of unintended pregnancies (i.e., induced abortion, spontaneous abortion and ectopic) since these outcomes do not end up satisfying a future need of the parents for a child. See Section SI-4 for a detailed discussion on how the estrogen contributions arising from unintended pregnancies were modeled and how the resulting model was parameterized.

In addition to leading to the release of natural estrogens over the course of the resultant unintended pregnancy, the failure of a contraceptive option is also a source of an additional contribution, $J_{L,n}$, due to unintended pregnancies that ultimately lead to the outcome of *unwanted* births (Figure 5.2). Since *unwanted* births are “extra” births that occur because the family planning expectations of the parents were not fully met by their contraceptive method, the estrogenic load released over the course of the unwanted child's lifespan as well that person's genetic lineage may also be attributed to the parents' choice to use a given contraceptive option. In this way, such a contribution can be viewed as a “legacy” load since it will manifest while the genetic lineage of the born unwanted child remains alive. See Section SI-5 for details on how this estrogen contribution was modeled and how the resulting model was parameterized.

Overall, the estrogenic load that can be associated with the choice to use a given contraception n by a given user can be estimated by summing the respective contributions $J_{d,n}$, $J_{f,n}$ and $J_{L,n}$ as follows (see Figure 5.2):

$$J_n = J_{d,n} + J_{f,n} + J_{L,n} \quad (1)$$

Eq. (1) forms the basis for the evaluation of all contraceptive methods and scenarios presented below.

As will be presented below, extensive analyses were conducted to understand how the choice to use a given contraceptive option or contraception collectively relates to the anthropogenic load of steroidal estrogens released to the environment.

The Supplementary Information section includes details on the development of models that were applied in this study to estimate the:

- estrogen load released directly via the use of a particular contraceptive option, $J_{d,n}$ (see Section SI-3);
- natural estrogen load released over the course of unintended pregnancies that can be associated with a user's choice of a particular contraceptive option, $J_{f,n}$ (see Section SI-4);
- legacy estrogenic load that can be associated with a user's choice of a particular contraceptive option, $J_{L,n}$ (see Section SI-5);
- net estrogenic load averted by a population's collective use of contraception (see Section SI-6);
- fraction of the net estrogenic load released over the course of all pregnancy events that results from those that are unintended, hence the failure and non-use of contraception among the user population (see Section SI-7); and
- changes in associated estrogenic loading when users of EE₂-OC users switch to other methods (see Section SI-8).

Detailed summaries of data used, model parameters, and their corresponding literature sources are provided in Section SI-9.

This work draws upon a wide variety of data sources in the environmental, family planning, reproductive health and clinical literature. Due to the very different natures of the data sources used, the parameterization of variables was accomplished using a multipronged approach. For variables whose parameterization drew upon environmental and clinical data, it was possible to capture uncertainty in parameterization by assigning appropriate distributions to the variables (see Section SI-9). However, this was not possible for variables whose parameterization drew upon family planning literature. For such cases, parameterization of relevant variables was accomplished by either choosing the best possible parameterization for the variable or, where doubts existed as to what the best possible parameterization for a given variable was, conservative estimates of parameters were assigned. Overall, all estimates

furnished through the modelling in this work were calculated using conservative values of inputs and parameters in order to arrive at readily defensible conclusions.

5.3 RESULTS AND DISCUSSION

5.3.1 Use of Contraceptives and their Associated Estrogen Loadings

In this section, an estimate is first furnished for the estrogenic load averted through the collective use of contraception (Section 5.3.1.1). An analysis is then conducted to evaluate and compare the estrogen loads that are attributable to the choice of individual contraceptive options (Section 5.3.1.2). Finally, given that some unintended pregnancies and, hence, births occur even with the use of currently available contraceptive choices, an evaluation is conducted to estimate the estrogenic load as it relates to pregnancy intent and to the effectiveness with which the population's current mix of contraceptive options is used (Section 5.3.1.3). All analyses presented are based on data reflecting trends in family planning in the USA.

5.3.1.1 Net Estrogenic Load Averted by the Collective Use of Contraception

The collective use of contraception by a population averts a number of unintended pregnancies [43] and, hence at the very least, a load of natural steroidal estrogens to the environment. The approach used to estimate the total associated estrogenic mass averted due to the collective use of various contraception options by the population over a given year, E_a , is detailed in Section SI-6.

It is conservatively estimated that the collective use of contraception over the course of a given year in the USA averts 8.8 million unintended pregnancies (Eq. (S5)); i.e., 2.1, 5.0, 1.6 and 0.07 million unwanted births, abortions, fetal losses and ectopic pregnancies are averted, respectively, as estimated using Eq. (S5a) to (S5d). The total estrogenic load averted by the collective use of contraception in the USA over a given year (E_a) can be estimated by adding the estrogenic load that would have been released over the course of 8.8 million unintended pregnancies (E_p) to the estrogenic load arising from the legacies of 2.1 million *unwanted* births (E_L) and subtracting from this sum the load that is directly released via excretions of users who currently use estrogen-based methods of contraception (E_e) (see Section SI-6).

Specifically, using Eq. (S5), the net quantity averted each year by the collective use of contraception in the USA, E_a , is estimated to be 4.80 tonnes of $E_{2\text{-eq}}$. This averted net load results from:

[0.66 tonnes of $E_{2\text{-eq}}$ that would have been released over the course of 8.8 million averted pregnancies (E_p)]

$$+ [4.44 \text{ tonnes of } E_{2\text{-eq}} \text{ estrogenic legacy of 2.1 million } \textit{unwanted} \text{ children whose births are averted } (E_L)]$$

$$- [0.31 \text{ tonnes of } E_{2\text{-eq}} \text{ estrogenic load directly released due to the current contraceptive mix } (E_c)]$$

The above estimates for E_a and E_p suggest that, on a per-pregnancy basis, the estrogenic load represented by an *unwanted* birth's legacy is substantially higher than that released over the course of an unintended pregnancy. The absolute magnitude with which the estrogenic load of an *unwanted* birth's legacy exceeds that released over the course of an unintended pregnancy is likely higher than what the above estimates would suggest since the manner with which we estimate the estrogenic legacy of an *unwanted* birth's legacy is highly conservative (see Section SI-5). Moreover, it should be noted that the overall estimate of 4.80 tonnes of estrogen load averted is also highly conservative due to the chosen parameterization for a number of variables of the estimating equation (see Section SI-6).

Overall, these results establish that the collectively use of contraception by the population of the USA averts a substantial estrogenic load from being released to the environment.

5.3.1.2 Estrogenic Loads Associated with Individual Contraceptive Options

Based on the methodologies presented in Sections SI-3 to SI-5 and using parameters evaluated from data collected in the USA (see Section SI-9), the estrogenic load associated with the first-year use of each contraceptive option was estimated through the application of Eq. (1). The results are summarized in Table 5.1.

Of the commonly used options evaluated, the use of EE₂-based oral contraceptives is the only one that results in a direct estrogen load ($J_{d,n}$) since it involves the direct consumption and subsequent excretion of estrogenic content by the user. Since all contraceptive options fail, indirect loads $J_{f,n}$ (loads arising over the course of the unintended pregnancies) and $J_{L,n}$ (the estrogen legacy of the “extra” children that are the outcome of resultant unintended pregnancies) can be associated with the choice to use each option. As is evident from the results in Table 5.1, the choice to use certain non-estrogen based contraceptive options have quite significant indirect loads associated with their use. Such results indicate that relationship between the choice to use a given contraceptive option and its associated estrogenic load is a much more complex choice than broadly assumed in literature, whereby the choice to use estrogen-based options such as EE₂-OC is the only one considered to impose estrogenic loading on the environment [26-28]. These results demonstrate that certain non-estrogen based contraceptive choices have higher overall estrogenic loads associated with their use than the one simply associated with the choice to use EE₂-OC.

Table 5.1 Evaluation of Contraceptive Options: Annual probability (A_n , %) with which unintended pregnancies are experienced by typical first-year users; estimated estrogenic loads associated with first year of use (J_n); proportion of resultant unintended pregnancies arising from inconsistent use; annualized cost of use; and rate of continuation of use of the option at the end of the first year.

Contraceptive Option (n)	$A_n^{(a)}$	$J_n^{(b)}$ [$J_{d,n}^{(c)}$, $J_{f,n}^{(d)}$, $J_{L,n}^{(e)}$]	Proportion of Unintended Pregnancies Due to Inconsistent Use ^(f)	Annualized Cost of Use ^{(g),(h)}	Rate of Continuation of Use ^(a)
	%	mg of $E_{2\text{-eq}}$ /user·first year of use	%	\$/ user·yr	% of women after first year of use
No method used	85	304 [0, 43, 261]		948	
Spermicide	28	101 [0, 14, 87]	36	529	42
Fertility awareness-based methods	24	86 [0, 12, 74]	79	378	47
Withdrawal	22	79 [0, 11, 68]	82	403	46
Sponge (Parous women)	24	86 [0, 12, 74]	17	560	36
Sponge (Nulliparous women)	12	43 [0, 6, 37]	25	560	36
Female condom	21	75 [0, 11, 64]	76	535	41
Male condom	18	65 [0, 9, 56]	89	315	43
Diaphragm	12	43 [0, 6, 37]	50	434	57
EE ₂ -based oral contraceptive	9	62 [29.5, 5, 28]	97	676	67
Progestin-only pill	9	33 [0, 5, 28]	97	n.a. ⁽ⁱ⁾	67
Progesterone Injection	6	22 [0, 3, 19]	97	536	56
Copper IUD (ParaGard)	0.8	2.8 [0.0, 0.4, 2.4]	25	180	78
Levonorgestrel IUS (Mirena)	0.2	0.4 [0.0, 0.1, 0.3]	0	230	80
Female sterilization	0.5	1.2 [0.0, 0.2, 1.0]	0	596	100
Male sterilization	0.15	0.5 [0.0, 0.1, 0.5]	33	143	100
Implant	0.05	0.2 [0.00, 0.03, 0.15]	0	319	84

Notes: J_n and all of its subcomponents are estimated on a pre-treatment basis. **(a)** Trussell et al.[29]; **(b)** Estimated using Eq. 1; **(c)** Estimated using Eq. (S1); **(d)** Estimated using Eq. (S2); **(e)** Estimated using Eq. (S3); **(f)** Estimated using the method of Trussell et al.[64] as follows: (failure rate with typical use – failure rate with perfect use)/ (failure rate with typical use) × 100, with failure rates as those reported by Trussell et al.[29]; **(g)** Annualized cost associated with the use of the contraceptive method over a time of horizon of 5 yrs., includes method related costs, cost of failures and the cost of side effects; **(h)** From Trussell et al.[42],[47]; **(i)** Not available.

When each contraceptive option's estimate for J_n is compared to that of not using any method at all (i.e., J_n for "no method" in the Table 5.1), the use of each and every method of contraception averts an associated estrogenic load from being released. This is consistent with the conclusion drawn earlier that the collective use of contraception, as opposed to using nothing at all, averts a substantial estrogenic load from being released. Hence, collectively and individually, the use of contraception prevents an estrogenic load from being released to the environment and, when evaluated in these terms, could be construed as being beneficial to the environment from the perspective of estrogen load only when compared to no contraception at all. Since each averted unintended pregnancy also averts the added risk of maternal and neo-natal mortality [45], [46], the use of contraception, collectively and individually, in the USA can also be taken to avert a number of maternal and neo-natal mortalities. Overall, the use of various forms of contraception by the population of the USA, as opposed to using nothing at all, averts a substantial estrogenic load from being released, prevents a significant number of undesired family planning outcomes, and further averts a number of maternal and neo-natal deaths. Furthermore, Trussell [43] estimated that the collective use of contraception in the USA annually averts direct medical costs of nineteen billion USA dollars.

In order to perform a broadly applicable analysis of individual contraceptive choices, Table 5.1 also lists a number of additional parameters which are of importance from a family planning perspective. A_n can be viewed to be indicative of the efficacy with which each option n is typically used in the USA. In addition, the proportion of unintended pregnancies that are a result of inconsistent use of each option is also estimated. Note that this can be taken to be indicative of the fraction of the associated loads $J_{f,n}$ and $J_{L,n}$ for a given option n that could potentially be averted by ensuring consistent use of that option. Two additional data entries listed for each option are the cost associated with the use of each and the continuation rate expected one year after initiating the use of each specific option. The cost estimates [42], [47] include method-related costs, cost of failures, and the cost of associated side effects.

Among all contraceptive options listed in Table 5.1, including all those that are reversible and irreversible, the implant has the lowest estrogenic load associated with its use, since its failure rate (reflected by A_n) is the lowest of all contraceptive options. Also, of all reversible contraceptive options, the implant, probably due to its inherent nature, also has one of the highest continuation rates (see Table 5.1). However, this contraceptive option has been adopted by a relatively minor fraction of the potential user population in the USA [48], [49].

EE₂-OC and the male condoms are the two most common forms of reversible contraception used in the USA [49]. Of the two, EE₂-OC is more effective in preventing unintended pregnancies, results in a lower associated estrogenic load, and is more likely to be continued to be used once adopted. Particularly striking is the fact that inconsistent use of EE₂-OC and the male condom results in 97% and 89% of all unintended pregnancies experienced by first-year users of the two options, respectively. Hence, the associated estrogenic loads $J_{f,n}$ and $J_{L,n}$ for these two options can be substantially reduced by improving the consistency with which they are typically used in the USA.

The copper IUD is the most cost effective of all reversible and irreversible contraceptive options [42], [47]. Furthermore, of all reversible contraceptive options, it results in one of the lowest associated estrogenic loads (see Table 5.1). Moreover, it is highly effective in preventing unintended pregnancies among its users and has one of the highest continuation rates of all reversible contraceptive options. Hence, the copper IUD performs exceptionally well on the various criteria against which the use of contraceptive options are evaluated in Table 5.1. This contraceptive option along with the use of Levonorgestrel-based intrauterine system (IUS) has, in recent years, experienced a renewed interest in use amongst contraceptive users in the USA [48]. Consider that, amongst users of contraception in the USA, the use of these two options has increased from 2.0% in 2002 to 8.8% in 2009 [48].

5.3.1.3 Estrogenic Loads Resulting from Unintended Pregnancies

Estimates suggest that nearly half of the 6.35 million pregnancy events experienced annually in the USA are unintended (see Figure 5.3) [30], [31]. Hence, it is particularly interesting to evaluate how the estrogenic load that is released due to, and over the course, of these events relates to pregnancy intent and, hence, to the effectiveness with which various contraceptive methods are currently used in the USA.

The various contributions to estrogenic loads of each of the major pregnancy events were estimated in terms of estradiol equivalents ($E_{2\text{-eq}}$). The results summarized in Figure 5.3 suggests that, over the course of these 6.35 million pregnancy events, an estimated 1.2 tonnes of $E_{2\text{-eq}}$ is released; however, only 35% of this load (i.e., 0.40 tonnes) arises from unintended pregnancies and, hence, from the failure and non-use of contraception. There are two reasons why an average unintended pregnancy event, when compared to an intended one, leads to the release of less estrogenic mass. First, only 45% of unintended pregnancies end up in the outcome of birth, in contrast to 81% of intended pregnancies [30]. Additionally, a pregnancy resulting in the outcome of birth leads to the release of an $E_{2\text{-eq}}$ load that is on average 20, 25 and 32 times

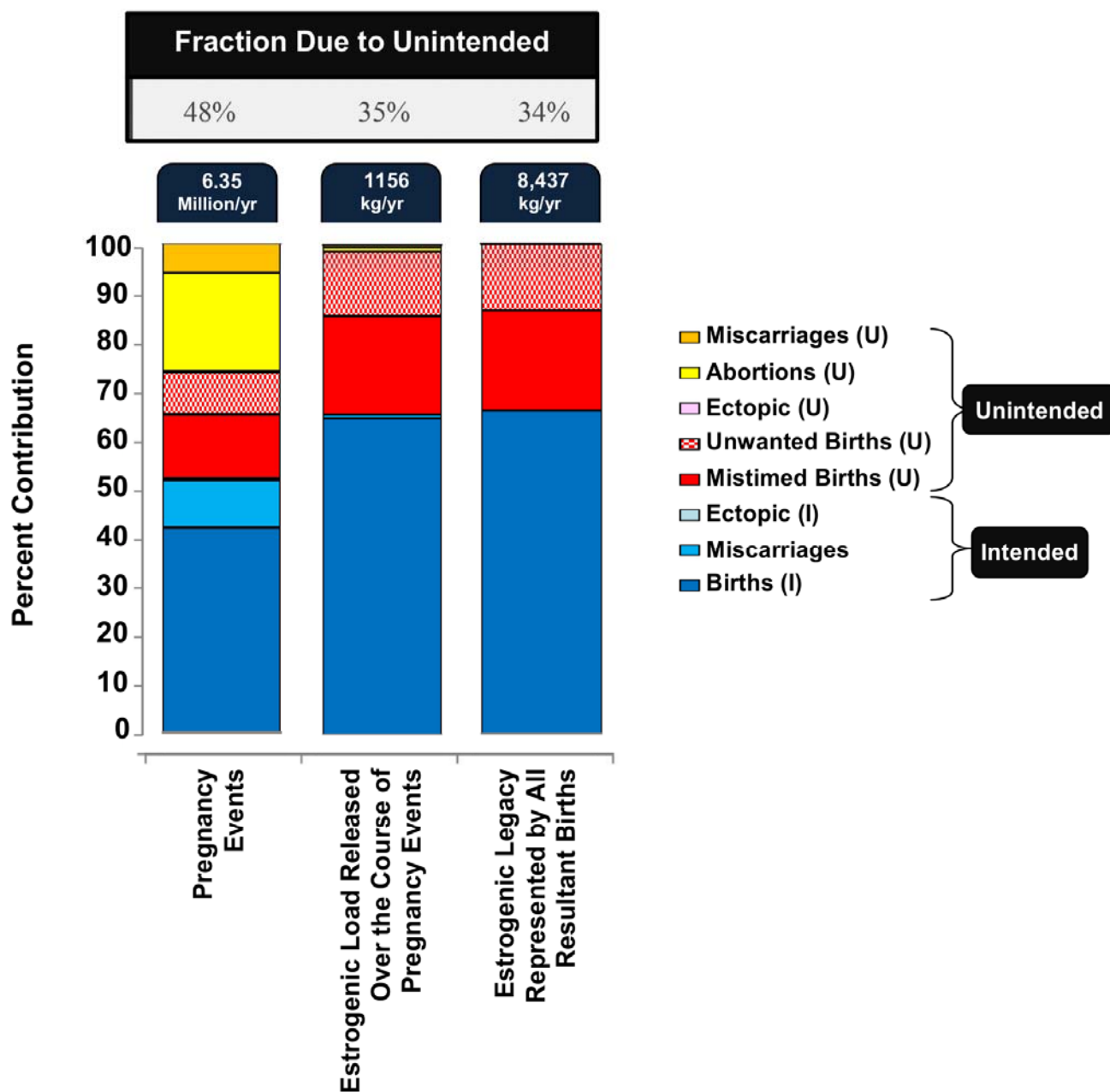


Figure 5.3: Relative contributions of intended (I) and unintended (U) pregnancy events to the total number of pregnancies, the estrogenic load released over the course of all pregnancies, and the estrogenic legacy represented by all resultant births. Refer to SI-7 to see how the various contributions were estimated.

higher than the levels released had the pregnancy instead concluded in the outcome of spontaneous abortion, induced abortion and ectopic pregnancy, respectively (see Section SI-1).

Of the 6.35 million pregnancy events experienced in the USA each year, 4.02 million events culminate in the birth of a child [30], [31]. Hence, each year, 4.02 million legacies are born to the population of the USA and these can be estimated to at least represent an estrogenic legacy load of 8.4 tonnes of $E_{2\text{-eq}}$ (see Figure 5.3). However, as indicated earlier, since an unintended pregnancy, when compared to an intended one, is less likely to end up in the outcome of birth, only 34% of the estrogenic legacy load results from unintended pregnancies (Figure 5.3). Hence, the failure and the non-use of contraception by the population of the USA results in 34% of the estrogenic legacy birthed each year.

5.3.2 Implications of Discontinuing the Use of EE₂-based Oral Contraceptives

To-date there has been a tendency in the literature to only account for the direct estrogen load associated with a given contraceptive method ($J_{d,n}$). Due to this and also the growing evidence of the impact of ethinylestradiol, EE₂, on aquatic species [12], [33], [50], particular focus has been placed on EE₂-based contraceptives. This has led some to suggest that, because of its environmental impacts and/or the high costs associated with the treatment of wastes containing this estrogen, the use of EE₂-based contraceptives should be a subject of further discussion [27], [32]. Such analyses and, more broadly, almost all equivalent literature concerning estrogen loads on the environment, fail to recognize the full extent of the relationships between a user's choice to use a given contraceptive option and estrogen loading to the environment. A more informative analysis would be one that aims to understand the trade-offs involved in the choice to use EE₂-OC. To this end, we will explore how the estrogenic flows would be expected to change should a group of EE₂-OC users discontinue the use of their method by switching to a range of other contraceptive methods that are currently available to them or by abandoning the use of contraception altogether. This assessment is performed by conducting a scenario analysis. Specifically, in Section 5.3.2.1, the estrogenic load under the *Status quo* scenario for a unit population of a 1,000 first-year EE₂-OC users is compared to a *Discontinue EE₂* scenario, the aim of which is to model the estrogenic load associated with the most likely contraceptive choices made by the user group upon discontinuing the use of the EE₂-OC; i.e., upon discontinuing the use of the EE₂-OC the switching population is expected to either adopt other available contraceptive options or discontinue the use of contraception altogether. The contraceptive choices made by the switching population are modeled using the data of Rosenberg and Waugh [51] who reported the contraceptive mix adopted by those in the USA who for various reasons discontinued the use of EE₂-OC but still wanted to prevent a pregnancy.

In addition to the *Discontinue EE₂-OC* scenario, we also consider in Section 5.3.2.2 three other explorative scenarios in which the population of a 1000 EE₂-OC users, P_s , is modeled to switch, as per the recommendation of Wise et al. [26], to using male condoms, diaphragms or copper IUDs. While these are not considered to be likely scenarios, they provide a basis for comparing the estrogenic loads arising from particular contraceptive choices. Among these, the scenarios that explore the switch to the use of male condoms and to the use of copper IUDs are particularly interesting. The male condom, after the use of EE₂-OC, is the most common form of reversible contraception used by couples in the USA [49]. The use of copper IUDs is not only the most cost-effective reversible contraceptive method [42] but is also one of the most effective in preventing pregnancies [29].

Recently, an oral contraceptive preparation that uses estradiol, E₂, as the active ingredient has been approved for sale in the USA under the brand name of Natazia[15], [21]. It is reasonable to assume that some users of EE₂-OC would switch to this new preparation. Hence, it is of particular interest to evaluate how the estrogenic flows to the environment would change when a group of EE₂-OC users adopts this unique estradiol-based oral contraceptive (E₂-OC). The results of this analysis are detailed in Section 5.3.2.3.

5.3.2.1 Scenario: Changes in Estrogenic Load upon Discontinuation of EE₂-OC

It was established above that the use of EE₂-OC averts an estrogenic load from being released to the environment when compared to using no contraceptive method at all. However, a particularly valuable and, perhaps, more realistic evaluation is one that compares the changes in loads of associated estrogens when EE₂-OC users discontinue the use of their method by switching to other contraceptive methods or by abandoning the use of contraception altogether. Such an assessment is performed here by conducting a scenario analysis as described in detail in Section SI-8. The results of the analysis are summarized in Figure 5.4.

Overall, it is estimated that, when first-year users of EE₂-OC discontinue the use of their option, they will experience unintended pregnancies at a rate of 297 per 1000 users per year, a level that is nearly 3.3 times higher than the levels they would have experienced had they continued using EE₂-OC (See Figure 5.4). Note that the estimated unintended pregnancy rate for those that discontinue the use of EE₂-OC is particularly sensitive to the fraction of those that abandon the use of contraception altogether. That is, it is estimated that a group of approximately 190 persons who completely abandon the use of EE₂-OC in favor

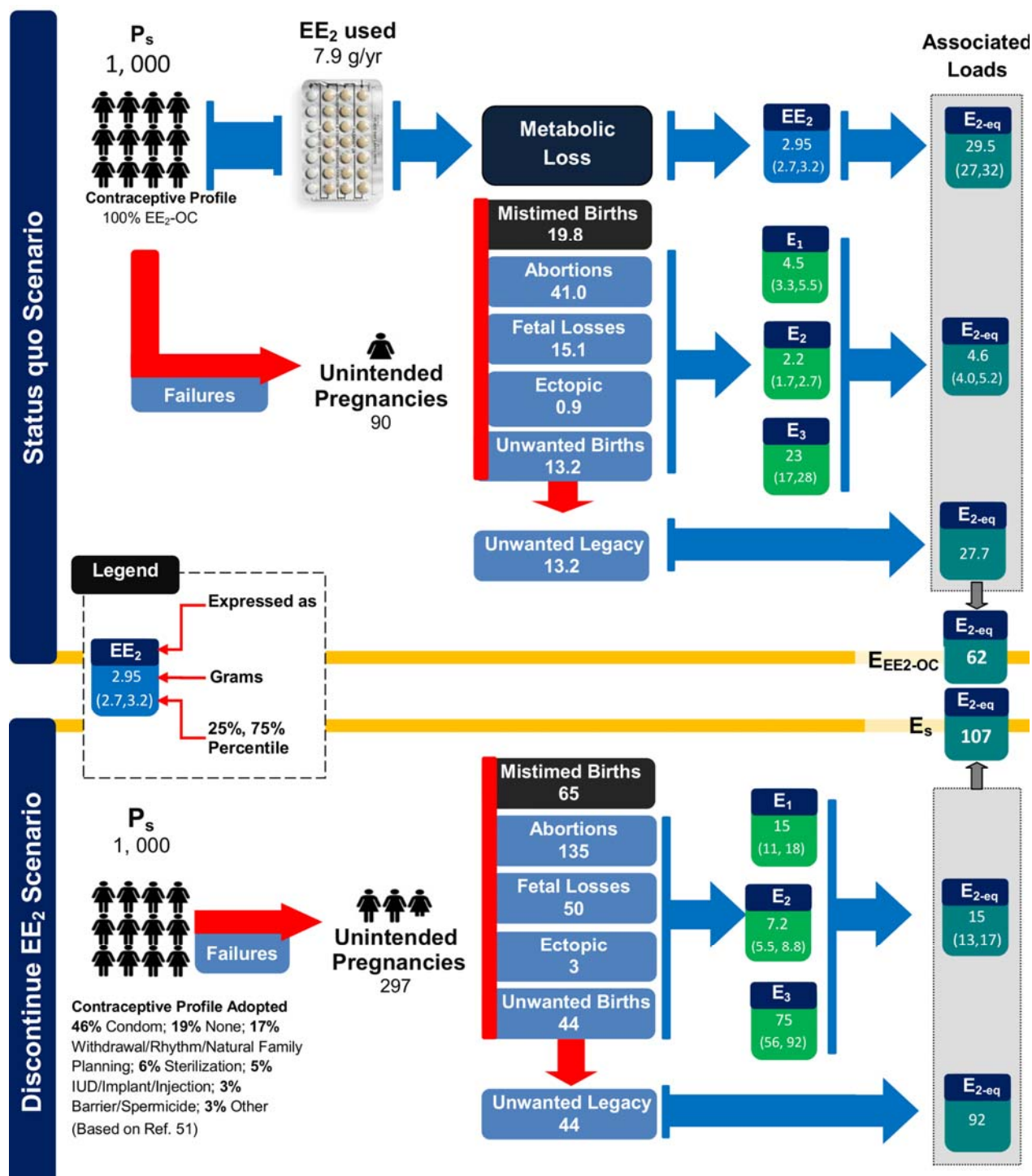


Figure 5.4: Changes in associated loads of steroidal estrogens when a unit of population of 1,000 first users of EE₂ based oral contraceptive switch to other contraceptive options. The total estrogen load associated with oral contraceptive use (EE₂-OC) was estimated using Eq. (S6). The total estrogen load associated with those who discontinue the use of oral contraception (E_s) was estimated using Eq. (S7).-

of no contraception at all will contribute to 162 (or 54%) of the anticipated 297 unintended pregnancies resulting from the original 1000 EE₂-OC users who switched to other options.

The scenario analysis suggests that under the *Status quo* scenario shown in Figure 5.4, 62 grams of E₂-_{eq}/yr (N_{EE_2-OC}) can be associated with the representative user population of 1,000 EE₂-OC users. Of this total load, 48% results from the direct excretions of the user population, another 7% is released over the course of unintended pregnancies experienced by the user population, and the remaining 45% is the estrogenic load represented by the legacies of unwanted children born to the representative user population. Upon discontinuing the use of EE₂-OC, it is estimated that the user population's total estrogenic load (N_s) will increase 1.7-fold to 107 grams of E₂-_{eq}/yr, of which 14% would be released over the course of 297 unintended pregnancies experienced by the discontinuing population and the remaining 86% would be the estrogenic load represented by the legacies of unwanted children expected to be born to that population. If the various contributions in Eq. (1) to the loads for the *Status quo* and *Discontinue EE₂* scenarios are compared, it can be seen that the increase in total estrogenic load upon discontinuing the use of EE₂-OC is driven by a substantial increase in the legacy contribution ($J_{L,n}$). Further, over and above the 1.7-fold increase in estrogenic load experienced upon discontinuing EE₂-OC use, the user population also experiences undesired family outcomes such as unintended pregnancies, abortions, miscarriages and unplanned births at levels that are approximately 3.3 times higher. Similarly, because the contraceptive needs of the parents could not be met, the number of extra births also increases by 3.3 times and the number of ectopic pregnancies experienced by the user population also increases by an estimated 3.4 times. Further, recognizing that each additional unintended pregnancy presents an added risk of maternal and neo-natal mortality [45], [46], [52], upon discontinuing the use of EE₂-OC, the user population would be expected to experience far higher rates of maternal and neo-natal mortality. Hence, whether the assessment of contraceptive options is performed by considering estrogenic loading, the number of undesired family planning events experienced, or maternal and neo-natal mortality rates, the continued use of EE₂-OC appears to be a much-preferred option over discontinuing its use and switching to a range of other options. Notably, nearly one-third of the EE₂-OC users discontinue the use of their option within the first year [29].

5.3.2.2 Scenario: EE₂-OC Users Switch to Specific Non-estrogen-based Contraceptive Options

The above assertion that discontinuing the use of an EE₂-based oral contraceptive will result in an increase in total estrogen load into the environment hinges on the assumption that users will switch to a particular set of alternative options, as described by the data of Rosenberg and Waugh [51]. However, this

analysis does not directly reveal the relative merits of individual contraceptive options that can be used in place of EE₂-based oral contraceptives. For this reason, and to concurrently evaluate the suggestion of Wise et al. [26], consider three explorative scenarios where, perhaps unrealistically, the unit population of a 1,000 EE₂-OC users are modeled as having discontinued the use of EE₂-OC by entirely switching to the use of either the male condom, the diaphragm, or the copper IUD. The results for each of these three scenarios are summarized in figures in Sections SI-10, SI-11 and SI-12, respectively.

If the entire user population switches to the use of male condoms, the associated estrogenic load would be slightly higher (specifically 1.05 times); moreover the level of unintended pregnancies, abortions, miscarriages and unplanned births experienced by the user population would approximately double (see Section SI-10). While on one hand, the switch to diaphragms results in some modest gains with respect to reduced estrogenic loading, it is also expected to lead to an unacceptable increase in the rate at which the user population experiences undesired family planning events (see Section SI-11). In contrast, should the entire user population switch to the use of copper IUDs, not only would their associated estrogenic load be approximately one-twentieth compared to the *Status quo* scenario, the user population would experience significantly fewer adverse personal, social and public health outcomes (see Section SI-12). Consider that, upon switching to the copper IUD, the user population would be expected to experience unintended pregnancies, abortions, miscarriages and unplanned births at rates that are one-twelfth the levels they would have experienced had they continued using EE₂-OC (see Section SI-12). In addition to these already substantial benefits, for each user that switches from the use of EE₂-OC to a copper IUD, the costs associated with the chosen method of contraception would be an estimated US \$500 less for each year of use [42], [47]. This gain in cost effectiveness is the highest that can be achieved for an EE₂-OC user who wishes to switch to another reversible contraceptive option, since the copper IUD is the most cost-effective reversible contraceptive option currently available to the population of the USA [42], [47].

The results of the above scenario analyses indicate that whether the switch of an EE₂-OC user population to alternative modes of contraception leads to an increase or decrease in estrogenic load on the environment is inherently dependent on the alternate forms of contraception chosen by the user population. Note that, even though the estrogenic load of the user population is expected to increase significantly for those who currently discontinue the use of EE₂-OC as reported above (see Section 5.3.2.1), this outcome is inherently dependent on the mix of contraceptive choices chosen by users upon discontinuation. Hence, this would have to be reevaluated should these patterns change in the future. In

addition, the results arising from the scenario analyses for users who switch to the male condom and diaphragms clearly suggest that the choice to use a given contraceptive option, or any recommendations that may influence that choice (e.g., the suggestions of Wise et al. [26]), should not only be evaluated on the basis of their associated estrogenic loads but also by considering broader public health and family planning implications for the user population.

5.3.2.3 Scenario: Users of EE₂-OC Switch to E₂-OC

Recently, an E₂-based oral contraceptive has been made available in the USA and, hence, it would be of interest to evaluate how the estrogen loading changes when a user switches to this form of contraception from the prior use of EE₂-OC.

The analysis presented in Section SI-13 suggests that the associated estrogenic load of an E₂-OC user is nearly 2.2 times higher than that of an EE₂-OC user. This increase is a direct result of 3.6-fold increase in the direct estrogenic load, $J_{d,n}$, since the contributions $J_{f,n}$ and $J_{d,n}$ for each of the two options, based on current knowledge, would be expected to be similar if not identical (See Section SI-8).

5.3.3 Impact of Contraceptive Choices on the Net Steroidal Estrogenic Loads

The results obtained above clearly suggest that the use of certain contraceptive options have a lower total estrogenic load associated with their use than others. Given this, a very important and pragmatic question must be raised; that is, since certain contraceptive options have lower estrogenic loads associated with their use than others, what absolute impact can contraceptive users in the USA have on the net estrogenic load released to the environment by switching to contraceptive choices that result in lower loads of estrogens?

To answer this question, consider the estimates presented in Figure 5.3. Overall, the failure of contraceptive options and also the non-use of contraception by the population of the USA over a given year represent an estimated total estrogenic load of 3.3 tonnes of E₂-eq, of which 0.40 tonnes is released over the course of 3.05 million unintended pregnancies and another 2.9 tonnes is the estrogenic load represented by the legacies of 1.37 million unintended births (see Figure 5.3). Note, however, that this entire load would not be eliminated in the event that the family planning needs of the population of the USA can be fully met. Specifically, a substantial fraction of these loads arises from those pregnancies that will result in the outcome of *mistimed* births. As argued earlier, such pregnancies represent a time-displaced estrogenic load and, hence, the estrogen release cannot be mitigated by meeting the family

planning needs of the experiencing population. Specifically, 0.23 tonnes of the 0.40 tonne load and 1.7 tonnes of the 2.9 tonne load result from those unintended pregnancies that end in an outcome of *mistimed* birth. Hence, by fully meeting the contraceptive needs of the population of the USA, an estrogenic load of 1.3 tonnes of $E_{2\text{-eq}}$ (i.e., $(2.9 - 1.7)$ tonnes + $(0.40 - 0.23)$ tonnes) can potentially be averted. Viewed another way, the failure and the non-use of contraception by the population of the USA currently represents a potentially preventable annual estrogenic load of 1.3 tonnes of $E_{2\text{-eq}}$. Further, if it is assumed that the contraceptive needs of contraceptive users in the USA can be fully met without the use of EE₂-OC, the release of an additional 0.31 tonnes of $E_{2\text{-eq}}$ (see Section SI-1) can be averted.

The potentially preventable estrogenic load of 1.3 tonnes of $E_{2\text{-eq}}$ should be compared to the net steroidal estrogenic load in the USA for a given year to answer the question raised above. The net steroidal estrogenic load in the USA in a given year is estimated to be 10.4 tonnes of $E_{2\text{-eq}}$, of which 2.0 tonnes of $E_{2\text{-eq}}$ are directly released via excretions of users (see Section SI-1) and the remainder of 8.4 tonnes of $E_{2\text{-eq}}$ is the estrogenic legacy that is born to them that year (see Figure 5.3). Therefore, by fully meeting the contraceptive needs of the population of the USA through a contraceptive option that is not estrogen-based, at most 13% (i.e., $(1.3 \text{ tonnes} + 0.3 \text{ tonnes})/10.4 \text{ tonnes} \times 100\%$) of the estrogenic load in the USA can be averted in a given year. This fraction is the absolute maximum that can be prevented, since it is inherently assumed that all users of contraception switch to methods that fully meet their needs. Note that this is an idealized condition since such methods do not exist given that even the most effective methods (e.g., implant, copper IUD and IUS) also fail, albeit at very low rates [29]. Further, consider that, in the estimate made here for the annual net steroidal estrogenic load in the USA, the fraction that is contributed by the release of equine estrogens has not been considered. This is due to considerable data gaps that exist for the release and the environmental relevance of such estrogens (see Section SI-14). The preliminary evaluation presented in Section SI-14 suggests that the release of such estrogens could be a minor but significant contributor to net steroidal estrogenic load in the USA each year.

Overall, the maximal estimate of 13% of the annual estrogenic load in the USA that can be averted through alternative forms of contraception suggests that the issue of estrogenic loading to the environment cannot be solved solely by meeting the population's contraceptive needs. That being said, significant gains in terms of reduced environmental impacts could be achieved by improving the level with which the contraceptive needs of the population are met.

Since the potentially preventable load in the USA of 1.3 tonnes of $E_{2\text{-eq}}$ estimated above results from users that are either experiencing failure or not using contraception altogether, it is of further interest to establish the relative impact of each user type on the estimated load. Before this is done, it is important to note that there are three types of users of contraception who experience unintended pregnancies: consistent users, inconsistent users, and non-users of contraception. Data from the Guttmacher Institute [53] can be used to estimate that non-users and inconsistent users are 42 and 29 times more likely, respectively, to experience an unintended pregnancy than consistent users. Further, consider that 52% and 43% of all unintended pregnancies experienced in the USA are by non-users and inconsistent users of contraception, respectively [53]. Hence, the estrogenic load of 1.3 tonnes of $E_{2\text{-eq}}$, estimated above largely results from the non-use and inconsistent use of contraception. Thus, gains can be made with respect to the estrogenic loading of the population in the USA by improving the consistency of use among inconsistent users and by improving the adoption of contraception among those who are currently at a risk of experiencing pregnancies but do not use any form of contraception. The former can be achieved by either directly improving the typical efficacy with which users use their chosen contraceptive options and/or, more plausibly, by encouraging users of those options that have high typical failure rates (e.g., withdrawal) to switch to those methods that have significantly lower typical use failure rates (e.g., copper IUD, IUS or the implant).

5.4 STUDY LIMITATIONS

The results of this study are intended to inform discussions concerning the relationships between contraception options and their estrogenic impacts on the environment. However, in the interest of clarity, it is also important to point out some limitation to this study, as follows.

With respect to the conclusion drawn in Section 5.3.2.2, it is important to note that even though the associated estrogenic load of users is expected to be higher upon discontinuing $EE_{2\text{-OC}}$ use, the higher load of estrogens in the environment for the Discontinue EE_2 scenario is expected to be considerably less persistent than that released under the Status Quo scenario. This assertion results from the recognition that EE_2 has been reported to be substantially more persistent than natural estrogens [25]. That being said, it is worth noting that emerging data suggests that a previously unrecognized photolysis product of estrone (i.e., lumiestrone) may not only be estrogenic but also persistent [54-56]. However, the environmental occurrence and relevance of this photolysis product is not yet fully understood. Hence, even though well-established data [17], [24], [25] suggests that the lesser estrogen load of the Status quo scenario is likely

to be more persistent, this assertion would need to be reevaluated once sufficient data on the environmental fate, occurrence and relevance of lumiestrone becomes available.

Similarly, with respect to the conclusion drawn in Section 5.3.2.3 that the associated loading of a previous EE_{2-OC} user increases 2.2-fold when she switches to the use of E_{2-OC} , one must also consider that, although lower in quantity, the total associated estrogenic load of an EE_{2-OC} user may be more persistent than the one released by the user of E_{2-OC} . That is, the excretion of EE_2 by the users of EE_{2-OC} are replaced by releases of E_1 , E_2 and E_3 by the users of E_{2-OC} , all of which are less persistent than EE_2 [17], [24], [25]. Therefore, before a definitive conclusion concerning the relative impacts of these estrogens can be made, a better understanding of the fate and relative environmental relevance of lumiestrone is required.

Although the focus of this research is to develop a better understanding of the relationship between contraceptive choices and the associated estrogenic loads, it is important to note that the choice to use a given a contraceptive option also has implication for the release of gestagens to the environment. Clearly, a user's choice to use a progestin-based contraceptive option (e.g., EE_{2-OC} , E_{2-OC} , progestin-only pill, Depo-Provera, levonorgestrel-IUS, and the implant) results in the direct release of a number of gestagens to the environment that is analogous to $J_{d,n}$ for estrogens. Moreover, similar to the situation when evaluating the total associated estrogenic load, the relationships are more complex than the simple consideration that the use of only gestagen-based options only leads to their direct release to the environment. In fact, analogous to the contributions $J_{f,n}$ and $J_{L,n}$ discussed above for estrogens, the choice to use every single contraceptive option has at least two indirect loads of gestagens associated with their use. First, the gestagen load analogous to $J_{f,n}$ results from the recognition that every contraceptive option has a failure rate associated with its use and the resultant unintended pregnancy leads to an increased release of progesterone [57], a natural gestagen, to the environment. And, second, the gestagen load analogous to $J_{L,n}$ results from the recognition that, had a chosen contraceptive option not failed and further the resultant unintended pregnancy not resulted in the outcome of unwanted pregnancy, the unwanted child's legacy load of gestagens would not have resulted. Therefore, overall, every contraceptive option comes with an associated gestagenic load. Unfortunately, since the eco-toxicological potential for only a handful of gestagens has been explored in sufficient detail in literature, [58-63] it is presently not possible to quantify on an equivalents basis the gestagenic load associated with the use of any given contraceptive option. Due to the absence of such data, it is also presently not possible to suggest whether the collective use of contraception or the use of a given contraceptive options averts a gestagenic load from being released to the environment.

Similarly, for the analysis presented in Section 5.3.2.3 the use of E_{2-OC} leads to the direct release of dienogest, a progestin that is only used in the USA with E_{2-OC} , while the users of EE_{2-OC} leads to the direct release of a range of other progestins [15]. However, again due to lack of sufficient eco-toxicological data for all progestins directly released by users of the two forms of oral contraceptive, it is presently not possible to determine whether the choice of using E_{2-OC} over EE_{2-OC} will result in a higher or a lower associated gestagenic load being released to the environment.

5.5 CONCLUSIONS

This research has focussed on developing an understanding of the relationships between the choice to use a given contraceptive option and the associated loads of steroidal estrogens on the environment. The conceptual approaches and models developed in this study were applied to the population of contraception users in the USA to establish the following:

- The use of each contraceptive option, even when it is not estrogen-based, has a load of steroidal estrogens associated with its use. However, when compared to the estrogenic load associated with the use of “no contraception” at all, the use of every contraceptive option, including those that are estrogen-based, prevents an estrogenic load from being released to the environment.
- The collective use of contraception in the USA over a given year conservatively averts 8.8 million unintended pregnancies and, in doing so, averts the release to the environment of an estimated estrogenic mass of 4.8 tonnes, expressed in estradiol equivalents.
- Almost half of all pregnancy events experienced in the USA in a given year are a result of contraception failure and the non-use of contraception. However, only 35% of the estrogenic load released over the course of resultant pregnancies and 34% the estrogenic load represented by all resultant legacies are a result of contraception failure and the non-use of contraception.
- When current users of EE_2 -based oral contraceptives discontinue the use of their option, not only is it expected that their overall estrogenic load increases 1.7-fold but they also would be expected to experience undesired family planning outcomes at a rate that is 3.3 times greater.
- Additional analyses were conducted on three idealized scenarios in which a group of EE_2 -based oral contraceptive users were modelled as having switched entirely to the use of male condoms or

diaphragms or copper IUDs. The results arising from all of these scenarios suggests that the outcome of whether higher or lower estrogen loads can be associated with the discontinuation of the use of EE₂-based oral contraceptives ultimately depends on the typical failure rates of the options adopted following discontinuation.

- In addition, explorative scenarios in which users were assumed to switch from EE₂-based contraceptives to alternative contraceptive options indicated that the choice of whether to use one contraceptive option versus another should not be assessed based on estrogenic load considerations alone but also by considering broader public health and family planning implications. When evaluated with such a broad framework, the switch from the use of EE₂-OC to that of copper IUDs seemed particularly interesting because its use is associated with an estrogenic load that is approximately one-twentieth of that associated with the use of EE₂-OC. However, any such recommendation should also be sensitive to cultural, physical, emotional, and psychological implications for the user.
- Another scenario considered was the plausible switch of users of EE₂-based oral contraceptives to the newly approved E₂-based oral contraceptive. Upon switching to this alternative estrogen-based contraceptive, the associated estrogen load of the user would be expected to increase by approximately 2.2-fold.
- At most, 13% of the net annual estrogenic load to the environment can be averted by fully meeting the contraceptive needs of the population of the USA. Hence, the issue of estrogen loading cannot solely be addressed by meeting the contraceptive needs of the population.

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Chapter 6: Refined Sewer Epidemiology Mass Balances and their Application to Heroin, Cocaine and Ecstasy

PREFACE

Chapters 2-5 viewed the release and, hence, the environmental presence of PhACs from an upstream perspective in which the degree of use or excretion of PhACs is used to estimate the environmental load of contaminants which, in turn, allows one to assess eco-toxicological and/or human-health concerns. This chapter, along with Chapters 7 and 8 that follow, view the environmental presence of PhACs from an alternate perspective in which the downstream load of drug residues in wastewaters is used to glean information about the behaviour of an upstream population. Specifically, this chapter addresses the objective of the thesis related to developing an understanding on how best to relate measurements of selected drug residues in wastewaters to the levels with which the parent illicit drugs are used in their respective upstream populations. To accomplish this, a number of aspects are considered and accounted for in the development of a generalized sewer epidemiology mass balance expression for the use of an illicit drug. The expression was developed based on the selection of an appropriate drug residue and also accounting for the excretion patterns of an illicit drug for its various routes of administration, illicit and licit sources that could lead to the release of the selected drug residue, sorption of the drug residue onto sewer-laden suspended solids, and the potential for the drug residue to degrade during sewer transmission. The generalized sewer epidemiology mass balance expression was then applied to the illicit use of cocaine, heroin and ecstasy.

Appendices for this chapter can be found at the end of this thesis.

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Refined Sewer Epidemiology Mass Balances and their application to Heroin, Cocaine and Ecstasy

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ABSTRACT

The detection of illicit drugs in environmental matrices may be a cause for concern, both from the perspective of their potential environmental impacts and the fact that their presence in detectable concentrations would be an indicator of significant drug use. The primary goal behind recent studies on this subject has been to use measured influent concentrations of selected illicit drugs or their in vivo metabolites in the environment as a means of estimating the abuse level of these drugs and patterns of consumption. Thus-far, such calculations have hinged on the use of solitary excretions estimates from single studies of limited scope and/or studies of limited applicability. Therefore, the need exists to conduct a comprehensive meta-analysis of metabolic disposition studies to construct excretions profiles for the various illicit drugs and their in vivo metabolites. The constructed excretory profiles should not only provide mean excretion values but also indicate the expected variations in excreted fractions that arise due to differences not only in the metabolic capacity of users but also in the efficiencies of various routes of administration for a given illicit drug. Therefore, the primary goal of the research presented here was to refine sewer epidemiology extrapolation mass balances for various illicit drugs of interest by constructing their excretory profiles segregated by route-of-administration. After conducting such a study with a multi-national scope on illicit drugs including cocaine, heroin and ecstasy, the results obtained clearly indicate that extrapolation factors currently being used in literature for these drugs to enumerate prevalence of abuse required significant refinement to increase their reliability.

KEYWORDS: Sewer epidemiology, route-of-administration, excretion profile, cocaine, heroin, ecstasy.

Abbreviations: 6MAM, 6-monoacetylmorphine; AEEE, anhydroecgonine ethylester; AEME, anhydroecgonine methylester; BNE, benzoynorecgonine; BE, benzoylecgonine; COC; cocaine; COE, cocaethylene; EC, ecgonine; ECD, ecgonidine; EME, ecgonine methylester; HER, heroin; HHMA, 3,4-dihydroxymethamphetamine; HMA, 4-hydroxy-3-methoxyamphetamine; HMMA, 4-hydroxy-3-methoxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; m-HOBE, m-hydroxybenzoylecgonine; m-HOCOC, m-hydroxycocaine; MOR; morphine; NCOC, norcocaine; NMOR, normorphine; p-HOBE, p-hydroxybenzoylecgonine; p-HOCOC, p-hydroxycocaine; SEEB, sewer epidemiology extrapolation mass balances; SEM, sewer epidemiology metabolite; STP, sewage treatment plant.

6.1 INTRODUCTION

The use of illicit drugs within a given population carries tremendous economic, social and public health costs (Degenhardt et al., 2009; Kilmer and Pacula, 2009; Nutt et al., 2007). Therefore, it is imperative to quantify the prevalence of their abuse within a given population so that appropriate control, prevention and rehabilitation measures can be put in place and their effectiveness monitored. Traditionally, epidemiologists have relied on a number of indirect subjective methods to estimate the prevalence of illicit drugs within a population of interest, where these methods typically require data from multiple lines of evidence, which may not necessarily be available for all geographical locations (EMCDDA, 1999; Kraus et al., 2003). Even when such data are available, the resultant prevalence estimate often needs to be adjusted for underreporting (Kilmer and Pacula, 2009). Most importantly traditional drug prevalence methods have an inherent time lag of at least a few years built into their outputs as retrospective data must be collected, processed and analyzed before prevalence estimates can be generated (UNODC, 2010). In an effort to overcome these limitations, an alternative approach has been suggested based on sewer epidemiology (Daughton, 2001; Zuccato et al., 2005; Zuccato et al., 2008). Sewer epidemiology relies on measuring concentrations of selected illicit drugs or their *in vivo* metabolites in the influent of sewage treatment plants (STP) as a means of back-calculating the epidemiological prevalence of these drugs and their patterns of consumption (Boleda et al., 2009; Bones et al., 2007; Castiglioni et al., 2007; Castiglioni et al., 2008; Huerta-Fontela et al., 2008; Kasprzyk-Hordern et al., 2009; Postigo et al., 2010; van Nuijs et al., 2009; Zuccato et al., 2005; Zuccato et al., 2008). Hence, in theory such a method can allow an epidemiologist to track real-time changes in drug consumption patterns within a given population by monitoring the concentrations of appropriate metabolites in the influents of wastewater treatment plants (Daughton, 2001).

The accuracy and hence the utility of the sewer epidemiology approach is heavily reliant on the back-extrapolated mass balances used to translate measured influent concentration into epidemiological prevalence. In almost all instances reported to-date (Boleda et al., 2009; Kasprzyk-Hordern, et al., 2009; Postigo et al., 2010; van Nuijs et al., 2009; Zuccato et al., 2005; Zuccato et al., 2008), extrapolation mass balance factors suggested by Zuccato et al. (2008) are used; however, Zuccato et al. (2008) primarily relied on excretion estimates arising from either single studies of limited scope and/or studies of limited applicability to develop their sewer epidemiology extrapolation mass balances (SEEB). More importantly, they did not consider the effects that route-of-administration has on the excretory profiles of such drugs. Hence, their suggested SEEBs need to be refined and improved upon if sewer epidemiology is to be used as a routine strategy to gauge the prevalence of illicit drug use within a community. Furthermore, the need

exists to conduct a comprehensive meta-analysis of metabolic disposition studies to construct excretions profiles for the various illicit drugs and their *in vivo* metabolites. Moreover, the constructed excretory profiles should not only provide mean excretion values but also indicate the expected metabolic variations so that sewer epidemiologists can put bounds on their illicit drug prevalence estimates. Therefore, the primary goal of the study presented here was to improve SEEBs for the various illicit drugs of interest by constructing their excretory profiles segregated by route-of-administration. Further, since the interest here is in developing generic SEEBs that can be readily adapted to various national situations, the development of SEEBs was conducted with a multi-national scope. An additional utility of the generated excretory profiles will be that they can serve as a complete inventory of all chemicals that are expected to enter the environment due to the abuse of a given illicit drug.

The development of comprehensive excretory profiles would also allow one to critically select the most suitable sewer epidemiology metabolite (SEM) for each illicit drug, which becomes the primary indicator of drug use. The SEM could be the illicit drug itself or one of its metabolic products. Conceptually, it is proposed here that an ideal SEM either originating from the use of a particular illicit drug would possess the following characteristics: (i) be released to sewers exclusively due to the abuse of the illicit drug of interest (Note: this suggests that a metabolite would be a better SEM than the parent drug, since the presence of the parent drug could also originate from the disposal/dumping of the unused drug into the sewer system); (ii) demonstrate a predictably well-defined excretory profile from all potential exogenous and endogenous excretory sources; (iii) be excreted in such quantities that allow for continuous monitoring of the SEM in the influent of the sewage treatment plants; (iv) demonstrate low adsorption potential to suspended matter since influent samples are typically filtered before analysis; and (v) be either reasonably stable during the sewer transit processes or have a predictable pattern of degradation such that the quantification of the SEM is not compromised. Hence, an additional goal of this study is to suggest the most appropriate SEM for selected illicit drugs by systematically evaluating their suitability using the aforementioned characteristics. No attempts have been to date to conduct such a systematic evaluation and use it as a basis for the selection of SEMs for the various illicit drugs of interest.

Following the development of a general approach that should be applicable for any drug of interest, illicit or licit, the methodology will be applied to the illicit drugs cocaine, heroin and 3,4-methylenedioxymethamphetamine (MDMA), which is commonly referred to as “ecstasy”. Where possible, an appropriate SEM for each of these was systematically selected using the criteria mentioned above.

6.2 Methods & Model Development

A nomenclature of all variables used below is contained in Appendix A.

6.2.1 Data sources for metabolic disposition data and excretion profiles

A comprehensive literature search was conducted to retrieve studies reporting urinary and fecal excretion profiles for the illicit drugs of interest by mining the following literature databases: Pub Med, EMBASE, SCOPUS, Google Scholar and Scifinder Scholar.

Means and standard deviations (σ) for the excreted fractions of the various metabolites were extracted from all relevant studies. In cases where standard errors were reported, they were converted to standard deviations by multiplying them by the square root of the number of observations. For those cases where the range was reported, σ was approximated by dividing the range by 4 as suggested by Massart et al (1997). Mean excreted fractions of the various metabolites from different studies for a particular illicit drug and a route-of-administration combination were pooled by weighting each mean by the number of subjects monitored in the study. Standard deviations were also combined by the number of subjects, specifically according to the pooled standard deviation method suggested by Massart et al. (1997).

6.2.2 Development of a generic mass balance (SEEB) for a selected SEM

A typical sewer epidemiology investigation would only measure the total dissolved concentration of an appropriate SEM in the influent of the STP being studied. This concentration (C_{in-s}) can be converted into a daily mass load of the SEM arriving at the STP being monitored as follows:

$$J_{T,s} = \frac{C_{in-s} \cdot Q_{in}}{P \cdot (1 - x_{s-s})} \quad (1)$$

where: $J_{T,s}$ is the total daily per capita load of the SEM arriving in the influent of the STP being monitored (μg of SEM/cap·d); C_{in-s} is the dissolved concentration of an appropriate SEM in the influent of the STP being monitored (μg of SEM/L); Q_{in} is daily flow arriving as the influent to the treatment plant (L/d); and P is the population served by the STP. The term $(1 - x_{s-s})$ is the factor that corrects for the influent mass load of the SEM that is expected to be sorbed onto suspended solids and, hence, likely to be unaccounted for in cases where influent samples are first filtered to facilitate chemical analyses. The typical fraction of an SEM likely to be sorbed onto influent suspended solids, x_{s-s} , (dimensionless), can be estimated using the following model suggested by Deo and Halden (2010):

$$x_{s-s} = 1 - \frac{1}{1 + x_{oc} \cdot D_{oc-s} \cdot C_{SS}} \quad (2)$$

where: x_{oc} is the fraction (dimensionless) of influent suspended solids that is organic carbon and for which a typical value for municipal suspended solids is 0.43 (Braga et al., 2005); D_{oc-s} is the organic carbon–water distribution coefficient (L/kg) at relevant pH values, which can be predicted using ACD Labs' property prediction software (2010)_embedded in SciFinder Scholar; and C_{ss} is the average concentration of suspended solids in the influent of a wastewater treatment plant, for which a typical value in municipal wastewater is 175×10^{-6} kg/L (Qasim, 1999). D_{oc-s} and, hence, x_{s-s} were evaluated at pH values of 7.5 and 2.0. The former evaluation recognizes the cases where the influent samples are filtered before they are preserved through acidification, where a pH value of 7.5 reflects the mean pH of wastewater influents (Qasim, 1999). The evaluation at a pH of 2.0 represents cases where the influents are preserved through acidification, typically by adjusting the pH this level before the suspended solids are filtered off (Deo and Halden, 2010).

Note that, in certain cases, the SEM arising from the use of a given illicit drug may also be produced due to the metabolism of other licit drugs. In this case, the fraction of the SEM resulting from licit use can be modeled as follows:

$$J_{L,s-m} = \sum_{b=1}^B L_b \cdot \frac{Mw_s}{Mw_b} \cdot \frac{Mo_s}{Mo_b} \cdot \left((1 - Y_{nb}) \left(\sum_{i=1}^I (U_{b,i,s} + F_{b,i,s}) \cdot x_i \right) \right) \quad (3)$$

where: $J_{L,s-m}$ represents the amount of $J_{T,s}$ that results from licit uses of other drugs (μ g of SEM/cap·d); B is the number of individual formulations, b , that can be metabolized to SEM; L_b is the daily per capita mass sold of formulation b that is expected to be metabolized to the SEM upon licit use within the community (μ g of b /cap·d); Mw_b is the molecular weight of formulation b (g of b /mole of b); Mw_s is the molecular weight of the SEM (g of SEM/mole of SEM); Mo_s/Mo_b is the molar stoichiometric ratio of metabolically-generating an SEM from a given formulation b (i.e., moles of SEM produced per mole of b transformed); Y_{nb} is the fraction of formulation b sold that ends up not being used by formulation b users (dimensionless); I is the number of individual routes-of-administration, i , typically used to administer a given formulation b ; $U_{b,i,s}$ is the net the fraction of L_b that is expected to be excreted as the SEM in the urine of formulation b users when administered via the route i (moles of b /moles of b); $F_{b,i,s}$ is a further fraction of L_b that is expected to be excreted as the SEM in the fecal matter of formulation b users when administered via route i (moles of b /moles of b); and x_i is the fraction of the users that administer formulation b through the route-of-administration i . Note that for the fecal release contribution of the SEM in the equation above (i.e., $F_{b,i,s}$), and all such fecal contributions in equations to follow, it is assumed that equilibrium is established between the fecal SEM content and the surrounding matrix. This

may not be true for cases where the SEM is highly nonpolar and/or is predominately excreted via the fecal route.

The SEM may also be licitly released to sewer if the SEM itself is clinically used. This contribution can be evaluated as follows:

$$J_{L,s-c} = L_s \cdot \left((1 - Y_{ns}) \left(\sum_{e=1}^E (U_{s,e,s} + F_{s,e,s}) \cdot x_e \right) + Y_{ns} \cdot Y_{fs} \right) \quad (4)$$

where: $J_{L,s-c}$ represents the amount of $J_{T,s}$ that results from the clinical use of the SEM itself (μg of SEM/cap·d); L_s is the daily per capita mass sold of the SEM itself for clinical purposes (μg of SEM/cap·d); Y_{ns} is the fraction of clinical SEM sold that ends up not being used by clinical SEM users (dimensionless); E is the number of routes-of-administration typically used to clinically administer SEM; $U_{s,e,s}$ is the molar fraction of L_s that is expected to be excreted as the unchanged SEM in the urine of clinical SEM users when administered via the route e (moles of SEM/moles of SEM); $F_{s,e,s}$ is the molar fraction of L_s that is expected to be excreted as unchanged SEM in the fecal matter of clinical SEM users, when administered via the route e (moles of SEM/moles of SEM); x_e is the fraction of the users that administered the clinical SEM through the route-of-administration e ; and Y_{fs} is the fraction of Y_{ns} that is expected to be flushed down the toilets and/or sinks (dimensionless).

In some situations, the SEM could also be naturally present in human excretions, either due to endogenous production of the SEM and/or its consumption through human diet. This licit contribution can be evaluated as follows:

$$J_{L,s-end} = (u_{e-s} + f_{e-s}) \quad (5)$$

where: $J_{L,s-end}$ represents the amount of $J_{T,s}$ that results from the endogenous excretion of the SEM itself (μg of SEM/cap·d); and u_{e-s} and f_{e-s} are per capita endogenous excretion of the SEM on a daily basis in the populations urinary and fecal excretions, respectively (μg of SEM/cap·d).

Therefore, the net load of all plausible licit sources ($J_{L,s}$) contributing to $J_{T,s}$ can be expressed by summing the contributions from $J_{L,s-m}$, $J_{L,s-c}$ and $J_{L,s-end}$:

$$J_{L,s} = J_{L,s-m} + J_{L,s-c} + J_{L,s-end} \quad (6)$$

Furthermore beyond licit sources, during the sewer transit process the SEM of interest could potentially be generated due to the degradation of other sewer-borne contaminant loads. Such in-transit generation of the SEM can be modeled as follows:

$$J_{G,s} = \sum_{g=1}^G L_g \cdot (1 - \text{EXP}(-k_{d,g} \cdot t_s)) \cdot x_{g-s} \cdot \frac{\text{Mo}_s}{\text{Mo}_g} \cdot \frac{\text{Mw}_s}{\text{Mw}_g} \quad (7)$$

where: $J_{G,s}$ represents the amount of $J_{T,s}$ that results from in-transit generation of the SEM due to the degradation of other sewer borne contaminants loads (μg of SEM/cap·d); G is the total number of individual contaminants, g , that could potentially degrade to the SEM of interest during the sewer transit process; L_g is the daily per capita release of a contaminant g to sewers (μg of g /cap·d); $k_{d,g}$ is first-order decay constant for contaminant g to the SEM (d^{-1}); t_s is the mean sewer residence time (d); Mo_s/Mo_g is the molar stoichiometric ratio corresponding to the moles of SEM generated due to the degradation of a particular contaminant g (moles of SEM/moles of g); and Mw_g is the molecular weight of contaminant g (g of g /mole of g).

Influent loads of the SEM exclusively originating from the use of the illicit drug of interest can now be evaluated by subtracting $J_{L,s}$ and $J_{G,s}$ from $J_{T,s}$:

$$J_{I,s} = J_{T,s} - J_{L,s} - J_{G,s} \quad (8)$$

where $J_{I,s}$ represents the contribution to $J_{T,s}$ that results exclusively from the use of the illicit drug of interest (μg of SEM/cap·d).

$J_{I,s}$ is the SEM load at the influent of the sewage treatment plant and, hence, represents the un-degraded portion of the net load that was initially excreted to the sewers. Hence, the daily load of the SEM actually excreted in the abusers' excretions ($R_{I,s}$) could be related to $J_{I,s}$ by accounting for the potential degradation of the SEM during the sewer-transit process as follows:

$$R_{I,s} = \frac{J_{I,s}}{\text{EXP}(-k_{d,s} \cdot t_s)} \quad (9)$$

where $R_{I,s}$ represents the daily per capita load of the SEM that is expected to be excreted by the abusers of the drug of interest (μg of SEM/cap·d) and $k_{d,s}$ is the first-order decay constant for the SEM (d^{-1}).

Ultimately, since the interest lies in estimating the net per capita consumption of the illicit drug of interest ($R_{I,d}$) that is generating the SEM being monitored, $R_{I,s}$ can be converted to the desired quantity as follows:

$$R_{I,d} = R_{I,s} \cdot \frac{\frac{\text{Mw}_d}{\text{Mw}_s}}{\sum_{h=1}^H (U_{h,s} + F_{h,s}) \cdot x_h} \cdot \left(\frac{\text{Mo}_s}{\text{Mo}_d} \right)^{-1} \quad (10)$$

where: $R_{l,d}$ is the net daily per capita illicit consumption of a particular drug within the population that is connected to the STP being monitored (μg of illicit drug/cap·d); H is the total number of individual routes-of-administration, h , typically used for an illicit drug; $U_{h,s}$ is the fraction of the illicit drug that is excreted as the SEM in the abusers' urine when the drug is administered via a typical route-of-administration h (moles of illicit drug /moles of illicit drug); $F_{h,s}$ is the additional fraction of the illicit drug that is excreted as the SEM in the fecal matter of the abuser when the drug is administered via a typical route-of-administration h (moles of illicit drug/moles of illicit drug); x_h is the fraction of the abusers that administer the illicit drug through the route-of-administration h ; Mw_d is the molecular weight of the illicit drug (g of illicit drug/moles of illicit drug); and Mo_s/Mo_d is the molar stoichiometric ratio of metabolically-generated SEM by abusing the illicit drug of interest (moles of SEM/moles of illicit drug of interest).

From an epidemiological and public health perspective, a desirable goal would be to estimate the number of abusers of the drug of interest rather than the net mass of illicit drug abused within a community. Recognizing this, conversion of $R_{l,d}$ to a measure of the number of abusers would be particularly useful. A “number of abusers” measure typically used by agencies such as the United Nations Office on Drugs and Crime (UNODC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the prevalence of all abusers for a particular illicit drug within a given population's 15-64 year age cohort. $R_{l,d}$ can be related to such a prevalence measure as follows:

$$R_{l,d} = xr_{15-64} \cdot \frac{p_{r-d}}{100} \cdot \left(\sum_{m=1}^M x_{m,d} \cdot d_{m,d} \right) \quad (11)$$

where: xr_{15-64} is the fraction of the wastewater-contributing population that is within the 15-64 year age cohort; p_{r-d} is the percentage of abusers for a particular illicit drug within the 15-64 year old cohort of the population being monitored (%); M is the number of individual groups of abusers, m , using a given drug with different intensities that are likely to be present within the population (e.g., when data is available for recreational users and chronic users of a particular drug, M would equal to 2); $x_{m,d}$ is the fraction of the total abusers of a particular illicit drug that are likely to use the drug with an intensity of group m ; and $d_{m,d}$ is the net daily-averaged amount of illicit drug demanded/consumed by intensity group m (μg of illicit drug/cap·d).

Equating Equations (10) and (11) and solving for p_{r-d} yields the following generic SEEB for a particular illicit drug:

$$p_{r-d} = \left[\frac{R_{I,s}}{x_{r_{15-64}} \cdot \left(\sum_{m=1}^M x_{m,d} \cdot d_{m,d} \right)} \cdot \frac{\frac{Mw_d}{Mw_s}}{\sum_{h=1}^H (U_{h,s} + F_{h,s}) \cdot x_h} \cdot \left(\frac{Mo_s}{Mo_d} \right)^{-1} \right] \cdot 100 \quad (12)$$

6.2.3 Estimating the net daily per capita demand for various illicit drugs in a national population

The net per capita daily demand of various illicit drugs (N_d) was estimated for a number of national populations, in order to establish the relative importance of licit use contributions to influent loads of SEMs. Wherever data permitted, the abusers for a particular illicit drug and also their demand for that drug were segregated based on the intensity of abuse (i.e., as either recreational users or chronic users). Conceptually, the methodology of Kilmer and Pacula (2009) was adapted in order to calculate N_d and, where available, data inputs were updated to reflect recent data. Specifically, the following equation was used to estimate N_d :

$$N_d = \frac{x_{n_{15-64}} \cdot \frac{p_{N-d}}{100} \cdot \left(\sum_{m=1}^M x_{m,d} \cdot d_{m,d} \right)}{1 - UN_d} \quad (13)$$

where: p_{N-d} is the reported national prevalence of all abusers for a particular illicit drug within the 15-64 year age cohort (%); $x_{n_{15-64}}$ is the fraction of a national population that is within the 15-64 year age cohort; UN_d is the fraction of the abusers that are likely to under-report their use of a particular drug of abuse; and all other parameters are as defined previously.

To illustrate the application of Equation (13) and the data sources used to quantify its various parameters, the procedure used to evaluate N_d for various drugs of interest in Spain has been summarized in Appendix B. Demand estimates for other countries, discussed below, were generated in a similar manner.

6.2.4 Estimating the nationally-averaged concentration of an SEM in the influents of a country

In order to evaluate whether a particular SEM being considered would yield detectable concentrations in wastewater influents, the predicted nationally-averaged influent concentrations (PIC_{d-s}) for a given country can be generated using the following equation:

$$PIC_{d-s} = \frac{\left(N_d \cdot \left(\sum_{h=1}^H (U_{h,s} + F_{h,s}) \cdot X_h \right) \frac{Mw_s}{Mw_d} + J_{L,s} + J_{G,s} \right) (1 - k_{d,s}) \cdot (x_{con})}{W} \quad (14)$$

where: W is the average wastewater produced per capita for a given country (L/cap·d); x_{con} is the fraction of the national population that is connected to wastewater treatment plants (dimensionless); and all other parameters are as defined above.

It is important to note that the purpose of Equation (14), and hence Equation (13), is not to suggest that the influent concentrations of SEMs should be modeled for predictive purposes. Rather, these equations serve to generate approximate estimates for PIC_{d-s} for various national populations so that the feasibility for the continuous monitoring of a potential SEM in wastewaters can be assessed. Further, the comparison of the generated estimates to reported field data (as will be done later) only serve to assess the plausibility of the predicted estimates.

6.3 Results and Discussion

The systematic approach taken here in developing an appropriate SEEB for an illicit drug of interest can be summarized as follows: (i) identify all relevant routes-of-administration; (ii) compile disposition data for each route; (iii) use the compiled data to construct excretory profiles for each route-of-administration; (iv) utilize the constructed profile and the SEM selection criteria mentioned above to select the most suitable SEM; and (v) develop an improved SEEB for the selected SEM with the aid of Equation (12). The application of the proposed approach is demonstrated below for cocaine, heroin and MDMA.

6.3.1 Cocaine

6.3.1.1 Routes of administration

Abusers typically administer cocaine by one or more of the following routes: nasal insufflation, smoking, injection or oral ingestion (SAMHSA, 2007). Of these, nasal insufflation and smoking are the dominant routes-of-administration (EMCDDA, 2009; Gossop et al., 1994; SAMHSA,

2007). Typically, “cocaine” refers to its hydrochloride (HCl) salt, while “crack” refers to free base cocaine (Hatsukami and Fischman, 1996). Cocaine’s HCl salt is predominately abused by nasal insufflation as it decomposes before its vaporization temperatures can be reached, while crack vaporizes relatively easily and therefore is typically smoked (EMCDDA, 2009; Gossop et al., 1994; Hatsukami and Fischman, 1996; SAMHSA, 2007). Thus, in geographical regions where crack cocaine is readily available and used, the primary route-of-administration is through smoking. For example in the United States, where the use of crack cocaine predominates, 73% of admissions to substance-abuse treatment programs reported smoking to be their primary route of administering cocaine (SAMHSA, 2007). The smoking proportions in a similar European population are reported to be significantly less, with a suggested continental average of 31.6 %, varying nationally from 0% to 45.9% (EMCDDA, 2009a). In Australia, the proportion of abusers smoking cocaine is minor, as crack is rarely available (NDARC, undated; Ross, 2007). It is important to recognize that the route-of administration trends listed above for Europe and the United States are for those who are in treatment for cocaine abuse and not necessarily representative for the whole cocaine-abusing population. Nevertheless, by comparing trends in such a population, for which a dataset is readily available, one can establish the relative importance of the various forms of cocaine and hence the routes used to administer them in different regions.

6.3.1.2 Excretion profiling

In total, nine suitable studies reported excretory profiles of cocaine administered through various routes (Ambre et al., 1984; Ambre et al., 1988; Cami et al., 1998; Cone et al., 1998; Fish and Wilson, 1969; Hamilton et al., 1977; Inaba et al., 1978; Jacob et al., 1990; Jeffcoat et al., 1989). The meta-analysis of compiled data (see Table 6.1) suggests that the urinary excretion profile is quite similar when cocaine is either administered through injections or through nasal insufflation; however, significantly lower amounts are likely in urinary excretion profiles when cocaine is smoked. This is expected due to the partial decomposition of crack during the vaporization process, losses in smoke streams not inhaled by the abuser, and due to the fact that un-vaporized residuals are often left behind in the smoking apparatus (Jeffcoat et al., 1989; Perez-Reyes et al., 1982).

Table 6.1 Excretory profile of cocaine upon various routes of administration.

Excretory profile (% of administered dose) of specific metabolites															
Reference	Dose (mg)	n	Age (yr)	Duration (hr)	EME	BE	COC	EC	NCOC	BNE	m-HOCOC	p-HOCOC	m-HOBE	p-HOBE	AEME
Oral															
Inaba et al., 1978	10	2	37-60	24 - 28	40.5	39	1								
I.V. Administered															
Ambre et al., 1984	48	1	21-25	48	37.0	52	1								
Ambre et al., 1988	226-624	5	24-35	24	13.4 ± 7.1	22.2 ± 10	1.8 ± 0.8								
Fish and Wilson, 1969	107	1	23	24		42.9	3.3								
Jeffcoat et al., 1989	20.5	4	19-32	72	19.3 ± 4.3	36.0 ± 4.1	0.6 ± 0.5	2.8 ± 0.5							
Jacob et al., 1990	34.8	7	20-33	48		44.9 ± 18	2.6 ± 1.4								≈ 0
Cone et al., 1998	22.3	6	-	72	15.4 ± 5.7	39.3 ± 9.0	1.0 ± 1.0		0.03 ± 0.04	0.62 ± 0.28	0.08 ± 0.06	0.004 ± 0.003	0.46 ± 0.40	0.43 ± 0.26	≈ 0
					U _{I.V.,s} 17.1 ± 5.9	39.2 ± 13	1.8 ± 1.1	2.8 ± 0.5	0.03 ± 0.04	0.62 ± 0.28	0.08 ± 0.06	0.004 ± 0.003	0.46 ± 0.40	0.43 ± 0.26	≈ 0
					U _{I.V.,s} +F _{I.V.,s} 18.4 ± 6.3	42.1 ± 14	1.9 ± 1.2	3.0 ± 0.5	0.03 ± 0.04	0.66 ± 0.28	0.09 ± 0.06	0.004 ± 0.003	0.49 ± 0.43	0.46 ± 0.28	≈ 0
Nasal Insufflation ^(a)															
Ambre et al., 1984	48,96	2	21-25	48	41.5	44.8	8.0								
Hamilton et al., 1977	67-110	6	23-34	168		28.4 ± 8.4	1.7 ± 1.5								
Jeffcoat et al., 1989	94.6	4	19-32	72	18.2 ± 2.9	39.0 ± 7.6	0.8 ± 0.5	2.7 ± 1.2							
Cami et al., 1998	100	6	-	48	22.8 ± 4.8	30.2 ± 6.1	0.9 ± 0.2		0.06 ± 0.03						
Jacob et al., 1990	116	6	20-33	48		24.7 ± 7.9	1.1 ± 0.8								≈ 0
Cone et al., 1998	28.5	6	-	72	12.9 ± 5.4	29.9 ± 8.3	0.5 ± 0.5		0.02 ± 0.02	1.0 ± 0.5	0.1 ± 0.07	0.007 ± 0.01	0.5 ± 0.2	0.5 ± 0.5	≈ 0
					U _{nasal,s} 20.5 ± 5.9	30.8 ± 7.7	1.5 ± 1.7	2.7 ± 1.2	0.04 ± 0.03	1.0 ± 0.5	0.1 ± 0.07	0.007 ± 0.01	0.5 ± 0.2	0.5 ± 0.5	≈ 0
					U _{nasal,s} + F _{nasal,s} 21.6 ± 6.2	32.5 ± 8.5	1.6 ± 1.8	2.8 ± 1.3	0.04 ± 0.03	1.1 ± 0.5	0.1 ± 0.07	0.007 ± 0.01	0.5 ± 0.2	0.5 ± 0.5	≈ 0
Smoked ^(a)															
Jeffcoat et al., 1989 ^(b)	50	6	19-32	72	17.7 ± 2.5	20.5 ± 6.4	0.6 ± 0.5	1.7 ± 0.7							
Jacob et al., 1990	100	9	20-33	48		6.5 ± 3.1	0.5 ± 0.3								0.26 ± 0.28
Cone et al., 1998	42	5	-	72	7.2 ± 4.7	16.4 ± 11.4	0.5 ± 0.4		0.003 ± 0.004	0.2 ± 0.2	0.04 ± 0.02	0	0.2 ± 0.2	0.2 ± 0.2	0.02 ± 0.02
					U _{smoke,s} 12.9 ± 3.6	13.0 ± 6.9	0.5 ± 0.4	1.7 ± 0.7	0.003 ± 0.004	0.2 ± 0.2	0.04 ± 0.02	0	0.2 ± 0.2	0.2 ± 0.2	0.17 ± 0.24
					U _{smoke,s} +F _{smoke,s} 14.8 ± 4.1	14.9 ± 7.9	0.6 ± 0.5	2.0 ± 0.8	0.003 ± 0.005	0.2 ± 0.2	0.05 ± 0.02	0	0.2 ± 0.2	0.2 ± 0.2	0.19 ± 0.27

(a) Commonly used routes to administer cocaine (SAMHSA, 2007; Gossop et al., 1994; EMCDDA, 2009a).

(b) Based on the mass of cocaine initially placed in the smoking device.

Metabolite abbreviations: ecgonine methylester (EME); benzoylecgonine (BE); cocaine (COC); ecgonine (EC); norcocaine (NCOC); benzoynorecgonine (BNE); m-hydroxycocaine (m-HOCOC); p-hydroxycocaine (p-HOCOC); m-hydroxybenzoylecgonine (m-HOBE); p-hydroxybenzoylecgonine (p-HOBE) and anhydroecgonine methylester (AEME).

In contrast to the vast body of literature reporting on the urinary excretion profile of administered cocaine, its fecal disposition is rarely studied. To date, only Jeffcoat et al. (1989) have reported on the fecal disposition of cocaine. Their data suggest that the ratio of the net fecal load to the net urinary load amounted to 7%, 5%, and 15% after injection, insufflating and smoking cocaine, respectively. Unfortunately, the authors did not further analyze the fecal samples to ascertain the exact fecal excretory profile. Hence, in the absence of more comprehensive data, one must assume that the fecal excretory profile of cocaine closely resembles its urinary profile for a particular route-of-administration. This assumption allows one to extrapolate the urinary excretion profile of the various metabolites for a given route-of-administration to the expected net excretory profile by using the extrapolation factors of 1.07, 1.05 and 1.15 for injection, insufflation and smoking, respectively (Table 6.1).

6.3.1.3 Relevant sewer epidemiology metabolite

The data in Table 6.1 suggest that, irrespective of the route-of-administration, cocaine is expected to be extensively metabolized. This, coupled with the fact that cocaine readily hydrolyses (Gheorghe et al., 2008; Hippenstiel and Gerson, 1994; Isenschmid et al., 1989; Zaitso et al., 2008) and is therefore expected to partially degrade during the sewer-transit process, eliminates it as a suitable SEM for tracking the abuse of cocaine within a community. Even though it is excreted in appreciable quantities, EME is also relatively unstable (Gheorghe et al., 2008; Isenschmid et al., 1989) and hence its candidacy would require comprehensive understanding of its in-sewer degradation potential.

In contrast, BE is relatively stable (Gheorghe et al., 2008; Hippenstiel and Gerson, 1994; Isenschmid et al., 1989; Zaitso et al., 2008) (i.e., $k_{d-BE} \approx 0$) and is the major excretory metabolite irrespective of the route-of-administration (Table 6.1). One possible source of BE during sewer transit is the potential degradation of cocaine (Hippenstiel and Gerson, 1994; Isenschmid et al., 1989; Kiszka et al., 2000); however, the contribution of degrading cocaine loads to BE loads is expected to be small. First, typical conditions in the sewer are not expected to be fully aerobic at all times (Guddjonsson et al., 2002) and, hence, the potential degradation of the cocaine loads is likely to be partially inhibited. Secondly, even if one considers cocaine loads to be susceptible to substantial decay during the transit process, the reported half-life of cocaine hydrolysis/biodegradation at room temperature under fully aerobic conditions is approximately 7 hours (Gheorghe et al., 2008), while typical sewer transit times have been reported to be less than this, with most reported values on the order of a few hours (D'Ascenzo et al., 2003; Holt et al., 1998; Ort et al., 2010a). Lastly, the ratio of cocaine to BE loads, either theoretically estimated from the

constructed excretion profiles shown in Table 6.1 or based on monitoring data, are expected to range between 4-6 % and 20-30% (see Fig D.2), respectively (Note: the discrepancy between the theoretically-predicted and monitored loads of cocaine is discussed in the Appendix D). Therefore, in light of current evidence suggesting that sewer-borne loads of cocaine are likely to be less than the loads of BE and, further, are not expected to appreciably degrade upon undergoing sewer-transit. The contribution of degrading cocaine to BE loads is assumed here to be of minor importance (i.e., $J_{G,BE} \approx 0$). However, in cases where the sewer residence times are much longer and/or the relative ratio of cocaine to BE are consistently monitored to be above the 20 to 30% level, the contribution of degrading cocaine could indeed become important. In such cases, the assumption that contribution from degrading sewer loads of cocaine can be neglected would not hold and hence may need to be modified.

An additional source of BE that should be considered is its release in abusers' sweat (Daughton and Ruhoy, 2009), which is expected to end up in sewers through bathing and/or laundering activities. Contrary to the observed urinary excretory profile, BE is a minor metabolite in released sweat (Cone et al., 1994; Uemura et al., 2004). Analysis detailed in Appendix E suggests that BE from released sweat is expected to contribute negligible amounts to the net BE load.

When evaluating BE's sorption potential onto influent suspended solids (x_{s-BE}), the model of Deo and Halden (2010) represented by Equation (2) suggests that the fraction of BE expected to sorb onto influent suspended solids is expected to be less than 0.01% (Appendix C) and hence $x_{s-BE} \approx 0$.

Additionally, BE has no clinical use at present and, hence, $J_{L,BE} = 0$.

The evaluation of whether BE is excreted in detectable quantities can be assessed on two levels. On a primary level, as was done earlier in this section, the judgment could be based on the relative fractions of the excreted metabolites. However, a more suitable evaluation from a sewer epidemiology perspective would be based on asking whether the excreted amounts of BE are likely to yield consistently detectable concentrations in wastewater influents. Further, it should also be asked whether, on a relative basis, the detection of BE more likely in certain countries than others and, as a consequence, whether the applicability of sewer epidemiology as a monitoring method is more feasible in certain locations than others. Figure 6.1(A) represents a first attempt at trying to address such questions, where the estimated nationally-averaged concentrations of BE in wastewater influents of various countries have been plotted (See Appendix F for a sample calculation of the procedure used).

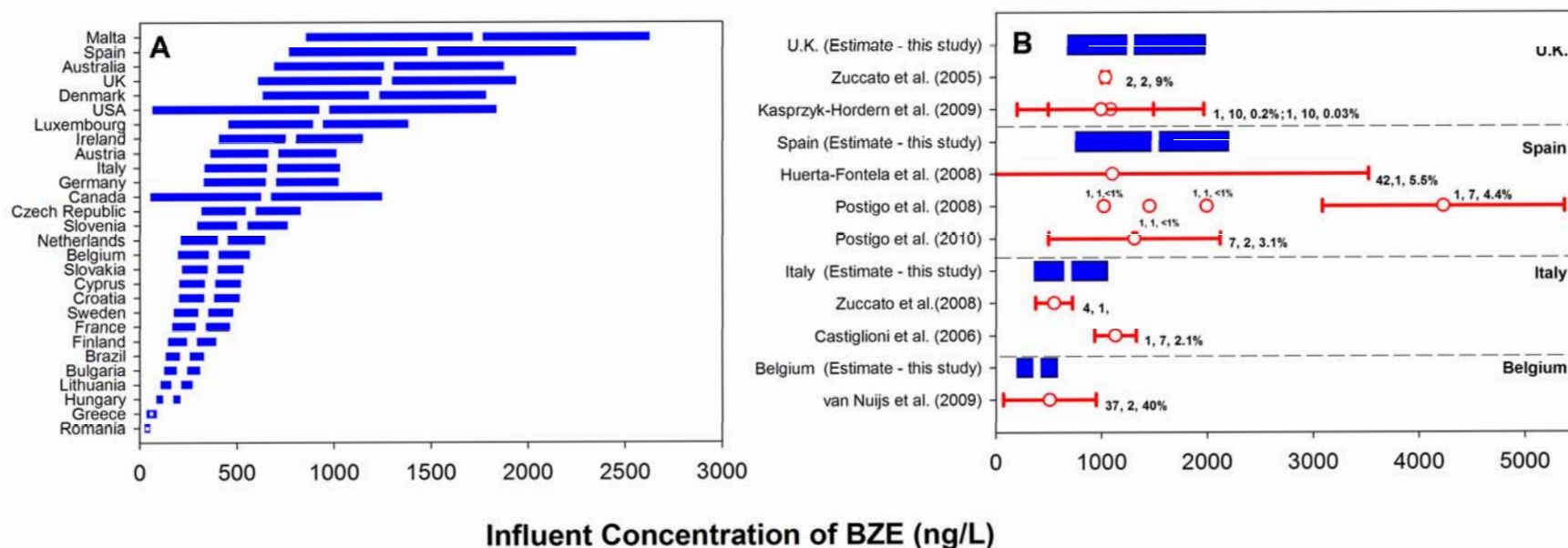


Figure 6.1(A) Theoretically-derived national estimates (■) of BZE concentrations in the influents of various countries (for a sample calculation see Appendix F). The extents of the filled bars represent one standard deviation of variation ($\pm\sigma$), while the vertical white line represents the mean.

Figure 6.1 (B) Comparison of theoretically-derived (■) nationally-averaged influent concentrations of BZE to those reported in sub-national monitoring studies (—○—). For monitored data, hollow circles represent means reported by each study while plotted error bars represent standard deviations of the reported values. The numerical values next to the monitored data represent, in order, spatial extent, temporal extent and percentage national coverage. Spatial extent is represented by the number of STPs monitored in the investigation; temporal extent is represented by the number of days each STP was monitored, and national coverage is the percentage of the national population that was contributing wastewater to the STPs monitored by a given study. For details on how the various theoretically-derived estimates were generated and the data sources required in the process, see Appendix G.

Before one can analyze and make observations based on such estimates, it is worth evaluating the plausibility of the estimates shown in this figure by comparing the generated concentrations with measured sub-national/regional concentrations. This is done in Figure 6.1(B) for a number of countries for which a sufficient level of monitoring data was available (i.e., either more than one monitoring study was available for a country or greater than 20% sampling of the national population was done). The figure suggests that the derived national estimates correspond reasonably well with the sub-national measured levels. The match is best for Belgian data reported by van Nuijs et al. (2009), where this was the only study in which the spatial extent of monitoring came close to providing a reasonable sampling of the national population. The match for other countries is still satisfactory, especially given the crude assumptions that were necessary to derive national consumption estimates of cocaine (see Appendix B), the poor spatial and temporal extent of the available measured data (see annotation next to measured data in Figure 6.1(B)), and the fact that the “trueness” of the measured data has been critically questioned by Ort and colleagues (2010; 2010a) since they originate in a limited number of sewer pulses (i.e., toilet flushes) and hence may not be accurately captured by present day sampling norms. Nevertheless, the reasonable correspondence suggests that the generated estimates are plausible and, more importantly for our purposes, the satisfactory match negates the possible existence of substantial “unaccounted-for” sources of BE.

Since the predicted nationally-averaged concentrations for all countries (see Figure 6.1(B)) were substantially higher than the limit-of-quantification of 0.2 – 2 ng/L presently reported for BE (Castiglioni, et al., 2006; Huerta-Fontela et al., 2007), it is concluded that BE can be used as suitable metabolite to monitor the abuse of cocaine within the population of all the countries analyzed. However, the possibility of consistently detecting BE and hence “without-fail” monitoring the abuse of cocaine within a country’s population increases as one progresses up the list of countries plotted on the y-axis of Figure 6.1(A). In other words, as one progress down the list, the likelihood that sewer epidemiology would need to be supplemented with traditional abuse record keeping methods increases. Nonetheless, the generated estimates suggest that sewer epidemiology may still be an available option, if not the lone preferred approach, to track cocaine’s use in low abuse countries such as Greece and Romania (UNODC, 2010).

Overall, the above analysis suggests that BE is the most suitable SEM to track the abuse of cocaine within a number of national populations.

6.3.1.4 SEEB to track cocaine abuse

As mentioned above, BE is not expected to degrade ($k_{d-BE} \approx 0$), or sorb on to influent suspended solids ($x_{s-BE} \approx 0$), or result significantly from the degradation of cocaine loads ($J_{G,BE} \approx 0$). Further, the respective chemical structures of BE and COC suggest that the *in vivo* stoichiometry of BE being metabolically-generated from administered COC (i.e., MO_{BE}/MO_{COC}) is equal to one. Therefore, the general equation for an SEEB, Equation (12), can be simplified to the following for BE:

$$p_{r-coc} = \frac{\left(\frac{C_{in-COC} Q_{in}}{P} \right)}{x_{r_{15-64}} \cdot \sum_{m=1}^M f_{m,COC} \cdot d_{m,COC}} \cdot \frac{1.05}{(0.39)x_{oral} + (0.42 \pm 0.14)x_{I.V.} + (0.33 \pm 0.09)x_{nasal} + (0.15 \pm 0.08)x_{smoke}} \cdot 100 \quad (15)$$

where 1.05 is the M_w ratio of COC to BE and the numbers in parentheses before the fractions of cocaine abusers for each route (i.e., x_{oral} , $x_{I.V.}$, etc.) are based on the excretion profiling presented in Table 6.1. For the sake of rigor and given the unforeseeable trends of future cocaine abuse, all four fractions of abusers are listed in Equation (15). However, patterns of abuse in most populations at present are such that by just enumerating x_{nasal} and x_{smoke} one can reasonably model the cocaine-abusing population.

Another aspect that may be important, and is often not acknowledged in the field of sewer epidemiology, is that co-abuse of ethanol and cocaine is quite common (Cami et al., 1998; Harris et al., 2003). Hence, it is important to establish any effect ethanol co-abuse may have on the excreted fractions of BE. However, currently available co-abuse urinary disposition data are such that it may be premature to confidently establish, and hence possibly adjust for, the effect ethanol of co-abuse (see Appendix H for a more extended examination of the available data).

Equation (15) is the suggested SEEB expression for cocaine. Not only does this equation capture the effect of route-of-administration on the excretory profile but it also accounts for the expected variation in the metabolic capacity of abusers. In their suggested SEEB, Zuccato et al. (2008) did not consider such effects but did suggest BE to be the most suitable SEM to track cocaine's abuse, albeit after a more limited analysis than the one conducted here. In the development of their SEEB, it was assumed that all cocaine abusers, irrespective of the route-of-administration, excreted 45% of the administered cocaine as BE by solely relying on the limited data (i.e., in a study of only 2 subjects) reported by Ambre et al. (1984). It is estimated that the continued use of the SEEB of Zuccato et al. (2008) instead of the refined one derived here, i.e., Equation (15), would tend to underestimate the national prevalence of cocaine abuse by an error of between 29% to 182%; where the former error refers to regions where nasal insufflation of cocaine dominates and the latter to regions where smoking of cocaine is predominant.

In conclusion, the use of the SEEB derived here will not only significantly improve the accuracy of back-extrapolating measured BE concentrations to cocaine prevalence measures but also allow sewer epidemiologist to put bounds on their generated estimates, based on variations in the metabolic capacities of the abusers and the efficiencies of various routes in delivering a desired dose.

6.3.2 Crack cocaine

Those individuals who smoke crack cocaine are more liable to become addicted than those whose administer the drug through insufflation (Hatsukami and Fischman, 1996); hence, from a public health perspective, it is of particular interest to monitor the prevalence of such abusers within a community. A number of unique pyrolysis products generated during the vaporization of crack have been detected in the urine of abusers (Langman et al., 2009; Martin et al., 1989; Paul et al., 1999; Paul et al., 2005; Riley et al., 2001). Therefore, the concentrations of such pyrolysis products could potentially be monitored in the influents of wastewater treatment plants to monitor the prevalence of crack abuse within a population of cocaine abusers or within the population as a whole. In particular, two pyrolytic products, anhydroecgonine methylester (AEME) and anhydroecgonine ethylester (AEEE) are of interest.

AEME is formed when crack is abused by itself (Langman et al., 2009; Martin et al., 1989; Paul et al., 1999; Paul et al., 2005; Riley et al., 2001), while AEEE is formed when crack is co-abused with ethanol (Langman et al., 2009; Paul et al., 2005). Since the co-abuse of ethanol and cocaine is quite common (Cami et al., 1998; Jatlow, 1993), one would need to track both AEME and AEEE to gauge the net prevalence of crack abuse within a population. At present, only $U_{smoke,s}$ values are available for the urinary excretion of AEME (Table 6.1), but comparable data is not currently available for AEEE. The reported $U_{smoke,AEME}$ values suggest that only trace or minor levels of AEME are to be expected in the net urinary excretions and even then the urinary fractions of AEME are expected to demonstrate a high degree of variability (e.g., compare mean $U_{smoke,AEME}$ reported by Jacob et al. (1990) to those reported by Cone et al. (1998) as listed in Table 6.1).

A more suitable marker to track crack abuse may be the hydrolytic product of AEME and AEEE, ecgonidine (ECD). Evidence suggests that ECD is excreted in substantially higher concentrations than AEME and AEEE (Paul et al., 1999; Paul et al., 2005; Riley et al., 2001). For example, Riley et al. (2001) reported that the ratio of concentrations of ECD to those of AEME were, on average, 19 times higher in spot urine collections from crack users. Limited data reported by Bisceglia et al. (2010), after the analysis of a single STP influent in the U.S.A., also reported ECD to be present at much higher concentrations

than AEME, while the detection of AEEE was not mentioned. Furthermore, ECD is expected to be more stable than AEME and AEEE since ECD is the product of AEME and AEEE hydrolysis itself and therefore does not contain the hydrolysis liable ester bond (Paul et al., 1999; Paul et al., 2005). Since AEME and AEEE can readily hydrolyze to ECD, it is worth considering the potential contribution of degrading AEME and AEEE loads to the loads of ECD during the sewer-transit process. The overall load contribution from the hydrolysis of the pyrolytic products is expected to be small, since spot urine collection data available suggests that AEME and AEEE loads are expected to be at least an order of magnitude smaller than ECD loads (Paul et al., 1999; Paul et al., 2005; Riley et al., 2001). Furthermore, the observed hydrolysis rates at wastewater relevant pH suggest that less than 5% of the AEME load is expected to be converted to ECD (Paul et al., 1999) ($J_{G,ECD} \approx 0$). Moreover, ECD is also expected to negligibly adsorb on to influent suspended solids (i.e., x_{s-ECD} being less than 0.01% at both pH values of interest, whereas AEME and AEEE demonstrate higher but acceptable adsorption potentials; see Appendix C).

Unfortunately, to-date only data on the urinary concentrations (ng/mL) of ECD in spot collections have been published (Paul et al., 1999; Paul et al., 2005; Riley et al., 2001), but the desired net cumulative fraction of ECD expected in the urine of crack abusers ($U_{smoke,ECD}$) has not been reported. Should such data become available, the SEEB than can be used to track prevalence of crack within a given population could be readily estimated using the following equation:

$$p_{r-crack} = \frac{\left(\frac{C_{in-ECD} Q_{in}}{P} \right)}{\text{EXP}(-k_{d-ECD} \cdot t_s) \cdot x_{r15-64} \cdot \sum_{m=1}^M f_{m,crack} \cdot d_{m,crack}} \cdot \frac{1.81}{(U_{smoke-ECD} + F_{smoke-ECD})} \cdot 100 \quad (16)$$

Here, the numerator of 1.81 represents the molecular weight ratio of cocaine to ECD (dimensionless) and x_{s-ECD} has been set equal to zero since ECD is expected to negligibly adsorb onto suspended solids. Further, the respective chemical structures of ECD and COC suggest that *in vivo* stoichiometry of ECD being metabolically-generated from smoked COC (MO_{ECD}/MO_{COC}) should be equal to one. Even though some evidence is available suggesting that ECD is not expected to degrade appreciably, k_{d-ECD} has been retained as an unknown in the equation above since conclusive evidence is desirable before one either disregards the degradation potential of ECD or accounts for it by enumerating k_{d-ECD} . Furthermore, based on the current evidence from spot urinary collections (Riley et al., 2001) and the values of $U_{smoke,AEME}$ listed in Table 6.1, when $U_{smoke,ECD}$ values do become available they are expected to be within the 1-5 % range. Recognizing this, ECD is expected to be a minor urinary metabolite and hence when its disposition data is sought, not only should attention be paid to its release in urine but potential contributions from

minor pathways such as elimination in fecal matter and sweat should also be considered since small contributions from such routes could conceivably end up being important for minor urinary metabolites (Daughton and Ruhoy, 2009).

6.3.3 Co-abuse of cocaine and ethanol

The co-abuse of cocaine and ethanol is also of epidemiological interest, since such co-abusers are at an increased risk of undesirable social, criminal and clinical consequences than those who exclusively administer cocaine (Cami et al., 1998; de la Torre et al., 1991; Henning et al., 1994). Cocaethylene (COE) is a unique metabolite which is only produced in instances of cocaine and ethanol co-abuse (Cami et al., 1998; de la Torre et al., 1991); hence, COE could be monitored in the influents of wastewater treatment plants to track the prevalence of such co-abuse within a population of interest.

Stability studies of blood and tissues samples (Moriya and Hashimoto, 1996; NCJRS, 2010) suggest that COE is expected to be more stable than cocaine in such samples. Nevertheless, there is a need for concrete data with respect to COE's degradation potential (i.e., k_{d-COE} is unknown). At a maximum, only 0.27% of COE (see Appendix C), is expected to be sorbed onto influent suspended solids, hence $x_{s-COE} \approx 0$. Thus-far, only urinary $U_{LN, COE}$ values have been reported in the literature. Specifically, 0.7 ± 0.3 % of nasally-insufflated cocaine is expected to be excreted as COE in the co-abuser's urine (Cami et al., 1998). To our knowledge, the net fraction of urinary COE expected after co-administering cocaine through the commonly-used route of smoking cocaine with oral ethanol has not been studied. Higher urinary concentrations of COE are to be expected to arise from routes that expose a larger fraction of the administered dose to first pass metabolism, since COE has been suggested to be a product of first pass metabolism (Song et al., 1999). Hence, one would expect $U_{oral, COE}$ to be higher than available $U_{LN, COE}$, while urinary $U_{IV, COE}$ would be expected to be lower. Further, $U_{smoke, COE}$ would be expected to be substantially smaller than the available $U_{LN, COE}$ due to the compounding effects of lower exposure of the administered dose to first-pass metabolism and losses in delivering and volatilizing the dose initially placed in the smoking apparatus. Furthermore, since COE is a product of both cocaine and ethanol, it is conceivable that its urinary concentrations for a particular route may show a dose-response relationship with the quantity abused for each of the two substances of co-abuse (i.e., cocaine and ethanol). Such dose dependence needs to be investigated further since available $U_{LN, COE}$ levels were derived upon co-administering a very limited concentration range of the two substances, 100 mg of cocaine HCL and 0.8-1 g/kg ethanol (Cami et al., 1998; de la Torre et al., 1991). Lastly, available urinary data for COE suggest that it is a minor urinary metabolite, again raising interest in considering the potential contributions of fecal and sweat loads to its net sewer loads. In summary, even though COE seems to be a suitable SEM to

track the co-abuse of cocaine and ethanol, many of the parameters for its SEEB still need to be established. Hence the best simplification one can make for such an SEEB at present is as follows:

$$p_{r\text{-co-abuse}} = \frac{\left(\frac{C_{\text{in-COE}} Q_{\text{in}}}{P} \right)}{\text{EXP}(-k_{\text{d-COE}} \cdot t_s) \cdot x_{r15-64} \cdot \sum_{m=1}^M f_{m,\text{COC}} \cdot d_{m,\text{COC}} \cdot \sum_{h=1}^H (U_{h,\text{COE}} + F_{h,\text{COE}}) \cdot x_j} \cdot 0.96 \cdot 100 \quad (17)$$

where the numerator value of 0.96 is the molecular weight ratio of cocaine to COE (dimensionless). Further, the derived SEEB also recognizes that the metabolic stoichiometry ($MO_{\text{COE}}/MO_{\text{COC}}$) associated with generating COE from co-abused COC *in vivo* is equal to one, as evident from the respective chemical structures of COE and COC.

6.3.4 Heroin

6.3.4.1 Routes of administration

Data from heroin abusers suggests that heroin is predominately administered by either injection and/or by “chasing” it, whereas nasal insufflation of heroin is of minor preference among heroin abusers but can become regionally important (Broz and Ouellet, 2008; EMCDDA, 2009b; Gossop et al., 2004; SAMHSA, 2004; SAMHSA, 2007a; Strang et al., 1997). “Chasing” of heroin implies inhalation of volatilized heroin fumes (Blanken et al., 2010; Gossop et al., 2004; Strang et al., 1997). Overall, injection of heroin is still the major route of heroin administration. For example, in the U.S.A. and Europe, heroin abusers in treatment programs reported 58% and 42%, respectively, of abusers preferring such a route-of-administration (Broz and Ouellet, 2008; EMCDDA, 2009b). Similarly, in Australia a domestic household survey suggested that 60% of the abusers preferred injecting heroin (AIHW, 2002). However, within certain European populations that are in treatment for heroin abuse, chasing can be the preferred route-of-administration (EMCDDA, 2009b; Sanchez-Niubo et al., 2009); for example, in the Netherlands, Spain, Ireland, Belgium, Slovenia and the U.K., it has been reported that heroin abusers in treatment programs predominately preferred chasing heroin (EMCDDA, 2009b; Sanchez-Niubo et al., 2009). Further, in most European countries where injection of heroin predominates, chasing is often the second most commonly used route-of-administration (EMCDDA, 2009b; Bretteville-Jensen and Amundsen, 2009). In the U.S, the proportions of “chasers” within the heroin population is low (Broz and Ouellet, 2008; Strang et al., 1997) and the second most important route-of-administration among heroin abusers presenting themselves for treatment is the nasal insufflation of heroin (Broz and Ouellet, 2008; SAMHSA, 2007a).

Heroin in the form of free base is typically chased, since it is thermally stable and demonstrates poor water solubility, while other forms of heroin are less thermally stable and hence are typically injected as they readily dissolve or dissolve upon heating (Ciccarone, 2009; Huizer, 1987). Hence, the prevalence of chasing in Europe would suggest that free base heroin is widely available in Europe, which is indeed the case (Ciccarone, 2009; EMCDDA, 2009c). In contrast, in the USA where injection of heroin predominates, the basic form of heroin is rarely seen (Ciccarone et al., 2009).

Injection is a term that could refer to any of the following: intravenous injection (into the vein), subcutaneous injection (under the skin) or even intramuscular injection (into the muscle). Of the three, one would expect abusers to typically inject heroin intravenously since this would directly release the drug into the blood stream. Indeed a survey of injectors in the City of Montréal suggests that most of them intended to intravenously administer heroin; however, when the abusers actually administered heroin, 13.1% and 3.8% of the injections unintentionally ended up being subcutaneous and intramuscular administrations, respectively (Hankins et al., 2000). Nevertheless such data suggest that in most countries heroin injectors are predominately expected to administer heroin intravenously. However, availability of certain forms of heroin, black tar and speculatively brown heroin, may eventually lead abusers to subcutaneously or intramuscularly inject heroin (Ciccarone, 2009).

Note that in certain German, Spanish, Swiss, Dutch, Canadian and Australian cities with large heroin abusing populations, there is an active effort to provide local abusers access to safe consumption facilities (EMCDDA, 2004). Such facilities in Spain, Australia and Canada only allow abusers to inject heroin, whereas chasing and nasal insufflation of heroin are not allowed (EMCDDA, 2004). Therefore, in communities where such facilities are present, the routes-of-administration used by abusers may be altered from those that would have been used had the heroin been administered without intervention. Hence, sewer epidemiologist should be aware of the presence of such facilities and account for them in their analyses using the approaches developed above.

6.3.4.2 Excretion profiling

The literature survey identified, in total, eight suitable studies (Cone et al., 1991; Cone et al., 1996; Elliott et al., 1971; Hendriks et al., 2001; Mo and Way, 1966; Smith et al., 2001; Twycross et al., 1974; Yeh et al., 1976) reporting on the urinary disposition of heroin that had been administered through various routes of interest (Table 6.2). The data available suggests that urinary excretion of heroin abusers is likely to contain unchanged heroin (HER), 6-acetylmorphine (6MAM), morphine (MOR) and normorphine

Table 6.2 Urinary profile of heroin upon various routes of administration.

					Excretory profile (% of administered dose) of specific metabolites			
Reference	Dose (mg)	n	Age (yr)	Duration (hr)	HER	MOR	6MAM	NMOR
I.V. Administered ^(a)								
Smith et al., 2001	2.7-10.7	8	-	72		73.2 ± 7.7	0.6 ± 0.2	
Yeh et al., 1976	8.1 - 12.7	10	26-47	96	0	74.9 ± 13.9	0.9 ± 0.4	4.8 ± 1.3
				24	0.05 ± 0.03		1.7 ± 1.0	2.8 ± 1.0
Mo and Way, 1966	137-387	16	18-58	24		68.0 ± 14.5		
				U _{I.V.,s}	0.025 ± 0.03	71.2 ± 13.1	1.1 ± 0.7	3.8 ± 1.1
Smoked (High dose delivery apparatus) ^(b)								
Smith et al., 2001	3.5-13.9	4	-	72		55.2 ± 26.3	0.47 ± 0.34	
				U _{smoked (high),s}		55.2 ± 26.3	0.47 ± 0.34	
Smoked (in cigarettes)								
Mo and Way, 1966	225-600	14	18-58	24		14 ± 4.8		
				U _{smoked (cigarette),s}		14 ± 4.8		
"Chasing" ^(a)								
Hendriks et al., 2001	25-100	15	30-55	24		45.2 ± 10.6		
Mo and Way, 1966	100-450	35	18-58	24		26.2 ± 7.2		
				U _{chased,s}		31.9 ± 8.4		
Intramuscular (I.M.)								
Cone et al., 1991	5.5- 10.9	6	-	60		61.8 ± 6.1	0.55 ± 0.21	
Cone et al., 1996	5.5	6	23-32	72		38.1 ± 11.1	0.42 ± 0.24	
				U _{I.M.,s}		50.0 ± 9.0	0.49 ± 0.22	
Intramuscular (I.M.)/Subcutaneous (S.C.)								
Twycross et al., 1974	-	12	61	24		70 ± 25		
				U _{I.M./S.C.,s}		70 ± 25		
Oral ^(c)								
Twycross et al., 1974	-	12	67	24		77 ± 27		
				U _{oral,s}		77 ± 27		
Prolonged Infusion								
Elliott et al., 1971	57-70	4	30-46	40.5	0.13 ± 0.11	43 ± 4	1.3 ± 1.05	
				U _{prolonged infusion,s}	0.13 ± 0.11	43 ± 4	1.3 ± 1.05	
Nasal Insufflation ^(c)								
Cone et al., 1996	5.5- 10.9	6	23-32	72		34.5 ± 7.2	0.21 ± 0.15	
				U _{nasal,s}		34.5 ± 7.2	0.21 ± 0.15	

(a) Most commonly used routes to administer heroin (Broz and Ouellet, 2008; EMCDDA, 2009b; SAMHSA, 2004; SAMHSA, 2007a; Strang et al., 1997); (b) The smoking apparatus used in this study was too refined to be representative of devices used on the street; (c) Minor, but still relevant routes of administration (Broz and Ouellet, 2008; SAMHSA, 2004; SAMHSA, 2007a).

Metabolite abbreviations: heroin (HER); morphine (MOR); 6-monoacetylmorphine (6MAM) and normorphine (NMOR).

(NMOR). Of these, MOR is the major urinary metabolite irrespective of the route-of-administration, while other metabolites are excreted in minor to negligible amounts. Hence, not surprisingly, most investigations only measure MOR in the urinary excretions of heroin abusers. For the two commonly used routes of heroin administration, Table 6.2 suggests that when heroin is administered intravenously, more than twice as much MOR can be expected in the urinary excretions of abusers than if the heroin had been chased. This is to be expected, given that the bioavailability (i.e., efficiency) of chased heroin has been reported to vary between 38-52% (Hendriks et al., 2001; Mo and Way, 1966; Rook et al., 2006).

To date, fecal elimination of heroin has not been investigated in humans but it has been shown that dogs and rabbits excrete minor amounts of intravenously administered heroin through the fecal route (Langer, 1913). Further, since a predominant amount of the bioavailable dose, irrespective of the route-of-administration, is eliminated via urinary excretions of humans (see Table 6.2), the net fraction eliminated in human fecal matter is expected to be of minor importance. Further evidence is provided in support of such an assertion is provided by recognizing that only minor (<10%) to trace levels (<1%) of structurally-similar compounds such as morphine and codeine, respectively, are eliminated through human fecal excretions (Abbott Labs, 2006; Adler et al., 1955).

6.3.4.3 Relevant sewer epidemiology metabolite-heroin

Of the four potential SEMs, MOR is the major excretory metabolite irrespective of the route-of-administration and hence comparatively more likely to be detected than the other metabolites, which are at best excreted in minor to trace quantities (Table 6.2). Furthermore, MOR is not only the major urinary metabolite but accounts for most of the administered dose. Noting this, its sewers loads are unlikely to be affected by contributions from presently uncertain sources such as its elimination in the fecal matter and sweat of heroin abusers (i.e., an analysis detailed in Appendix E suggests that the sweat load of MOR from heroin abusers is unlikely to be significant). Such an assertion cannot be made for other metabolites without concrete disposition data since they are minor urinary metabolites (Daughton and Ruhoy, 2009). MOR is also the only metabolite which has a well-defined excretion profile for both of the commonly used routes for heroin administration (i.e., intravenous injection and chasing). Further, as is the case with other potential SEMs of heroin, it is expected to show negligible adsorption onto suspended solids at both pH values of interest ($x_{s-MOR} \approx 0$; see Appendix C). Additionally, the urinary elimination half-life of MOR of approximately 8 hrs (Cone et al., 1991) is almost an order of magnitude higher than those reported for 6MAM (Cone et al., 1991) and HER (Smith et al., 2001). Hence, in comparison to 6MAM and HER, MOR is expected to be gradually eliminated to the sewers and therefore likely to be present in a larger

number of sewer pulses (i.e. toilet flushes). As a result, the gradual elimination of MOR would facilitate downstream detection by allowing a typical sampling campaign to capture a large fraction of the MOR-laden pulses. Lastly, MOR is considered to be more stable than HER and 6MAM (Chang et al., 2000; Poochikian and Cradock, 1979).

Urinary MOR is predominantly conjugated to glucuronide moieties (Yeh et al., 1976). Nevertheless research primarily with glucuronides of endogenous estrogens suggests that such conjugates will essentially be deconjugated to the free form during the sewer transit process (D'Ascenzo et al., 2003; Gomes et al., 2009). Such an assertion is assumed to hold true here for the glucuronide conjugated fraction of excreted morphine and supported by limited monitoring data available in this respect (Castiglioni et al., 2006).

MOR could also be possibly generated due to the degradation of HER and 6MAM, since HER degrades to MOR via 6MAM (Poochikian and Cradock, 1979). However the relative contribution of degrading HER and 6MAM loads is expected to be minor at best. That is, conditions in sewers are likely to fluctuate between aerobic and anaerobic states (Guddjonsson et al., 2002), thereby partially inhibiting the potential degradation of the MOR and 6MAM loads. Further, the reported hydrolysis half-lives of HER (Poochikian et al., 1983) and 6MAM (Zaitsev et al., 2008) are on the order of days and, hence, significantly greater than typical sewer transit times of a few hours reported in literature (D'Ascenzo et al., 2003; Holt et al., 1998; Ort et al., 2010; Ort et al., 2010a). Moreover, Table 6.2 suggests that, even if one makes the extreme assumption that excreted loads of 6MAM and HER are fully biodegraded to MOR upon undergoing sewer transit, the resultant contributions to the excreted loads of MOR are expected to amount to no more than negligible levels. Hence, $J_{G,MOR}$ is expected to be negligibly small and therefore assumed, to be equal to zero here.

However, a limitation of using MOR to track heroin abuse within a population of interest is that MOR could be released to sewers not only due to the illicit abuse of heroin but also due to the licit use of a number of licit clinical formulations (see Appendix I for all sources). Particularly in regions where a predominant fraction of the net sewer MOR load is expected to arise from the licit use of relevant clinical formulations, the suitability of 6MAM warrants further examination. One of the clearest advantages that 6MAM offers over MOR is that, in most cases, it can be considered to be a unique sewer marker of heroin abuse. An important exception to this assertion would be regions where Mexican or “black tar” heroin is commonly available, since this form of heroin characteristically contains 6 to 12% of 6MAM (UNODC, 2005). The presence of 6MAM in the parent heroin is of importance because this would imply that the

sewer loads of 6MAM would be susceptible to direct dumping events. Further, to-date, the levels of 6MAM in the fecal matter of heroin abusers, whether heroin was administered through intravenous injection or through chasing, has not been reported. This is an important knowledge gap since 6MAM is a minor urinary metabolite (Table 6.2) and, hence, even small contributions from such a source could substantially factor into the net amounts of 6MAM released to sewers. Additionally, it currently remains unknown what levels of 6MAM are eliminated via urinary excretions when heroin is chased. In this respect, one might be tempted to approximate such levels by multiplying the available urinary levels of 6MAM excreted after heroin has been intravenously injected (Table 6.2) with the bio-availability of chased heroin. However, this cannot be justified if one recognizes that 6MAM is also a major pyrolysis product of heroin (Cooke and Brine, 1985; Cooke and Jeffcoat, 1985). Further, there is also a need to establish the urinary and fecal disposition of heroin to 6MAM after heroin has been nasally insufflated, a route-of-administration that is of significance among American heroin users (Broz and Ouellet, 2008; SAMHSA, 2007a). An order-of-magnitude estimate detailed in Appendix E suggests that sweat would be expected to contribute negligible amounts to the net sewer loads of 6MAM and hence can safely be neglected. Similarly, adsorption of 6MAM onto suspended solids can also be neglected (Appendix C). Lastly, and perhaps most importantly, consistent detection of 6MAM is already an issue in a number of sewer epidemiology investigations. Boleda et al. (2009) failed to detect 6MAM with a limit of detection of 0.3 ng/L in 15 STP influents, while Postigo et al. (2010) were only able to detect 6MAM in 2 out of the 14 samples (i.e., 2 samples each from 7 sewage treatment plants) they examined using an analytical method that allowed for a limit of detection of 1.9 ng/L. Both studies originated from Spain, which reports lower levels of heroin abuse within its population compared to some other European populations (EMCDDA, 2010). The inability to detect 6MAM in Spanish influents essentially eliminates the potential candidacy of this SEM to track the abuse of heroin by Spanish users and, possibly, in other countries where lower levels of heroin abuse prevalence exists. However, very recent evidence from the cities of Zagreb and Brussels reported continuous detection of 6MAM (Tezic et al., 2010; van Nuijjs et al., 2011), possibly because the levels of heroin abuse in these cities is higher than the levels used within in Spanish cities monitored thus-far. Nevertheless, this suggests that the detectability of 6MAM may not be possible in certain populations of interest while continuous detection may be possible in others. Only in the latter cases would 6MAM have some potential as a SEM for tracking a population's heroin abuse.

Overall, a few limitations and knowledge gaps must be considered before one selects the use of 6MAM over MOR as the more suitable SEM to establish the abuse of heroin within a population of interest. However, even though not possible at the moment due to unavailable disposition data (i.e., fecal disposition for intravenously-administered heroin and both fecal and urinary for chased heroin), 6MAM

may be an interesting candidate SEM to track a population's abuse of heroin. This would be particularly the case in regions where the majority of the MOR load is expected to result from sources other than the consumption of heroin. Due to the unknowns summarized above, the discussion immediately below will focus only on MOR. However, the possible candidacy of 6MAM as an SEM will be revisited at the end of the section.

As mentioned above, an additional complication associated with using MOR as an SEM to track the abuse of heroin is that MOR can be released to sewers through numerous licit sources. Hence, contributions from such licit sources must be accounted for. Medicinal licit sources of MOR include the use of morphine, codeine, ethylmorphine, nicomorphine and pholcodine (Brunk et al., 1974; Hedenmalm et al., 1997; Koopman-Kimenai et al., 1995; Maurer and Fritz, 1990; Ripel et al., 1992). Furthermore, a basal level of MOR has been reported to be naturally present in anthropogenic excretions (Mikus et al., 1994). Lastly, morphine could also result in humans excretions through the consumption of poppy seeds (Rohrig and Moore, 2003). Comprehensive excretion profiling for all these sources and hence their potential to release MOR to sewer has been detailed in Appendix I. For medicinal sources, the comprehensive analysis suggests that $77.7 \pm 9.1\%$, $6.0 \pm 2.6\%$, $14.5 \pm 5.4\%$, $0.75 \pm 0.13\%$ and $62.7 \pm 9.1\%$ of the mass consumed of morphine, codeine, ethylmorphine, pholcodine and nicomorphine, respectively, is expected to be released to sewers as MOR. The endogenous level of MOR in human's excretions was established to amount to the highly variable level of $0.63 \pm 1.84 \mu\text{g}$ of MOR/cap.d. Even though the morphine content of poppy seeds is excreted unchanged (Pettitt et al., 1987), the net contribution to sewers loads of MOR due to poppy seed consumption was established to be of negligible importance (see the analysis presented in Appendix J) and hence not considered further.

Figure 6.2(A) summarizes the outcome of an analysis to estimate the relative importance of the various sources to the licit MOR sewer load. The analysis is limited to 21 countries since the levels of consumption of morphine, codeine, ethylmorphine, nicomorphine and pholcodine for only these countries were available in literature or a database (see Appendix K). Of the various licit sources, the consumption of codeine and morphine are both important contributors to the net sewer loads of licit MOR (Figure 6.2(A)). For certain countries, the majority of the licit MOR originated from the consumption of morphine (e.g., Estonia and U.S.A.), while in other countries the majority resulted from the population's use of codeine (e.g., U.K. and Finland). Contribution to the net licit MOR loads due to the clinical use of ethylmorphine for most countries is expected to range from minor levels to essentially zero, either because low levels of the drug are used nationally or because ethylmorphine has not been approved for

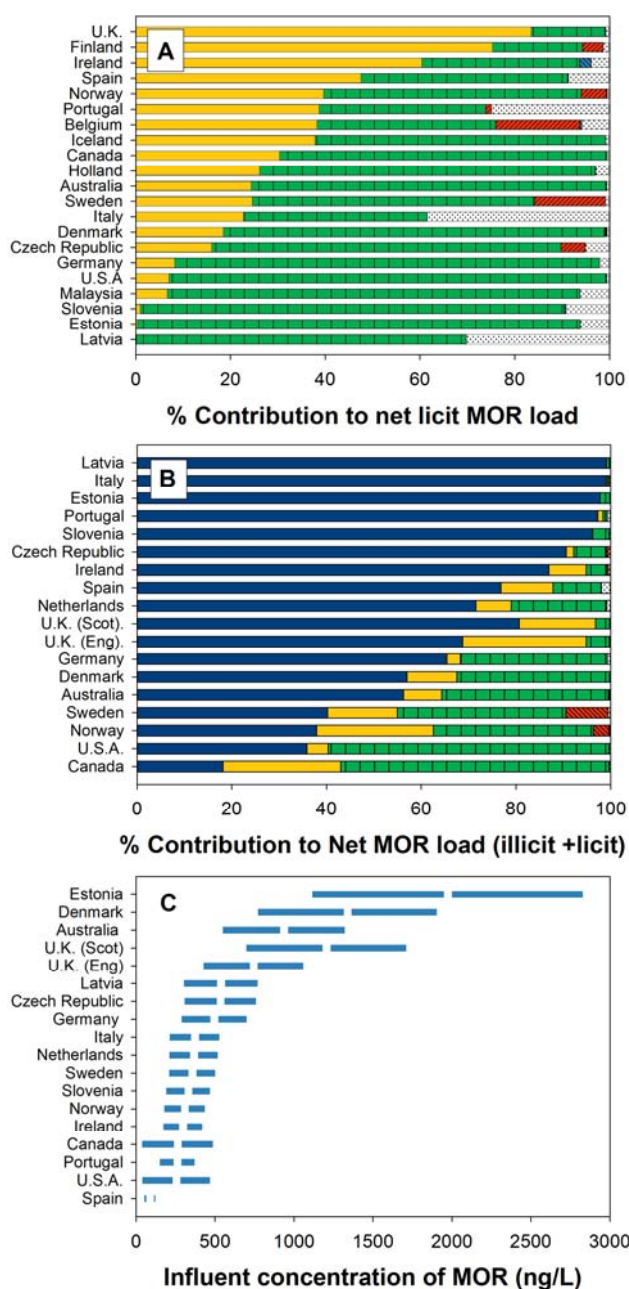


Figure 6.2(A) Relative contribution of various sources to the net licit load of MOR in the influent of various countries. Licit sources: codeine (■); morphine (■); ethylmorphine (■); pholcodine (■); nicomorphine (■) and endogenous morphine (■). **Figure 6.2(B)** Relative contribution of all licit and illicit (i.e. use of heroin) sources (■) to the net load of MOR in the influent of various countries. **Fig. 2(C)** Theoretically-derived nationally-averaged estimates (■) of MOR concentrations in the influents of various countries (for a sample calculation see Appendix L). The extents of the filled bars represent one standard deviation of variation ($\pm\sigma$), while the vertical white line represents the mean. For details on how the various theoretically-derived estimates were generated and the data sources required in the process, see Appendix G.

Footnote for Figure 6.2

(¶) No recent estimate for the prevalence of heroin abuse were available for the whole of United Kingdom (U.K.) (UNODC, 2010); hence two estimates were generated, U.K. (Eng). estimate assumes the national prevalence of heroin abuse in whole of the U.K. was similar to the available regional prevalence of opiate abuse in England and Wales, while the second estimate (U.K. (Scot).) set national abuse prevalence equal to the available regional prevalence of opiate abuse in Scotland.

clinical use (see Appendix K). However in certain cases, such as in Sweden, the levels used are such that MOR contributions from this source can become significant. In contrast, pholcodine is expected to contribute negligible fractions to the net sewer loads of MOR in all countries analyzed. Of the 21 countries, nicomorphine was only approved for sale in the Netherlands and Denmark (see Appendix K) and in both countries the contributions to the licit loads of MOR amounted to only negligible or trace levels. Further, the contribution of endogenous morphine to net licit loads of MOR are only expected to be significant in those countries where the level of relevant opioids prescription on a per capita basis is low such as Italy and Latvia (see Appendix K).

Since the sewer epidemiologist's interest would lie in the fraction of MOR that originates exclusively due to the use of heroin within a given population, it is important to compare the relative contributions resulting from heroin use to those expected through licit sources. This has been attempted in Figure 6.2(B). The analysis is limited to 17 countries of the 21 for which consumption of relevant licit sources of MOR was available. Excluded from this analysis were Belgium, Finland, Malaysia and Iceland since for Belgium, no recent estimate of heroin prevalence in the national population was available (UNODC, 2010), while for Finland, Malaysia and Iceland the routes-of-administration used by heroin abusers were either not available or could not be confidently approximated.

Figure 6.2(B) suggests that in most European countries, with the notable exception of Scandinavian countries, a dominant or a significant fraction of the sewer MOR load is expected to originate due to the population's abuse of heroin, whereas the majority in North American countries is expected to primarily originate due to the consumption of medicinal drugs that are metabolized to MOR. This is not surprising since the U.S.A., Canada and the Scandinavian countries are amongst the highest consumers of relevant prescription opioids on a per capita basis (see Appendix K). Furthermore, heroin abusers in North America have been suggested to consume almost two and a half times less heroin on a yearly basis than their European counterparts (Kilmer and Pacula, 2009). Lastly, it is also worth noting the highly variable contribution from endogenous MOR is expected to be insignificant for all countries analyzed and can be neglected.

It must be stressed that the licit codeine contributions in Figures 6.2(A) and (B) are primarily based on the mass of codeine sold through prescriptions. A notable exception to this would be the data from Scandinavian countries, which also include over-the-counter sales of a given formulation in their national databases. Hence, in countries where codeine is available over-the-counter but data sources used do not account for sales through such channels, the relevant contribution due to the consumption of codeine is

likely to have been underestimated in Figures 6.2(A) and (B). As a consequence, in Figure 6.2(B) the contribution due to the consumption of heroin is most likely overestimated. Specifically, this is the case for the United Kingdom (Ford and Good, 2007), Canada (Schuchman, 2008), Australia (Leong et al., 2009), Ireland (O'Connell, 2010), Belgium (PAGB, 2010) and the Netherlands (PAGB, 2010). Over-the-counter codeine consumption data are not readily available for most relevant countries; however, in the United Kingdom between 14-21% of the net mass of codeine sold to the British population is done over-the-counter (see Appendix M for the analysis). Further, it is worth highlighting that compared to certain other countries where codeine is available over-the-counter, the access to codeine in the United Kingdom is relatively liberal in that pharmaceuticals containing codeine can be bought online (Boots, 2011). Compare this situation to those of Canada (Schuchman, 2008) and Ireland (O'Connell, 2010) where access to over-the-counter codeine is limited by placing relevant preparations “behind the counter”, where the consumer can only obtain them after consulting with the pharmacist.

Figure 6.2(C) summarizes estimates of nationally-averaged morphine concentrations in wastewater influents (see Appendix L for a sample calculation). Compared to BE (cocaine's SEM), monitoring data reported for MOR in literature is still sparse and generally of poorer temporal and spatial resolution to warrant a detailed analysis. However the estimate generated here for Spain agrees well with reported measurements (Boleda et al. 2009; Postigo et al., 2008; Postigo et al., 2010; see Appendix L.2). Not surprisingly, Spain is also the country for which most MOR data has been published. The nationally-generated estimate for Italy was higher than the data reported for a single wastewater treatment plant monitored in the city of Milan (Castiglioni et al., 2006). Nevertheless, recognizing the limited spatial and temporal extent of available MOR data, the questionable reliability of such data (Ort et al., 2010; 2010a) and the limitations of the theoretical estimates highlighted earlier, it is premature to suggest if there exist discrepancies between the theoretically-predicted and the monitored data. More importantly, for the purposes of the present study, the comparison suggests that the theoretical estimates are plausible. Further, in countries where codeine is available over-the-counter (see list above), the predicted influent MOR estimates should be considered as conservative estimates. This should be acceptable since the aim of Figure 6.2(C) is to simply assess the detectability of MOR in various national influents. Nevertheless, if the over-the-counter sales of codeine had been considered for the United Kingdom, a country for which such a contribution could be estimated (see Appendix M), the predicted mean MOR influent concentration would have been higher by 27 - 40 ng/L. This represents a percent increase of 2.2 to 5.2%, which is relatively small.

Given that typical detection limits for MOR in sewage influents are in the range of 1.5 ng/L (Postigo et al., 2008) to 2.5 ng/L (Boleda et al., 2007), Figure 6.2(C) suggests that MOR should be measureable in all 17 countries considered. However, considered together, Figures 6.2(B) and (C) suggest that in certain countries such as the U.S.A., Canada, Norway and Sweden, even though one might be able to consistently detect MOR in the influents of such countries, the fraction of MOR originating exclusively due to heroin abuse in these countries is expected to amount to a minor fraction of the net MOR sewer load. Therefore, for these countries, it is necessary to exercise greater caution when trying to estimate the heroin abusing population using MOR as the SEM. As an alternative, particularly in regions where majority of the MOR load results from licit use of clinical preparations, the use of 6MAM as an alternative SEM may be considered. However, this would imply that the sewer epidemiologist is consistently able to detect 6MAM, suitable disposition data does indeed becomes available, the degradation potential of 6MAM can be modeled and, lastly, black-tar heroin (Mexican heroin) is not a commonly available form of heroin available. The last consideration would in particular be a concern in certain parts of the U.S.A. but not Europe (Ciccarone et al., 2009; Díaz-Briseño, 2010; EMCDDA, 2008).

Further, in the theoretical estimates of the MOR originating due to a given population's heroin consumption, it is assumed that enough heroin is available that the demand of the abusers is met. Hence, in temporal episodes where heroin shortage arises, such as the recent ones documented in Australia (Degenhardt et al., 2005) and Western Canada (Woods et al., 2006), the relative contribution to sewer loads of MOR due to the abuse of heroin is expected to be less than levels predicted in Figure 6.2(B). Hence, the sewer epidemiologist should be aware of such supply dynamics when trying to assess the plausibility of using MOR in STP influents to monitor a given population's abuse of heroin.

6.3.4.4 SEEB to track heroin abuse

Using the aforementioned observations and noting that the respective chemical structures of MOR and HER suggest that the *in vivo* stoichiometry of metabolically-generating MOR from administered HER (MO_{MOR}/MO_{HER}) is equal to one, the following improved SEEB can be suggested to track the abuse of heroin within a population of interest:

$$P_{r-HOR} = \frac{\left(\frac{C_{in-MOR} Q_{in}}{P} \right) - J_{L,MOR}}{x_{r15-64} \cdot \sum_{m=1}^M x_{m,HOR} \cdot d_{m,HOR}} \cdot \frac{1.29}{(0.71 \pm 0.13) x_{I.V.} + (0.32 \pm 0.08) x_{chasing} + (0.77 \pm 0.27) x_{oral} + (0.35 \pm 0.07) x_{nasal}} \cdot 100 \quad (18)$$

where $J_{L,MOR}$ in Equation (18) can be expanded with the aid of Equation (6) to the following:

$$J_{L,MOR} = J_{L,MOR-m} + J_{L,MOR-c} + J_{L,MOR-END} \quad (18a)$$

The individual contribution in Equation (18a) can in turn be expanded using Equations (3), (4) and (5), yielding:

$$J_{L,MOR-m} = [L_{codeine} \cdot (0.057 \pm 0.025) \cdot (1 - Y_{n,codeine}) + L_{ethylmorphine} \cdot (0.145 \pm 0.054) \cdot (1 - Y_{n,ethylmorphine})] \quad (18b)$$

$$J_{L,MOR-c} = L_{morphine} \cdot ((1 - Y_{n,MOR}) \cdot (0.77 \pm 0.09) + Y_{n,MOR} \cdot Y_{f,MOR}) \quad (18c)$$

$$J_{L,MOR-end} = (0.64 \pm 1.64) \mu\text{g of MOR/cap}\cdot\text{d} \quad (18d)$$

In Equation (18b), the contributions from the population's consumption of pholcodine and nicomorphine have been neglected in light of the analysis detailed in the preceding section. However, if such data are available, the contributions to the sewer loads of MOR due to their consumption can be readily accounted for by adding on the following expressions to Equation (18b) for pholcodine and nicomorphine, respectively: $L_{pholcodine} \cdot (0.0053 \pm 0.0008) \cdot (1 - Y_{n,pholcodine})$ and $L_{nicomorphine} \cdot (0.363 \pm 0.053) \cdot (1 - Y_{n,nicomorphine})$. However, the analysis conducted here suggests that the current consumption levels of these formulations is such that their contribution to net sewer loads of licit MOR is of negligible importance and can be neglected in most instances. Further, the highly variable contribution from endogenous morphine (Equation 18(d)) can also be neglected as it is expected to be of negligible importance (see Figure 6.2(B)).

As mentioned in the previous section, codeine may be available over-the-counter in certain countries; such sales are difficult to track and may not necessarily be captured by relevant data sources such as a country's national prescription tracking databases. In this respect, Appendix O presents a mathematical development on how measured influent STP concentration of codeine could be used to estimate the mass of codeine actually being consumed by a population (i.e., $L_{codeine} \cdot (1 - Y_{n,codeine})$). A similar sewer measurement based method could also be used to estimate the mass of ethylmorphine used within a population of interest (i.e., $L_{ethylmorphine} \cdot (1 - Y_{n,ethylmorphine})$). For further details, see Appendix P.

Again, it must be stressed that in regions where a majority fraction of the net MOR sewer load is expected to result from the population's consumption of relevant clinical preparations (see Figure 6.2(B)), the use of MOR as the SEM, and hence the use of Equations (18) to (18c), are discouraged. For such cases, the use of 6MAM may be explored, provided that the limitations highlighted in the previous section can be addressed. Further, once the knowledge gaps detailed earlier are addressed, the concurrent use of 6MAM may also be explored in cases where majority of the sewer MOR load is expected to arise due to the population's consumption of heroin, since in most instances 6MAM's sewer loads would only be expected to result due to the upstream population's abuse of heroin.

Overall, Equations (18) to (18c) represent the suggested SEEB to track the abuse of heroin within a population. The resultant SEEB for heroin not only captures the effect that route-of-administration has on the metabolic disposition of heroin, but also comprehensively accounts for all relevant licit sources of MOR. Furthermore, not only does the suggested SEEB account for these factors but also captures the variations they are likely to manifest in the resultant heroin prevalence estimates.

Zuccato et al. (2008) also suggested MOR to be the most suitable metabolite to track the abuse of heroin within a population. However, their preliminary SEEB estimate assumed that all heroin abusers, irrespective of their route-of-administration, excrete 42% of the administered dose as MOR. In doing so, they solely relied on the heroin disposition data reported by Elliott et al. (1971). However, in the latter study, the researchers administered heroin to their subjects by prolonged infusion, which is not a relevant route-of-administration used by drug abusers. Therefore, continued use of the SEEB of Zuccato et al. (2008) would tend to overestimate abuse prevalence in regions where heroin is primarily injected intravenously (i.e., as shown in Table 6.2, the actual excreted fraction is 72%) and conversely underestimate abuse prevalence in regions where the abuser predominately prefer chasing heroin (i.e., as shown in Table 6.2, the excreted fraction is 32%). Beyond these already substantial sources of error in accounting for the disposition of heroin in abusers, Zuccato et al. (2008) assumed that the only licit contributions that needed to be accounted for were those from licit consumption of morphine. Even then they assumed, without full justification, that 85% of the net mass of morphine sold for consumption enters the sewers unchanged. Furthermore, they considered the consumption of codeine to a negligible contributor to the net sewer loads of MOR by citing the small fraction of codeine that is converted to morphine. Lastly, they failed to recognize or evaluate the importance of other licit sources of MOR.

The improved SEEB for heroin presented above addresses all of these limitations. Firstly, excretion profiling of oral morphine suggests that only 77.7 % of the consumed dose is excreted as unchanged MOR. Secondly, excretion profiling followed by analysis of relative loads of licit MOR suggests that even though approximately 6% of the administered codeine dose is excreted as MOR (see Appendix I.2), the relative mass of codeine consumed compared to that of morphine in some countries is such that use of codeine contributes significantly to MOR loads; i.e., of the 21 countries represented in Figure 6.2(A), in 5 of them consumption of codeine contributes more licit MOR than does the consumption of morphine. Further, the importance of codeine contributions would be further enhanced in countries where codeine is available over-the-counter, a contribution which could not be accounted for in Figure 6.2(B). Additionally the SEEB derived here also establishes the relative importance of licit MOR originating from previously unrecognized sources in the field of sewer epidemiology such as the clinical use of ethylmorphine,

pholcodine and nicomorphine, the endogenous excretion of MOR, and the release of MOR due to the populations' consumption of poppy seeds.

6.3.5 MDMA

6.3.5.1 Routes of administration

MDMA is almost exclusively consumed orally, since it is primarily available and sold as “ecstasy” tablets, while other minor routes-of-administration reported by users include nasal insufflation and injection of MDMA (Battisti et al., 2006; EMCDDA, 2010; Topp et al., 1999; White et al., 2006).

6.3.5.2 Excretion Profiling

Six suitable studies were identified in literature reporting on the urinary disposition of orally-administered MDMA (Abraham et al., 2009; de la Torre et al., 2000; Fallon et al., 1999; Pizarro et al., 2002; Segura et al., 2001; Verebey et al., 1988). A unique trait of MDMA disposition that has largely gone unrecognized by sewer epidemiologists is its reported non-linear pharmacokinetics where the mass of unchanged MDMA released via urinary excretions increases non-linearly as the dose administered is increased (de la Torre et al., 2000; Mueller et al., 2009). However, the levels of 4-hydroxy-3-methoxymethamphetamine (HMMA), a major urinary metabolite, approximately amount to the same level (i.e., mass) irrespective of the MDMA dose administered (de la Torre et al., 2000).

Recognizing this unique aspect of MDMA disposition, the identified data were pooled by the dose of MDMA administered and the results of the individual disposition studies compiled in milligrams of respective metabolites rather than the percent of the administered MDMA dose (see Table 6.3).

Not included in Table 6.3 are the datasets reported by Abraham et al. (2009) and Verebey et al. (1988). Abraham et al. (2009) reported doses administered to their subjects in units of mg/kg without explicitly stating the weight of the subjects (kg) and hence yielding uncertainty about the mg of MDMA actually administered to their subjects. Nevertheless, they reported similar values and trends to all other data previously published in the literature, already included in the data compilation presented in Table 6.3. The data of Verebey et al. (1988) was excluded from the analysis, for several reasons: firstly, they only studied the disposition of a single dose in a single subject and, secondly, their suggested fraction of 65% unchanged MDMA in the urinary excretions of the sole subject is inconsistent with all other values reported in literature where unchanged fractions of between 18 and 31% are reported (Abraham et al., 2009; de la Torre et al., 2000; Fallon et al., 1999; Pizarro et al., 2002; Segura et al., 2001).

Table 6.3 Urinary profile of MDMA upon oral administration.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Excretory profile (mg) of specific metabolites				
					MDMA	MDA	HMMA	HHMA	HMA
Fallon et al., 1999	40	8	22-32	24	12.3 ± 5.0	0.89 ± 0.1			
de la Torre et al., 2000	50	2	21-31	24	5.94	0.23	23.5		0.80
					11.0 ± 4.8	0.76 ± 0.1	23.5		0.80
de la Torre et al., 2000	75	8	21-31	24	13.7 ± 2.6	0.63 ± 0.16	25.0 ± 4.3		0.98 ± 0.07
					13.7 ± 2.6	0.63 ± 0.16	25.0 ± 4.3		0.98 ± 0.07
de la Torre et al., 2000	100	2	21-31	24	29.7	0.63	17.9		0.88
Segura et al., 2001	100	4	25.5	24	15.0 ± 4.9	1.40 ± 0.54	22.9 ± 7.8	16.6 ± 4.3	1.27 ± 0.29
Pizarro et al., 2002	100	6	-	24	23.9 ± 4.7	1.65 ± 0.30	17.3 ± 6.2		1.74 ± 1.00
					21.9 ± 8.4	1.39 ± 0.42	19.3 ± 7.1	16.6 ± 4.3	1.44 ± 0.78
de la Torre et al., 2000	125	8	21-31	24	32.7 ± 13.4	1.15 ± 0.48	28.9 ± 20.1		1.12 ± 0.67
					32.7 ± 13.4	1.15 ± 0.48	28.9 ± 20.1		1.12 ± 0.67
de la Torre et al., 2000	150	2	21-31	24	47.7	0.65	20.0		0.71
					47.7	0.65	20.0		0.71

Metabolite abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; HMMA, 4-hydroxy-3-methoxymethamphetamine; HHMA, 3,4-dihydroxy-methamphetamine; HMA, 4-hydroxy-3-methoxyamphetamine.

The compiled disposition data suggests that the HMMA and unchanged MDMA are the major urinary metabolites, whereas HHMA is found in lesser amounts and to-date its detection in urine has only been attempted by Segura and colleagues (2001) (see Table 6.3). In contrast, HMA and MDA are relatively minor urinary metabolites (see Table 6.3). To-date, fecal deposition of MDMA in humans has not been reported. However, minor to trace amounts of structurally and chemically similar compounds such as amphetamine, lisdexamfetamine and methamphetamine are eliminated via the fecal route (Caldwell et al., 1972; Dring et al., 1970; Krishnan et al., 2008) and hence it is assumed here that the fecal disposition of MDMA is expected to be of minor importance.

6.3.5.3 Relevant sewer epidemiology metabolite

Of the five metabolites quantified to-date in the urine of MDMA users, HMMA and unchanged MDMA are the major urinary metabolites (Table 3) and hence the likely SEM candidates. Further, MDMA and HMMA are expected to negligibly adsorb onto suspended solids (x_{s-MDMA} and $x_{s-HMMA} \approx 0$; see Appendix C). Recalling that typical conditions in sewers are not ideal for degradation (Guddjonsson et al., 2002), MDMA and HMMA loads are not expected to degrade appreciably during the transit process. Such an assertion can be further supported for HMMA in particular, since HMMA is predominately excreted as sulphate conjugates (i.e., on average > 70% of the total HMMA levels (Shima et al., 2008)) and these conjugates have been reported to be relatively robust during sewer transmission (D'Ascenzo et al., 2003; Johnson and Williams; 2005; Gomes et al., 2009). Further, both MDMA and HMMA do not readily hydrolyze when stored at room temperature (Clauwaert et al., 2001; Jimenez et al., 2006; Mueller et al., 2009a; Phonchai et al., 2010). Thus, the excreted loads of both MDMA and HMMA are not expected to appreciably degrade/hydrolyze during the sewer transit process (i.e., $k_{d,MDMA}$ and $k_{d,HMMA} \approx 0$). Additionally, at present there is no evidence to suggest that either MDMA or HMMA are likely to be generated due to the degradation of other contaminant loads (i.e., $J_{G,MDMA}$ and $J_{G,HMMA} \approx 0$). Lastly, the sweat of ecstasy abusers is unlikely to significantly add to the excreted loads of either MDMA or HMMA (see Appendix E for analysis).

Presently, MDMA is not a drug that is available through prescriptions. However, clinical trials are underway in a number of countries to establish its use for healing psychotherapeutic trauma (MAPS, 2010). INCB (2010) estimated the global stock of MDMA for such and other licit uses amounted to a mere 0.66 kg/yr and, hence, at present, $J_{L,MDMA}$ & $J_{L,HMMA}$ can be assumed to be approximately zero.

Compiled data (see Appendix N) on the MDMA content of seized ecstasy pills in various national markets suggests that in most countries the mean content of such pills is within the 40-100 mg range.

Japanese and Thai seizures on the other hand contained higher MDMA content on average, with specific reported means within the 100-144 mg range. At the other end of the spectrum were the pills seized in Italy, England, Luxembourg and Czech Republic, with reported average mean contents within the 17-33 mg range. Such variation in the content of ecstasy pills coupled with the non-linear pharmacokinetics of MDMA would suggest that the amount of MDMA released via urinary excretions per pill abused, and hence found in STP influents on a per pill basis, would vary simply because the MDMA content being consumed by a given population is different.

The pharmacokinetics of MDMA *in vivo* are such that approximately the same amount of HMMA, i.e., 20-25 mg, is released in the urine of users within the dose range of 40-150 mg (see Table 6.3). This has been suggested to be a consequence of MDMA induced inhibition of cytochrome P450 enzymes that are responsible for the formation of HMMA from MDMA (de la Torre et al., 2000; Mueller et al., 2009). However, at present it remains uncertain at what MDMA dose below the lowest studied dose of 40 mg the leveling-off of urinary HMMA occurs. Recognizing that MDMA and HMMA on all other evaluation criteria are equally suitable as SEMs, as discussed earlier in this section, HMMA offers the slight advantage that its amount released in the urine of users is approximately the same within studied dose range of 40 to 150 mg of MDMA. Further, excreted MDMA sewer loads are susceptible to direct dumping events, a source whose relative importance is uncertain at present.

To-date, the suitability of HMMA to track MDMA abuse within a population of interest has not been recognized, as evident from the fact that HMMA is yet to be tracked in any sewer epidemiology investigation reported thus-far. This in itself is also a limitation, in that detectability of HMMA at relevant concentrations in wastewater influents is yet to be established. Hence, barring possible analytical issues, HMMA appears to be the most suitable SEM to track MDMA's abuse within a population of interest. Nevertheless, discussion in the next section also leaves open the possibility for MDMA to be used as an alternative SEM should the quantification of HMMA in wastewater influents indeed become an analytical challenge.

6.3.5.4 SEEB to track MDMA abuse

As mentioned above, HMMA is not expected to significantly degrade ($k_{d-HMMA} \approx 0$) or sorb onto influent suspended solids ($x_{s-HMMA} \approx 0$), or be excreted in significant quantities due to the licit use of MDMA ($J_{L-HMMA} \approx 0$), or result from the degradation of other contaminant loads ($J_{G-HMMA} \approx 0$). Taken together, these simplifications allow one to adapt the general SEEB expression, Equation (12), to the following for HMMA:

$$p_{r\text{-MDMA}} = \frac{\left(\frac{C_{\text{in-HMMA}} Q_{\text{in}}}{P} \right) \cdot \frac{Mw_{\text{MDMA}}}{Mw_{\text{HMMA}}}}{x_{r_{15-64}} \cdot \sum_{m=1}^M x_{m,\text{MDMA}} \cdot d_{m,\text{MDMA}} \cdot (U_{\text{oral,HMMA}} + F_{\text{oral,HMMA}})} \cdot 100 \quad (19)$$

The derived SEEB also recognizes that the *in vivo* stoichiometry of metabolically-generating HMMA from administered MDMA ($MO_{\text{HMMA}}/MO_{\text{MDMA}}$) is equal to one; as supported by the respective chemical structures of HMMA and MDMA.

Furthermore, pooling all data available in Table 6.3 for HMMA suggests that for every 40-150 mg MDMA pill abused, $22,900 \pm 10,700$ μg of HMMA would be expected in the abusers' urine. Further, if one defines NX as the number of pills consumed on a daily averaged basis by ecstasy abusers who have used the drug within the last year (a typical timeframe used to distinguish current users from lifetime users), then $NX \cdot (22,900 \pm 10,700)$ has units of μg of HMMA/cap·d and can be used to replace the expression $\sum x_{m,\text{MDMA}} \cdot d_{m,\text{MDMA}} \cdot (U_{\text{oral,HMMA}} + F_{\text{oral,HMMA}})$ in Equation (19) to yield the following equation:

$$p_{r\text{-MDMA}} = \frac{\left(\frac{C_{\text{in-HMMA}} Q_{\text{in}}}{P} \right)}{x_{r_{15-64}} \cdot (22,900 \pm 10,700) \cdot NX} \cdot 100 \quad (20)$$

Note that in Equation (20) the molecular weight adjustment ($Mw_{\text{MDMA}}/Mw_{\text{HMMA}}$) has been set equal to one since both the numerator and denominator have consistent units of μg of HMMA/ cap·d. Further, the best available estimate for NX at present suggests that it is approximately 0.23 – 0.25 pills/day (Kilmer and Pacula, 2009).

Barring any issues with the detectability of HMMA, Equation (20) is the proposed SEEB to track ecstasy abuse within a population of interest where a majority of the pills available to users contain 40-150 mg of MDMA. Potentially, the suggested SEEB could even be used in regions where a substantial quantity of MDMA pills have a lower content than 40 mg (i.e., the lowest dose for which urinary disposition data is available), but before that can be used with confidence, the minimum MDMA dose that results in leveling-off of urinary HMMA levels at the 20-25 mg mark would need to be established. Until such a dose is established, sewer epidemiologists are cautioned at trying to extrapolate ecstasy prevalence measures in countries or regions where primarily low content MDMA pills (< 40 mg) are available.

Should the quantification of HMMA in wastewaters become an unresolvable analytical challenge, the use of MDMA itself as an SEM could be explored to track the abuse of ecstasy within a population of

interest. However, such use must come with a few cautions. First, the use of unchanged MDMA as the SEM will be susceptible to influence by direct dumping events (i.e., direct disposal of the drug into the sewer), a source whose contribution to sewers loads of MDMA is expected to be highly uncertain and virtually impossible to model. Secondly, and perhaps more importantly, the nonlinear pharmacokinetics of MDMA may imply that estimates of MDMA loads derived from sewer measurements may not be temporal or spatially comparable and, as a consequence, may limit the applicability of the approach. Noting these cautions, an SEEB for MDMA may be derived, as discussed below.

As mentioned above, MDMA is not expected to significantly degrade ($k_{d-MDMA} \approx 0$) or sorb onto influent suspended solids ($x_{s-MDMA} \approx 0$), or be excreted in significant quantities due to the licit use ($J_{L-MDMA} \approx 0$), or result from the degradation of other contaminant loads ($J_{G-MDMA} \approx 0$). Taken together, these simplifications allow one to adapt the general SEEB expression, Equation (12), to the following for MDMA:

$$p_{r-MDMA} = \frac{\left(\frac{C_{in-MDMA} Q_{in}}{P} \right)}{xr_{15-64} \cdot \sum_{m=1}^M x_{m-MDMA} \cdot d_{m-MDMA} \cdot (U_{oral-MDMA} + F_{oral-MDMA})} \cdot 100 \quad (21)$$

Further, if one notes that within the MDMA content range of 40 to 100 mg, the fraction of MDMA excreted unchanged only varies slightly. A reasonable assumption can be made that the fraction of MDMA excreted unchanged is approximately linear when ecstasy pills with an MDMA content of 40 to 100 mg are abused. Pooling all data for this range in Table 6.3, suggests that on average 22.6% of MDMA is excreted unchanged. Hence, a SEEB to track ecstasy abuse with unchanged MDMA as the SEM can be simplified to the following:

$$p_{r-MDMA} = \frac{\left(\frac{C_{in-MDMA} Q_{in}}{P} \right)}{xr_{15-64} \cdot \sum_{m=1}^M x_{m-MDMA} \cdot d_{m-MDMA} \cdot (0.226 \pm 0.08)} \cdot 100 \quad (22)$$

Again it must be stressed that this SEEB should be used with caution and is only applicable for populations where the clear majority of the pills available to the population fall within the 40 to 100 mg range.

Overall, as soon as the detectability of HMMA is established at relevant concentrations in STP influents, Equation (20) could become the preferred SEEB to monitor a population's abuse of ecstasy pills.

Zuccato et al. (2008) suggested unchanged MDMA to be the most suitable SEM to track a population's abuse of ecstasy pills by relying on data reported by Verebey et al. (1988). However, Verebey et al.'s suggested unchanged MDMA fraction of 65%, obtained after studying the disposition of a single dose in a single subject, is inconsistent with the range of 18 – 31% reported by all other studies (as listed in Table 6.3). Therefore, continued use of the SEEB of Zuccato et al. (2008) would substantially underestimate the prevalence of ecstasy abuse in a population of interest. Specifically for the mean reported MDMA content in most countries of 40-100 mg, Table 6.3 suggests that the actual fraction excreted of unchanged MDMA ranges from 18 to 22 %; hence the continued use of the SEEB of Zuccato et al. (2008) for the abuse of such MDMA pills would underestimate abuse prevalence by 195 to 261%. The error would be even greater in regions where a substantial number of pills available to users contain less than 40 mg of MDMA, since in such cases the actual fraction of unchanged MDMA in the urine of abusers would be expected to be disproportionately lower than 18%. Further, and perhaps more importantly, the SEEB of Zuccato et al. (2008) did not recognize the non-linear nature of MDMA pharmacokinetics and the resulting limitations associated with using unchanged MDMA to track the prevalence of ecstasy abuse within a region of interest.

6.4 Overall Perspectives and Limitations

The methods developed and applied above represent a refined mass balance approach that can be used to evaluate the prevalence of use of illicit drugs based on the identification of suitable SEMs and accounting for their possible licit and illicit sources. It is a generalized approach that could potentially be used for all types of illicit drugs, provided that reliable data is available to develop the relevant SEEB expressions.

Conceivably, sewer epidemiology investigations can be done with two primary purposes. From one perspective, the interest may simply be to gain an understanding of short-term temporal trends. For example, an investigation could be done to determine whether a given population consumes more of an illicit drug on weekends or special occasions. If this is the limited aim, then the estimation of the mass load of an SEM through Equation (1) may be used to accomplish this task. However, if a study is to be done with the intent of estimating the prevalence of abuse or number of abusers within a population, then the use of Equation (12), or at the very least the use of Equation (10), is warranted. The advantage of the latter approach is that these measures are not only comparable over long temporal scales, but over spatial scales as well. Hence, this would allow one to not only assess whether the number of abusers for a given illicit drug is changing over time within a population but also to assess how the generated estimates compare to those obtained for other regions. Therefore, it is suggested that the application of Equation

(12) represents an important complimentary approach to traditional epidemiological methods to establish the prevalence of drug abuse within various populations of interest.

Even though best available information was used to derive the general SEEB equation and to develop the specific SEEBs for cocaine, heroin and MDMA, certain limitations to the approach should be noted. That is, Equation (12) represents a rigorous tool that can be applied to translate measurable concentrations of selected SEMs into prevalence measures of relevant illicit drugs of abuse. However, the application of this equation requires one to not only measure the concentrations of appropriate SEMs in STP influents in a representative manner, but also requires an understanding of their behaviour under sewer transit conditions, and some prior knowledge of a number of important characteristics of the abusing population that is being monitored. These are all important inputs into the equations developed above, the accuracy of which will influence the quality of the estimates of prevalence of abuse.

In theory, the detailed parameterization of the various inputs to Equation (12) can be accomplished through experimental studies and targeted surveys (see Appendix Q) that will require contributions from not only analytical/environmental chemists and environmental engineers but also pharmacologists, social workers, traditional epidemiologists, police forensic services and other local experts. Of course, often it will not be possible to directly measure some of the variables associated with a particular local situation. However, in certain cases, it would be reasonable to assume that the contribution of certain parameters is negligible and thus do not require quantification, as was illustrated in several of the cases discussed above. In other situations, it may become necessary to use the best available approximations of some of the key inputs, until better information becomes available. For example, at present, there are limited data available on the tendency of selected SEMs to biodegrade. In such cases, the sewer epidemiologist should first attempt to choose SEMs that are stable; but, when this is not possible, estimates of the degradation tendencies may be required. As demonstrated above, for the specific SEEBs for cocaine, heroin and MDMA, the lack of definitive data forced us to rely on plausible deductions to establish the sewer behaviour of the selected SEMs (i.e., k_d and $J_{G,s}$). Hence there is a need to concretely verify the assumptions made here by further studying the sewer behaviour of the selected SEMs. In addition, as was shown above, the route-of-administration has important implications on the excretion of individual SEMs by abusers. Hence, in cases where it may not be possible to survey a population of interest for their route-of-administration preferences, a reasonable approximation (see Appendix Q) is the assumption that the abusing population has the same or similar preferences to those reported by abusers who are in drug-abuse treatment programs (i.e., a population for whom such data is often available). Nevertheless, such an

approximation warrants further study, particularly so for the cocaine abusing population. Overall, the parameterization of the various variables of Equation (12) is discussed in detail in Appendix Q.

Beyond the parameterization of Equation (12), an assumption made when deriving the general SEEB model is that a given STP downstream of a population of interest continuously captures all excretions from the abusers of a given illicit drug that are served by a sewer system. This assumption would not be entirely correct in the case where a portion of the population cohort is homeless and a significant portion of their excretions are not routed to the STPs. This may be an important consideration because the prevalence of certain types of illicit drug abuse in such a population cohort has been reported to be substantially higher than in the general population (Grinman et al., 2010; Kemp et al., 2006; Neale, 2001; Street Health, 2008). A counter-argument to this would be that in most developed countries the homeless represent a minor fraction of the total population (Edgar and Meert, 2006; Homelessness Australia, 2010). Overall, the significance of not fully capturing the excretions of the homeless and therefore potentially under-predicting abuse prevalence is uncertain at present and in need of further analysis. Future research can pragmatically establish such significance by addressing the following two sequential questions. First, it should be determined whether a significant fraction of the net abusers for a given illicit drug are homeless. And, if so, drawing on knowledge of the typical toilet behaviour of homeless people, it should be established whether a large fraction of their excretions are not routed to sewers and hence unlikely to be present in STP influents.

One additional factor that was not included in the generalized SEEB expressed by Equation (12) is the possible influence of leakage from the sewer. When this is significant, the SEEB can be adjusted to reflect the fraction of the collected wastewater that is lost in sewer transmission,

6.5 Conclusions

A generalized approach was developed to improve sewer epidemiology extrapolation mass balances (SEEBs) for illicit drugs. As a first step, a multi-criteria evaluation was used to select appropriate sewer epidemiology metabolites (SEM) for each illicit drug of interest. In certain cases, due to knowledge gaps, it was not possible to suggest a single most suitable SEM and, hence, for these cases more than one SEM was suggested. The derived SEEBs for the suggested SEM utilize all disposition data available in literature, incorporate various routes-of-administration of the drug of interest, account for the likely variations in the metabolic capacity of the abusers, and quantify the contributions of all sources that could lead to the selected SEM being released to the sewers.

The proposed methodology was applied to evaluate the SEEBs for the three illicit drugs cocaine, heroin and MDMA (ecstasy). Cocaine is an example of a relatively simple case where there were no significant licit sources of the selected SEM, benzoylecgonine (BE), to complicate the analysis. Heroin is a more complicated case in that two potential SEMs must be considered; namely MOR and 6MAM. MOR offers the advantages of relatively complete disposition data, expected stability during sewer transit, and likely detectability in STP influents. However, it has the disadvantage that the sewer loads of this SEM would need to be corrected for licit contributions, which in certain cases can be more than the fraction released through the abuse of heroin. The alternative SEM, 6MAM, offers the very important advantage that in most cases it is likely to be a unique marker of heroin abuse, but it suffers from disadvantages that its consistent detection may be an issue, it may not be stable during the sewer transit process, and lastly, certain key disposition data still need to be established for this compound. MDMA is another case where two potential SEMs must be considered for now; namely, HMMA and MDMA itself. HMMA seems to be theoretically the most suitable SEM to track a population's abuse of ecstasy but its quantification in wastewater influents is yet to be attempted and hence the ability to reliably quantify it in STP influents remains unproven. In contrast, MDMA has been reported in a number of studies of STP influents but its non-linear pharmacokinetics may tend to make its measured mass loads temporally and spatially incomparable, thereby limiting the potential of its use as an SEM. It may also be subject to distortions created by occasional direct dumping of unused MDMA directly into the sewer system.

The results obtained from the application of the proposed sewer epidemiology approach to these three illicit drugs indicate that extrapolation factors currently being used in literature for these drugs to assess epidemiological prevalence required further refinement to improve their reliability. Hence, this work is timely and should allow sewer epidemiologists to improve their prevalence estimates for cocaine, heroin and ecstasy abuse within a population of interest. Indeed a number of limitations addressed here were highlighted as research needs by a recent critical review of sewer epidemiology literature (van Nuijs et al., in press). Further, preliminary attempts were made here to derive SEEBs for the abuse of crack cocaine and the co-abuse of cocaine with ethanol, since both forms of cocaine abuse are of public health interest. However, certain knowledge gaps need to be addressed before sewer epidemiologists can further refine the suggested SEEBs for these forms of cocaine to readily-useable expressions.

Overall, it is recommended that the methodological framework developed here should be used to derive improved SEEBs for other illicit drugs such as amphetamine, methamphetamine, and cannabis' active ingredient tetrahydrocannabinol, among others.

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Chapter 7: Sewer epidemiology Mass Balances for Assessing the Illicit use of Methamphetamine, Amphetamine and Tetrahydrocannabinol

PREFACE

This chapter extends the generalized sewer epidemiology mass balances developed in Chapter 6 to the illicit use of amphetamine, methamphetamine and tetrahydrocannabinol.

The appendices for this chapter can be found at the end of this thesis.

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Sewer epidemiology Mass Balances for Assessing the Illicit Use of Methamphetamine, Amphetamine and Tetrahydrocannabinol.

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ABSTRACT

In sewer epidemiology, mass balances are used to back-extrapolate measurements of wastewater influent concentrations of appropriate drug residues to assess the parent illicit drug's level of use in upstream populations. This study focussed on developing and refining mass balances for the use of illicit methamphetamine, amphetamine and tetrahydrocannabinol. As a first step, a multi-criteria evaluation was used to select unchanged methamphetamine, unchanged amphetamine and 11-nor-9-carboxy-tetrahydrocannabinol as the most appropriate drug residues to track a selected population's use of illicit methamphetamine, amphetamine and tetrahydrocannabinol, respectively. For each of these selected drug residues, mass balances were developed by utilizing all disposition data available for their release from all their respective sources, incorporating route-of-administration considerations where relevant, and accounting for variations in the metabolic capacity of users of the various relevant licit and illicit sources. Further, since the selected drug residues for the use of methamphetamine and amphetamine can not only result from their use but numerous other licit and illicit sources, comprehensive general source models were developed for their enantiomeric-specific release to sewers. The relative importance of the sources identified in the general source model was evaluated by performing national substance flow analyses for a number of countries. Results suggested that licit sources of methamphetamine are expected to be only of significance in populations where its illicit use is minor. Similarly, in populations where the use of illicitly produced amphetamine is currently of relevance, licit contributions to the sewer loads of amphetamine are likely to be of negligible importance. Lastly, the study of tetrahydrocannabinol back-extrapolation mass balances suggested that further research is required to assess the importance of fecal elimination of 11-nor-9-carboxy-tetrahydrocannabinol.

KEYWORDS: Amphetamine; methamphetamine; tetrahydrocannabinol; excretion; urine; enantiomers; sewer epidemiology; wastewater

Abbreviations

AMP, amphetamine; AMPIL, amphetaminil; BAMP, benzphetamine; CLOB, clobenzorex; DMAMP, dimethylamphetamine; EAMP, ethylamphetamine; FAMP, famprofazone; FENE, fenethylline; FENP, fenproporex; FENC, fencamine; FURF, furfenorex; HO-AMP, hydroxyamphetamine; HO-MAMP, hydroxymethamphetamine; LDAMP, lis-dexamfetamine; MAMP, methamphetamine; MEF, mefenorex; MES, mesocarb; PMA, para-methoxyamphetamine, PMMA, para-methoxymethamphetamine, PRA, prenylamine, SELG, selegiline; SEEB, sewer epidemiology extrapolation mass balances; SEM, sewer epidemiology metabolite; THC, tetrahydrocannabinol; 11OH-THC, 11-hydroxy-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-tetrahydrocannabinol

7.1 INTRODUCTION

Almost a decade ago, Daughton (2001) conceptualized what has developed into the present-day field of sewer epidemiology. Sewer epidemiology in itself is an evolving approach used to monitor the use of illicit drugs in a given population of interest (Daughton, 2011; van Nuijs et al., 2011a, 2011b). Specifically, such a methodology utilizes measured influent concentrations of selected sewer epidemiology metabolites (SEM) (which is defined here to refer to all excreted drug residues, including metabolites as well as the unchanged parent compound) to back-extrapolate the prevalence or the level of illicit drug use within a population of interest (Khan and Nicell, 2011; van Nuijs et al., 2011b; Zuccato et al., 2005, 2008). The selected SEM could be the illicit drug itself or one of its *in vivo* metabolites (Khan and Nicell, 2011; van Nuijs et al., 2011b; Zuccato et al., 2008). However, wherever possible, the use of an *in vivo* metabolite as a SEM rather than the parent illicit drug is preferred since sewer loads of the parent illicit drug will always be susceptible to intentional and unintentional events where drugs are dumped into sewers. Typically, if the objective is to back-extrapolate measured influent concentrations of an appropriate SEM to infer the prevalence or the level of use for the parent illicit drug within a population of interest, sewer epidemiology extrapolation mass balances (SEEBs) must be performed. To this effect, Zuccato et al. (2008) were the first to derive such mass balances for a number of illicit drugs. To-date, the use of their suggested mass balances for back extrapolation purposes has been the norm in the field (e.g. Postigo et al., 2010; Metcalfe et al., 2010; Terzic et al., 2010).

In recent work, Khan and Nicell (2011) suggested, based on a study of the relevant aspects of cocaine, ecstasy and heroin use, that the mass balances of Zuccato et al. (2008) should be further refined to increase their applicability and reliability. To-date, such detailed refinements of the SEEBs suggested by Zuccato et al. (2008) for evaluating the illicit use of methamphetamine (MAMP), amphetamine (AMP) and cannabis' primary active ingredient tetrahydrocannabinol (THC) have not been attempted. Hence, the overall objective of the current communication is to refine the SEEBs suggested by Zuccato et al. (2008) for the illicit use of MAMP, AMP and THC.

7.2 METHODS AND MODELS

7.2.1 Excretion profiling of relevant sources: data sources and processing

A detailed literature survey was conducted to identify all illicit and licit sources that could lead to the release of a potential SEM to sewers. In turn, for each identified source, studies reporting on their cumulative urinary and/or fecal excretions were identified. Subsequently, from all identified studies, mean and standard deviations for the excreted fractions of the various SEMs were extracted. In turn,

extracted means were combined by weighting the data by the number of subjects monitored in a given study. Standard deviations were also pooled by the number of subjects studied using the method of Massart et al. (1997).

Statistical significance where required was established using a t-test, with the level of significance set at a p value of less than or equal to 0.05. Such statistical analyses were performed using Minitab (V. 16 Minitab, State College, PA).

7.2.2 Selection of appropriate sewer epidemiology metabolite (SEM)

The selection of the appropriate SEM to track a population's use of an illicit drug-of-interest was based on the traits of an ideal SEM suggested by Khan and Nicell (2011). That is, an ideal SEM is one that: (i) is released to sewers exclusively due to the use of the illicit drug-of-interest; (ii) demonstrates a well-defined excretory profile from all potential sources; (iii) is excreted in such quantities that the lack of detection issues are minimized; (iv) possess minimal adsorption potential to influent suspended solids; and (v) exhibits minimal degradation upon undergoing sewer-transit.

7.2.3 Substance flow modeling of the selected SEM

In certain cases, one may have no choice but to select a SEM that not only results from the use of the illicit drug-of-interest itself but also other licit and illicit sources. For such cases, the relative importance and contributions of the various sources of the SEM can be assessed by performing a substance flow analysis. In order to perform such an analysis, various contributions that could lead to a SEM being released to sewers must be modeled. That is, the net load of a SEM of interest ($J_{T,s}$) in the influent of a sewage treatment plant (STP) may be composed of at least three distinct contributions:

$$J_{T,s} = J_{L,s} + J_{I,s} + J_{G,s} \quad (1)$$

where: $J_{L,s}$ is the contribution that results from the consumption of licit formulations; $J_{I,s}$ is the additional contribution that results from the use of illicit drugs; and $J_{G,s}$ is the contribution that accounts for the possible generation of the SEM due to the degradation of other sewer-borne contaminants, including those that are dumped into sewers (all in μg of SEM/cap·d). Moreover, $J_{L,s}$ and $J_{I,s}$ can themselves be composed of distinct sub-contributions. Mathematical expressions to quantify such sub-contributions are detailed in sections 7.2.4 and 7.2.5.

In addition to the individual contributions that amount to $J_{T,S}$ (Eq. (1)), two additional contributions are worth noting. First, if the selected SEM is used illicitly or licitly in an upstream population, then an episodic load would be expected to arise from the deliberate or unintentional dumping of the relevant formulations (Daughton and Ruhoy, 2009). Further, if the selected SEM is manufactured licitly/illicitly in the upstream population, an additional load could be released to sewers due to manufacturing losses (Philips et al., 2010). Hence, in studies of short temporal durations and/or studies conducted in populations where significant licit/illicit manufacturing of the SEM exists, the aforementioned contributions are expected to be significant and hence may need to be included in Eq. (1).

7.2.4 Modelling licit contributions to the sewer load of a SEM ($J_{L,s}$)

A component of $J_{L,s}$ maybe released due to the clinical use of the SEM itself ($J_{L,s-c}$). Such a contribution is modeled as follows (Khan and Nicell, 2011):

$$J_{L,s-c} = \left(\sum_{p=1}^P L_{s,p} \cdot \left((1 - Y_{nsp}) \cdot \left(\sum_{e=1}^E (U_{p,e,s} + F_{p,e,s}) \cdot x_e \right) + Y_{nsp} \cdot Y_{fsp} \right) \right) \cdot \left(\text{EXP}(-k_{d,s} \cdot t_s) \right) \quad (2)$$

where: P is the total number of individual preparations, p , of the SEM that are clinically used; $L_{s,p}$ is the per capita mass sold daily of the preparation p (μg of SEM/cap·d); Y_{nsp} is the fraction of a preparation p that is not used (dimensionless); E is the total number of routes used to administer a given formulation p (dimensionless); $U_{p,e,s} + F_{p,e,s}$ is the molar fraction of an individual preparation p that is excreted as the SEM in the urine and fecal matter of users when administered via the route e (moles of SEM/moles of SEM); x_e is the mass fraction of a given preparation p that is administered through the route-of-administration e (dimensionless); Y_{fsp} is the fraction of Y_{nsp} that is expected to be directly disposed to sewer systems via toilets and/or sinks (dimensionless); $k_{d,s}$ is the first-order decay constant for the SEM (hr^{-1}); and t_s is the duration of sewer-transit (hr). Note that in Eq. (2), and all such equations to follow, the release of the SEM through the user's sweat has not been explicitly accounted for. However, sweat patch data for the particular SEM that will be selected below are such that minor levels are expected to be released via such a route to sewers (Barnes et al., 2008; Staub, 1999).

An additional contribution to $J_{L,s}$ may result from the use of other drugs that have the potential to be metabolized to produce the SEM ($J_{L,s-m}$). This contribution is expressed as follows (Khan and Nicell, 2011):

$$J_{L,s-m} = \left(\sum_{b=1}^B L_b \cdot (1 - Y_{nb}) \cdot \left(\sum_{i=1}^I (U_{b,i,s} + F_{b,i,s}) \cdot x_i \right) \cdot \frac{Mw_s}{Mw_b} \cdot \frac{Mo_s}{Mo_b} \right) \cdot \left(\text{EXP}(-k_{d,s} \cdot t_s) \right) \quad (3)$$

where: B is the total number of individual formulations, b , that can be metabolized to the SEM; L_b is the per capita mass sold daily of formulation b that is expected to be metabolized to the SEM upon use within the population (μg of $b/\text{cap} \cdot \text{d}$); Mw_b is the molecular weight of formulation b (g of b/mole of b); Mw_s is the molecular weight of the SEM (g of SEM/ mole of SEM); Mo_s/Mo_b is the molar stoichiometric ratio indicating the amount of the SEM generated through the metabolism of a given formulation b (moles of SEM/ moles of b); Y_{nb} is the fraction of formulation b sold that ends up not being used (dimensionless); I is the total number of individual routes-of-administration, i , typically used to administer a given formulation b (dimensionless); $U_{b,i,s} + F_{b,i,s}$ is the net fraction of an individual formulation b that is expected to be excreted as the SEM in the urine and fecal matter of users when administered via route i (moles of b/moles of b); and x_i is the mass fraction of a given formulation b that is administered through route i (dimensionless).

Furthermore, if the SEM is produced endogenously ($J_{L,s-end}$), then an additional licit contribution load should be accounted for as follows:

$$J_{L,s-end} = (u_{e-s} + f_{e-s}) \cdot \left(\text{EXP}(-k_{d,s} \cdot t_s) \right) \quad (4)$$

where $u_{e-s} + f_{e-s}$ is the endogenous excretion of the SEM (μg of SEM/ $\text{cap} \cdot \text{d}$).

Overall, the licit contribution to the net load of the SEM as present in STP influents ($J_{L,s}$) can be established by summing the respective contributions from $J_{L,s-c}$, $J_{L,s-m}$ and $J_{L,s-end}$:

$$J_{L,s} = J_{L,s-c} + J_{L,s-m} + J_{L,s-end} \quad (5)$$

7.2.5 Modelling illicit contributions to the sewer load of a SEM ($J_{L,i}$)

When considering the illicit contributions to the sewer load of a SEM, it is first necessary to evaluate the load arising from the population's use of the particular illicit drug-of-interest ($J_{L,i}$). Such a contribution is modeled using the following expression:

$$J_{I,d} = \left(\sum_{q=1}^Q N_{d,q} \cdot \left(\sum_{h=1}^H (U_{q,h,s} + F_{q,h,s}) \cdot x_{h,q} \right) \cdot \frac{Mw_s}{Mw_d} \cdot \frac{Mo_s}{Mo_d} \right) \cdot \left(\text{EXP}(-k_{d,s} \cdot t_s) \right) \quad (6)$$

where: Q is the number of individual groups, q , that use the illicit drug-of-interest with different intensities; $N_{d,q}$ is the population-normalized consumption/demand of the illicit drug-of-interest by the group q (μg of illicit drug-of-interest/cap·d); H is the total number of individual routes-of-administration, h , typically used to use the illicit drug-of-interest (dimensionless); $U_{q,h,s} + F_{q,h,s}$ is the fraction of the illicit drug-of-interest that is excreted as the SEM in the users' urine and fecal matter when administered via the route-of-administration h by the group q (moles of illicit drug-of-interest/moles of illicit drug-of-interest); $x_{h,q}$ is the mass fraction of the $N_{d,q}$ that is administered through the route-of-administration h (dimensionless); Mw_d is the molecular weight of the illicit drug-of-interest (g of illicit drug-of-interest/moles of illicit drug-of-interest); and Mo_s/Mo_d is the molar stoichiometric ratio of metabolically generating the SEM by using the illicit drug-of-interest (moles of SEM/moles of illicit drug-of-interest).

Potentially, a SEM of interest could also be released to sewers due to the use of illicit drugs other than the one of particular interest. This contribution ($J_{I,o}$) can be modeled in a similar manner to Eq. (6) as follows:

$$J_{I,o} = \left(\sum_{o=1}^O N_o \cdot \left(\sum_{a=1}^A (U_{a,s} + F_{a,s}) \cdot x_a \right) \cdot \frac{Mw_s}{Mw_o} \cdot \frac{Mo_s}{Mo_o} \right) \cdot \left(\text{EXP}(-k_{d,s} \cdot t_s) \right) \quad (7)$$

where: O is the total number of “other” illicit drugs, o , that can be metabolized to the SEM; N_o is the per capita consumption/demand of an “other” illicit drug by the population (μg of other illicit drug/cap·d); Mw_o is the molecular weight of an “other” illicit drug (g of other illicit drug/moles of other illicit drug); Mo_s/Mo_o is the molar stoichiometric ratio describing the metabolic generation of the SEM through the use of an “other” illicit drug (moles of SEM/moles of other illicit drug); A is the total number of individual routes-of-administration, a , typically used to administer an “other” illicit drug (dimensionless); $U_{a,s} + F_{a,s}$ is the molar fraction of an “other” illicit drug that is excreted as the SEM in the users' urine and fecal matter when administered via the route a (moles of other illicit drug /moles of other illicit drug); and x_a is the mass fraction of an “other” illicit drug administered through the route a (dimensionless).

Taken together, the net contribution of illicit sources to the influent load of a SEM can be established by summing respective contributions from $J_{I,d}$ and $J_{I,o}$:

$$J_{I,s} = J_{I,d} + J_{I,o} \quad (8)$$

7.2.6 Sewer epidemiology extrapolation mass balance (SEEB)

From an epidemiological perspective, a desirable goal is to estimate the number of abusers of the drug of interest within a community. A “number of users” measure typically used in traditional epidemiological literature on illicit drugs is the prevalence of all users for a particular illicit drug within a given population's 15–64 age-cohort (p_{r-d}). Such a measure can be estimated from measured influent concentrations of suitable SEMs using the following adaption of the sewer epidemiology extrapolation mass balance (SEEB) model developed previously by Khan and Nicell (2011):

$$Pr-d = \left[\frac{\left(\frac{C_{in-s} \cdot Q_{in}}{P \cdot (1-x_{s-s})} \right) - J_{L,s} - J_{G,s} - J_{I,o}}{\text{EXP}(-k_{d,s} \cdot t_s) \cdot x_{r15-64} \cdot \sum_{m=1}^M x_{m,d} \cdot d_{m,d}} \cdot \frac{\frac{Mw_d}{Mw_s}}{\sum_{h=1}^H (U_{h,s} + F_{h,s}) \cdot x_h} \cdot \left(\frac{Mo_d}{Mo_s} \right) \right] \cdot 100 \quad (9)$$

where: p_{r-d} is the prevalence of an illicit drug in the 15-64 age-cohort of the population being monitored (%); C_{in-s} is the dissolved influent concentration of the SEM (μg of SEM/L); Q_{in} is the daily influent flow (L/d); P is the population served by the STP; x_{s-s} is the fraction of the SEM that would be expected to be adsorbed onto sewer-borne suspended matter (dimensionless), which can be estimated at equilibrium using the model of Deo and Halden (2010); x_{r15-64} is the fraction of the population being monitored that is within the 15-64 year age cohort, M is the number of individual groups, m , that use the illicit drug-of-interest with different intensities; $x_{m,d}$ is the fraction of the total users of a particular illicit drug-of-interest that belong to group m ; $d_{m,d}$ is the net daily-averaged amount of illicit drug demanded/consumed by intensity group m (μg of illicit drug/cap·d); H is the total number of individual routes-of-administration, h , typically used to use the illicit drug-of-interest (dimensionless); $U_{h,s} + F_{h,s}$ is the molar fraction of the illicit drug-of-interest that is excreted as the SEM in the users' urine and fecal matter when administered via the route-of-administration h (moles of illicit drug-of-interest / moles of illicit drug-of-interest); and x_h is the mass fraction of the illicit drug-of-interest that is administered through the route h (dimensionless).

7.3 RESULTS AND DISCUSSION

The systematic approach taken here in developing an appropriate SEEB for each illicit drug of interest was as follows: (i) identify all relevant routes-of-administration; (ii) construct enantiomeric-specific route-of-administration segregated excretory profile; (iii) utilize the constructed profile and the SEM

selection criteria mentioned in Section 7.2.2 to select the most suitable SEM; (v) develop general source model for the selected SEM if it is determined to be released to sewers due to additional sources over and above the use of the illicit drug of interest; (vi) assess the importance of all sources identified in the general model for the selected SEM by performing substance flow analyses for a number of national populations and, finally (vii) develop an SEEB for the selected SEM with the aid of Eq. (9) using information gathered in previous six steps.

7.3.1 Methamphetamine (MAMP)

At present, a record of methamphetamine's (MAMP) illicit use is fairly well established in Australia, New Zealand, Southeast/East Asia and United States of America (U.S.A.) (Kilmer and Pacula, 2009; McKetin et al., 2008; NDRI-AIC, 2007). Conversely, in the recent past, the level of illicit use of methamphetamine has been suggested to be of minor importance in most European countries, with notable exceptions being Slovakia and the Czech Republic (EMCDDA, 2010b; Griffiths et al., 2008; Zabransky, 2007). However, recent evidence from sewer epidemiology investigations suggests that the use of MAMP maybe be increasing in number of European countries/regions where its illicit use was once of lesser significance (Harman et al., 2011; Zuccato et al., 2011).

7.3.1.1 Route-of-administration trends for MAMP

Illicit users of the drug typically administer MAMP by one or more of the following routes: nasal insufflation, smoking, injection or oral ingestion (ACMD, 2005; NDRI-AIC, 2007; SAMHSA, 2008). Illicitly produced MAMP is available in the form of tablets, powder, base or crystals (ACMD, 2005). Although the powdered and tablet forms are also smoked by users in certain locations, it is typically the crystalline form that tends to be smoked (Cho, 1990; NDIC, 2006), as is the case in the U.S.A. and Southeast/East Asia (McKetin et al., 2008; NDIC, 2006). In contrast, for example, both injection and smoking of MAMP crystals is of importance in Australia (McKetin et al., 2005; NDRI-AIC, 2007). Furthermore, crystals of MAMP are predominantly injected in Japan (McKetin et al., 2008).

7.3.1.2 Excretion profiling of MAMP

Given that a number of routes are used to administer MAMP, it is of interest to establish the effect that route-of-administration may have on the excretory profile of MAMP. Further, since MAMP is a chiral molecule, it is also of interest to establish the effect that the enantiomeric nature of the administered MAMP may have on its excretory profile. In this respect, it is worth noting that of the two enantiomers of MAMP, it is the psychoactive S(+) enantiomer that is used, either by itself or as part of an enantiomeric

mixture. Typically, due to its significantly lower psychoactive potency, the R(-) enantiomer of MAMP is not intentionally used by itself (EMCDDA, 2010a; Schep et al., 2010).

In total, ten suitable studies were identified that reported on the urinary excretory profiles of MAMP administered through various routes (See Table 7.1). The identified data was segregated at two levels before being pooled; firstly, by the enantiomeric nature of the administered MAMP and, within that classification level, by the route-of-administration (see Table 7.1). This was done to facilitate identification of any effects that route-of-administration or enantiomeric-composition may have on the urinary profile of MAMP. Fecal disposition of MAMP is rarely studied. However, wherever such data are available, the indication is such that only minor levels of an administered dose of MAMP is expected to be eliminated via the fecal route (Caldwell et al., 1972a; Yamamoto et al., 1979).

The analysis of compiled data (see Table 7.1) suggests that, irrespective of the route-of-administration or enantiomeric-composition, the major urinary drug residue of MAMP is unchanged MAMP. Amphetamine (AMP) is the primary metabolite, while hydroxymethamphetamine (HO-MAMP) and hydroxyamphetamine (HO-AMP) are all minor metabolites of MAMP use.

The effect of route-of-administration on MAMP's excretory profile can be assessed by examining the excretory profiles of the S(+) enantiomer, which is the only enantiomeric form for which disposition data was available for all relevant routes-of-administration (see Table 7.1). The compiled data for this enantiomeric form suggest that only when MAMP is smoked is the effect of route-of-administration statistically significant. That is, substantially lower levels of urinary AMP and unchanged MAMP would be expected when methamphetamine is smoked. This is expected, since significant amounts of MAMP initially placed in smoking devices ends up not being delivered to users (Cook, 1991; Cook et al., 1993; Harris et al., 2003; Martyny et al., 2008; Sekine and Nakahara, 1987).

It is important to note that the data of Cook et al. (1993), as tabulated in Table 7.1, is possibly only relevant for MAMP that has been smoked via glass pipes and are likely not representative of other manners in which MAMP is smoked by users. Specifically, smokers of MAMP have been reported to smoke the drug in cigarettes by mixing it with tobacco or by "chasing" it (Sekine and Nakahara, 1987; Zhang et al., 2008). Smoking of MAMP with tobacco has been reported in Japan (Sekine and Nakahara, 1987).

Table 7.1 Urinary profile of methamphetamine (MAMP) upon various routes of administration.

Reference ^(a)	Dose (mg)	Route	n	Age (yrs)	Duration (hr)	Fraction of administered dose (%)											
						MAMP			AMP			HO-MAMP			HO-AMP		
						Total ^(d)	S (+) ^(e)	R(-) ^(f)	Total ^(d)	S (+) ^(e)	R(-) ^(f)	Total ^(d)	S (+) ^(e)	R(-) ^(f)	Total ^(d)	S (+) ^(e)	R(-) ^(f)
Racemic MAMP																	
Li et al., 2010a	0.5 ^(c)	I.V.	12	21-45	48	45.4 ± 13.2	19.2 ± 7.1	26.2 ± 6.1	4.4 ± 1.6	3.2 ± 1.0	1.2 ± 0.5	9.7 ± 4.9	5.1 ± 2.2	4.6 ± 2.7	0.4 ± 0.2	0.2 ± 0.1	0.2 ± 0.1
					Pooled data ⁽ⁱ⁾	45.4 ± 13.2	19.2 ± 7.1	26.2 ± 6.1	4.4 ± 1.6	3.2 ± 1.0	1.2 ± 0.5	9.7 ± 4.9	5.1 ± 2.2	4.6 ± 2.7	0.4 ± 0.2	0.2 ± 0.1	0.2 ± 0.1
^(b) Caldwell et al., 1972a	13.7	Oral	2		24	27.2, 18.1			2.2,3.2			14.1,15.8			1.1,1.0		
S (+) MAMP																	
^(b) Harris et al., 2003	10	I.V.	8	21-45	24	27.2 ± 13.4	27.2 ± 13.4	n.a. ^(g)									
Li et al., 2010a	0.25/0.50 ^(c)	I.V.	12	21-45	48	44.1 ± 16.4	44.1 ± 16.4	n.a.	6.6 ± 2.4	6.6 ± 2.4	n.a.	10.9 ± 5.4	10.9 ± 5.4	n.a.	0.3 ± 0.2	0.3 ± 0.2	n.a.
Mendelson et al., 1995	24.1	I.V.	8	24-38	48	38.7 ± 10.1	38.7 ± 10.1	n.a.	10.6 ± 3.7	10.6 ± 3.7	n.a.						
Cook et al., 1993	12.4	I.V.	6	26.7	72	45.0 ± 23.3	45.0 ± 23.3	n.a.	7.1 ± 2.4	7.1 ± 2.4	n.a.						
					Pooled data ⁽ⁱ⁾	42.6 ± 16.7	42.6 ± 16.7	n.a.	7.9 ± 2.9	7.9 ± 2.9	n.a.	10.9 ± 5.4	10.9 ± 5.4	n.a.	0.3 ± 0.2	0.3 ± 0.2	n.a.
^(b) Harris et al., 2003	50	Nasal	8	21-45	24	22.6 ± 11.5	22.6 ± 11.5	n.a.									
Beckett & Rowland, 1965a	13.7	Oral	3		48	36.9 ± 15.7	36.9 ± 15.7	n.a.	8.3 ± 2.0	8.3 ± 2.0	n.a.						
Cook et al., 1992	9	Oral	4	19-32	72	40.6 ± 16.5	40.6 ± 16.5	n.a.									
Kim et al., 2004	4x10	Oral	8	26-40	192	41.3 ± 16.4	41.3 ± 16.4	n.a.	9.9 ± 3.9	9.9 ± 3.9	n.a.						
					Pooled data ⁽ⁱ⁾	40.2 ± 16.3	40.2 ± 16.3	n.a.	9.5 ± 3.6	9.5 ± 3.6	n.a.						
^(b) Harris et al., 2003	40	Smoke	8	21-45	24	9.6 ± 4.8 ^(h)	9.6 ± 4.8	n.a.									
Cook et al., 1993	24.1	Smoke	6	26.7	72	26.7 ± 7.7 ^(h)	26.7 ± 7.7	n.a.	5.0 ± 1.6 ^(h)	5.0 ± 1.6	n.a.						
					Pooled data ⁽ⁱ⁾	26.7 ± 7.7	26.7 ± 7.7	n.a.	5.0 ± 1.6	5.0 ± 1.6	n.a.						
R (-) MAMP																	
Mendelson et al., 2008	5	I.V.	12	28-51	36	55.0 ± 10.0	n.a.	55.0 ± 10.0	3	n.a.	3						
Li et al., 2010a	0.25/0.50 ^(c)	I.V.	12	21-45	48	52.4 ± 13.5	n.a.	52.4 ± 13.5	2.2 ± 0.8	n.a.	2.2 ± 0.8	7.5 ± 4.3	n.a.	7.5 ± 4.3	0.3 ± 0.2	n.a.	0.3 ± 0.2
					Pooled data ⁽ⁱ⁾	53.7 ± 11.9	n.a.	53.7 ± 11.9	2.6 ± 0.8	n.a.	2.6 ± 0.8	7.5 ± 4.3	n.a.	7.5 ± 4.3	0.3 ± 0.2	n.a.	0.3 ± 0.2
Li et al., 2010b	1-10	Oral	8	18-50	48?	44.2 ± 17.7	n.a.	44.2 ± 17.7	2.9 ± 2.0	n.a.	2.9 ± 2.0						
Beckett & Rowland, 1965a	14	Oral	3		48	49.8 ± 15.6	n.a.	49.8 ± 15.6	3.6 ± 0.5	n.a.	3.6 ± 0.5						
					Pooled data ⁽ⁱ⁾	45.7 ± 17.3	n.a.	45.7 ± 17.3	3.1 ± 1.8	n.a.	3.1 ± 1.8						
S (+) MAMP plus Ethanol																	
Mendelson et al., 1995	24.1	I.V.	8	24-38	48	48.7 ± 19.4	48.7 ± 19.4	n.a.	8.9 ± 2.5	100	8.9 ± 2.5						

(a) Since the excretion of unchanged methamphetamine is highly dependent on the pH of urine (Beckett and Rowland, 1965a), only those studies where the urinary pH was not deliberately controlled were considered for inclusion; (b) Since the elimination half-life of methamphetamine (MAMP) is typically reported to be between 9- 12 hours (Schep et al., 2010), most studies that monitored their subjects for less than 48 hours were not including in the pooling of the excreted fractions; (c) Dose administered was reported as mg/kg; (d) Total fraction of the administered dose excreted as the metabolite (% dose administered); (e) Fraction of the administered dose that is excreted as the S(+) enantiomer (% dose administered); (f) Fraction of the administered dose that is excreted as the R(-) enantiomer (% dose administered); (g) n.a. = Not applicable; (h) Based on the mass of methamphetamine initially placed in the smoking device; (i) Data pooled by number of subjects studied (i.e., n). **Drug residue abbreviations:** amphetamine (AMP); hydroxyamphetamine (HO-AMP); hydroxymethamphetamine (HO-MAMP); methamphetamine (MAMP).

“Chasing” has been suggested to be the route most commonly used by users of MAMP in Beijing, China (Zhang et al., 2008). No concrete disposition data have been reported for either of these variations of smoking MAMP. However, minor levels of unchanged MAMP are expected in the excretions of those who smoke the drug in cigarettes by mixing it with tobacco since, of the mass of MAMP initially mixed with tobacco, only 5-17% is available for inhalation to users (Cook, 1991; Sekine and Nakahara, 1987).

The effect of administered MAMP's enantiomeric composition can be assessed by examining the excretory profiles for intravenously (I.V.) administered MAMP, the only route for which disposition data was available for all enantiomeric compositions of interest (see Table 7.1). The compiled data suggest that the effects of enantiomeric composition are only statistically significant when MAMP is administered as the R(-) enantiomer; i.e., higher levels of unchanged MAMP and lower levels of AMP would be expected when MAMP is intravenously-administered as the R(-) enantiomer. However, it is worth noting that the levels of MAMP excreted unchanged after R(-) MAMP has been orally administered are no different from the levels expected when S(+) MAMP is orally administered (see Table 7.1). Hence, the effect of enantiomeric composition of administered MAMP may depend on the route used to administer MAMP.

Lastly, since the co-use of ethanol and MAMP is quite common (McKetin et al., 2005; Mendelson et al., 1995), it is important to establish any effect that ethanol co-use may have on MAMP's excretory profile. Mendelson et al. (1995) found that when ethanol was co-used with intravenously-injected MAMP, the level of MAMP excreted unchanged increased. However, the increase was statistically insignificant, thereby suggesting that the effect of ethanol co-use was largely masked by inter-individual variation in the metabolic capacity of co-users (see Table 7.1). However, it remains to be established if statistically insignificant effects of ethanol co-use are also to be expected had the MAMP been co-used via other routes-of-administration.

7.3.1.3 Sewer epidemiology metabolite (SEM) for MAMP

Of the various drug residues arising from the use of MAMP, unchanged MAMP and HO-MAMP are the most likely candidates for an effective SEM. Both are expected to negligibly adsorb onto sewer-borne suspended solids (see Appendix A and Baker and Kasprzyk-Hordern (2011b)). Furthermore, degradation studies of MAMP available to-date suggest that excreted loads of this compound are expected to be largely conserved during the sewer-transmission process (Bisceglia, 2010; Baker and Kasprzyk-Hordern, 2011a). Unfortunately, such stability data have not been reported for HO-MAMP, but it is worth noting that HO-MAMP is predominantly eliminated in human urine as sulphate conjugates (Shima et al., 2006)

and these are expected to be fairly stable during the sewer-transit process (D'Ascenzo et al., 2003). The sewer loads of both MAMP and HO-MAMP are expected to partially arise from licit contributions from an upstream population's consumption of a number of relevant formulations (see Table 7.2). Unchanged MAMP is the major urinary drug residue, while HO-MAMP is released in lower but appreciable amounts (see Table 7.1). Based on this, the use of MAMP as the SEM will allow for monitoring/detection of lower levels of MAMP use than would be the case if HO-MAMP was chosen as the SEM. Furthermore, not only are the sewer loads of HO-MAMP expected to be substantially smaller than those of MAMP, but they are also expected to be significantly more variable (see Table 7.1). In addition, as mentioned earlier, HO-MAMP is mainly eliminated as its sulphate conjugates and these conjugates are expected to survive sewer transmission to a fair degree. This implies that if HO-MAMP were selected as the SEM, not only would one need to measure its free form but also its sulphate conjugate. Furthermore, presence of HO-MAMP in sewers could also be ascribed to an upstream population's use of the illicit designer drug *para*-methoxymethamphetamine (PMMA) (Staack et al., 2003). Compared to the use of HO-MAMP as the SEM, the only major disadvantage of using MAMP would be that its sewer load would always be susceptible to direct dumping events. However, since dumping events are largely expected to be episodic rather than continuous, such spikes in theory could be accounted-for by temporally monitoring the sewer loads of MAMP over an extended duration. Overall, it is concluded that, at-present, unchanged MAMP is the more suitable of the two candidate SEMs to track an upstream population's use of illicit methamphetamine. However, HO-MAMP may be used as a secondary SEM provided that its wastewater influent concentrations are indeed detectable and the use of PMMA in the upstream population is negligible.

7.3.1.4 General source model for MAMP

Before a substance flow analysis for MAMP is presented for a number of national case studies, it would be particularly advantageous to develop a general source model for MAMP. Such a model should not only identify all licit and illicit sources that could lead to the release of MAMP to sewers but also further suggest the fractions of identified sources that are expected to be excreted as MAMP. Further, since MAMP is a chiral molecule, such a model should be enantiomer-specific. An enantiomeric-specific analysis of MAMP sewer loads should serve to minimize the relative importance of contributions from sources other than the population's use of illicit methamphetamine, since a number of sources of MAMP to sewers are either preferentially and/or exclusively metabolized to one enantiomer or the other (see Table 7.2). As an example, consider that if the total sewer loads of MAMP are measured, a potential

Table 7.2 Urinary profiling of licit AMP and MAMP precursors.

Precursor	Reference	Dose (mg)	n	Age (yrs)	Duration (hr)	Fraction of administered dose (%)											
						AMP			MAMP			HO-AMP			HO-MAMP		
						Total ^(a)	S(+) ^(b)	R(-) ^(c)	Total ^(a)	S(+) ^(b)	R(-) ^(c)	Total ^(a)	S(+) ^(b)	R(-) ^(c)	Total ^(a)	S(+) ^(b)	R(-) ^(c)
AMPIL	Remberg et al., 1972	30	2		24	3.3			n.a. ^(d)	n.a.	n.a.				n.a.	n.a.	n.a.
BAMP	Cody and Valtier, 1998	43	10	>18	> 92.5	4.2 ± 1.8	100	n.a.	1.9 ± 0.6	100	n.a.						
	Inoue & Suzuki, 1986	43	3	27-38	72	8.3 ± 0.7	100	n.a.	2.5 ± 0.5	100	n.a.	< 0.1 ^(l)	100	n.a.	< 0.1 ^(l)	100	n.a.
				Pooled data ^(h)		5.1 ± 2.4	100	n.a.	2.1 ± 0.6	100	n.a.	< 0.1	100	n.a.	< 0.1	100	n.a.
CLOB	Valtier & Cody, 2000	30	5		168	10.1 ± 4.2	100	n.a.	n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
DMAMP	Inoue & Suzuki, 1987		2	28/39	72	1.3			11.3			n.d. ^(g)			0.95		
EAMP	Beckett et al., 1969	16, 29	3		24	6.9 ± 3.1			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
	Nagai et al., 1997	16	2		24	15.5	69	31	n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
	Delbeke & Debockers, 1986	25.4	4		72	12.3 ± 2.3			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
				Pooled data ^(h)		11.2 ± 4.1	69	31	n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
FAMP	Chan et al., 2010	25	6	25 ± 2	48		44	56		29	71						
	Tseng et al., 2007	50	3		48	0.6 ± 0.3			3.0 ± 1.3								
	Cody, 1996	50	1		96	3.0			14.6								
	Shin, 1997a	50	3	27-37	48	0.7 ± 0.1	40	60	14.5 ± 7.0	33	67	1.0 ± 0.1	26	74	3.2 ± 0.6	29	71
	Neugebauer et al., 1997	50	6		48				12.9 ± 6.1	25	75						
	Oh et al., 1992	25,50	4	20-38	72				12.4 ± 4.6								
				Pooled data ⁽ⁱ⁾		1.0 ± 0.9 ^(h)	43	57	11.4 ± 6.2 ^(h)	28	72	1.0 ± 0.1	26	74	3.2 ± 0.6	29	71
FENE	Ellison et al., 1970	100	4	25-28	24	24.5 ± 5.0			n.a.	n.a.	n.a.	6.6 ± 0.9			n.a.	n.a.	n.a.
	Yoshimura et al., 1988	30	3	21-30	48	26.7 ± 5.6			n.a.	n.a.	n.a.	Trace ^(l)			n.a.	n.a.	n.a.
	Nickel et al., 1986	50	3		24	8.4 ± 5.7			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
				Pooled data ⁽ⁱ⁾		20.3 ± 5.4			n.a.	n.a.	n.a.	< 6.6 ± 0.9			n.a.	n.a.	n.a.

FENP	Togoni et al., 1972	2.5	2		24	29.1			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
	Cody and Valtier, 1996	10	5		120	27-34			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
					Pooled data ⁽ⁱ⁾	30.1			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
FURF	Inoue and Suzuki, 1986	50	3	27-38	72	7.2 ± 1.2			3.8 ± 0.6						< 0.1 ⁽ⁱ⁾		
LDAMP	Krishnan et al., 2008	70	6	22-52	48	41.5 ± 11	100	n.a.	n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
MEF	Rendic et al., 1994	40,80	2		72	5.5, 10.4			n.a.	n.a.	n.a.				n.a.	n.a.	n.a.
MES	Ventura et al., 1993	10	2		72	n.d. ^(g)			n.a.	n.a.	n.a.						
	Shumin et al., 1993		1		84	Trace ⁽ⁱ⁾			n.a.	n.a.	n.a.						
PRA	Remberg et al., 1977	100		27-60	240	1-1.5			n.a.	n.a.	n.a.	0.05 - 0.1			n.a.	n.a.	n.a.
SELG- Oral ^(e)	Hasegawa et al., 1999	5	10	25-50	48	12.8 ± 3.0	n.a.	100	27.7 ± 3.5	n.a.	100						
	Shin, 1997b	10	4	25-34	48	3.1 ± 1.1	n.a.	100	37.0 ± 8.2	n.a.	100	3.0 ± 0.9	n.a.	100	7.9 ± 4.6	n.a.	100
	Azzaro et al., 2007	10	12	28.9	96	14.4 ± 3.0	n.a.	100	32.9 ± 9.2	n.a.	100						
	Katagi et al., 2002	2,7	6	27-54	72	9.0 ± 1.4	n.a.	100	21.9 ± 5.3	n.a.	100						
					Pooled data ⁽ⁱ⁾	11.5 ± 2.6	n.a.	100	29.7 ± 7.0	n.a.	100	3.0 ± 0.9	n.a.	100	7.9 ± 4.6	n.a.	100
SELG- T.D. ^{(f),(k)}	Azzaro et al., 2007	6 ⁽ⁱ⁾	12	28.9	96	7.2 ± 2.9	n.a.	100	17.6 ± 7.0	n.a.	100						

(a) Total fraction of the administered dose excreted as the metabolite (% of administered dose); (b) Fraction of the metabolite that is excreted as the S(+) enantiomer (expressed relative to the total levels of the metabolite excreted); (c) Fraction of the metabolite that is excreted as the R(-) enantiomer (expressed relative to the total levels of the metabolite excreted); (d) n.a. = Not applicable; (e) Excretion profile for orally-administered selegiline; (f) Excretion profile for transdermally-applied selegiline; (g) n.d. = Not detected; (h) Based on the pooling of individual data points; (i) Data pooled by number of subjects studied (i.e., n), unless otherwise indicated; (j) Administered with a dosage in units of mg/24 hour; (k) Disposition data relative to the amount of selegiline released from transdermal patches; (l) Not explicitly quantified. To our knowledge cumulative urinary disposition of FENC to AMP and MAMP in humans has not been reported. Nevertheless, this formulation is no longer clinically used (INCB, 2010; Sweetman, 2009).

Precursor abbreviations: amphetaminil (AMPIL); benzphetamine (BAMP); clobenzorex (CLOB); dimethylamphetamine (DMAMP); ethylamphetamine (EAMP); famprofazone (FAMP); fencamine (FENC); fenethyliline (FENE); fenproporex (FENP); furfenorex (FURF); Lis-dexamfetamine (LDAMP); mefenorex (MEF); mesocarb (MES); prenylamine (PRA); selegiline (SELG).

Drug residue abbreviations: amphetamine (AMP); hydroxyamphetamine (HO-AMP); hydroxymethamphetamine (HO-MAMP); methamphetamine (MAMP).

contribution that must be accounted for is the upstream population's use of selegiline (SELG), a licit pharmaceutical. However, if instead the sewer load of the S(+) enantiomer of MAMP is measured, the contribution due to the population's use of SELG would not need to be accounted for, since SELG is only metabolized to R(-) MAMP (Azzaro et al., 2007). Further, from an environmental loading perspective, it is of interest to establish the relative loads of the two enantiomeric forms, since their environmental relevance may differ significantly (Kasprzyk-Hordern, 2010).

Licit loads of MAMP can be released to sewers due to a population's consumption of the following precursors: benzphetamine (BAMP), dimethylamphetamine (DMAMP), famprofazone (FAMP), furfenorex (FURF), and selegiline (SELG) (Azzaro et al., 2007; Inoue & Suzuki, 1986, 1987; Oh et al., 1992). The enantiomeric-specific urinary profiling of these licit precursors of MAMP is summarized in Table 7.2. Typically, the fecal disposition of licit precursors is rarely reported, but the limited data available in this respect suggest that the fecal elimination of such drugs is a minor elimination pathway (Caldwell et al., 1972a; Caldwell, 1976; Dring et al., 1970, 1975; Krishnan et al., 2008; Yamamoto et al., 1979). Among the various precursors that are metabolized to MAMP, at present DMAMP, FENC and FURF appear to not be in clinical use anywhere in the world (INCB, 2010; Sweetman, 2009). However, the illicit use of DMAMP has been documented in Asia (Sato et al., 2002). BAMP is exclusively prescribed in the U.S.A., FAMP is available over-the-counter in Taiwan, and SELG is available in most countries (Chan et al., 2010; INCB, 2010; Sweetman, 2009; US FDA, 2010).

In Chile and the U.S.A., licit loads of S(+) MAMP are expected to be released to sewers due to their respective populations' clinical consumption of S(+) MAMP (DEA, 2008; Sweetman, 2009). Furthermore, licit loads of R(-) MAMP are expected to be released to American sewers due to the population's use of Vicks inhalers[®] (Mendelson et al., 2008).

Illicit contributions to the sewer load of MAMP, include the obvious contribution from the population's use of illicit methamphetamine and, if present, the contribution from the use of DMAMP. Further, depending on the precursor chemical used to manufacture it, illicitly-used MAMP within a population may be available as the S(+) enantiomer alone and/or as a racemic mixture (Lee et al., 2007; UNODC, 2008).

Considering the aforementioned licit and illicit sources, the enantiomeric-specific excretion profiling of MAMP precursors presented in Table 7.2, and the excretion profiling of the relevant enantiomeric forms

of MAMP detailed in Table 7.1, one can produce a general source model for the release of the two enantiomers of MAMP to sewers (see Appendix B).

7.3.1.5 Substance flow analyses for MAMP

The relative importance of various licit and illicit sources identified in the general source model (see Appendix B) can be assessed by performing substance flow analyses. Herein, substance flow analyses are performed on a national scale for the U.S.A., Czech Republic and Scotland. These three countries were selected for analysis because the mass of MAMP (and AMP as will be seen in Section 7.3.2) illicitly consumed within these populations could reasonably be evaluated (see Appendix C). These countries were also selected because they offer very different use and consumption patterns of relevant licit formulations (see Appendix D) and, hence, are likely to yield trends that may be representative of other situations in countries not studied here. The results of the substance flow analysis are summarized in Figure 7.1 and discussed below.

The analysis suggests that, circa 2006, the predominant fraction of MAMP released nationally to U.S.A. sewers was due to the population's use of illicit MAMP. All licit contributions were of minor importance. Further, the net load of MAMP in U.S.A. sewers was predominantly expected to be S(+) in enantiomeric nature, due to the relative contribution of the illicit MAMP flows to the net sewer loads of MAMP (see Figure 7.1) and its expected S(+) enantiomeric nature (DEA, 2011). However, such a trend may not presently hold true since a significant fraction of illicit MAMP currently available in the United States is expected to be enantiomerically-mixed in nature (NDIC, 2010). Lastly, it is worth noting that the regional prevalence of illicit MAMP use within the various American states varies substantially; i.e., at present its use is rampant in most western and south-western states, whereas in north-eastern states its use remains fairly limited (SAMHSA, 2006). As a result, in the sewers of north-eastern states, substantially smaller illicit loads of MAMP are to be expected and as a consequence of this the licit sources of MAMP for such cases could become significant.

The analysis of MAMP flows in the Czech Republic, circa 2006, yields a similar picture to that of the U.S.A., in that, almost the entire load of MAMP released to sewers is expected to originate from the population's use of illicit MAMP (see Figure 7.1). The use of selegiline by the Czech population amounted to a negligible fraction of the net load of MAMP released. Further, due to the relative contributions of illicit MAMP flows to the net sewer loads (see Figure 7.1) and its expected S(+) enantiomeric nature (Jirovsky et al., 1998), the net load of MAMP in Czech sewers was predominantly expected to be S(+) in enantiomeric nature.

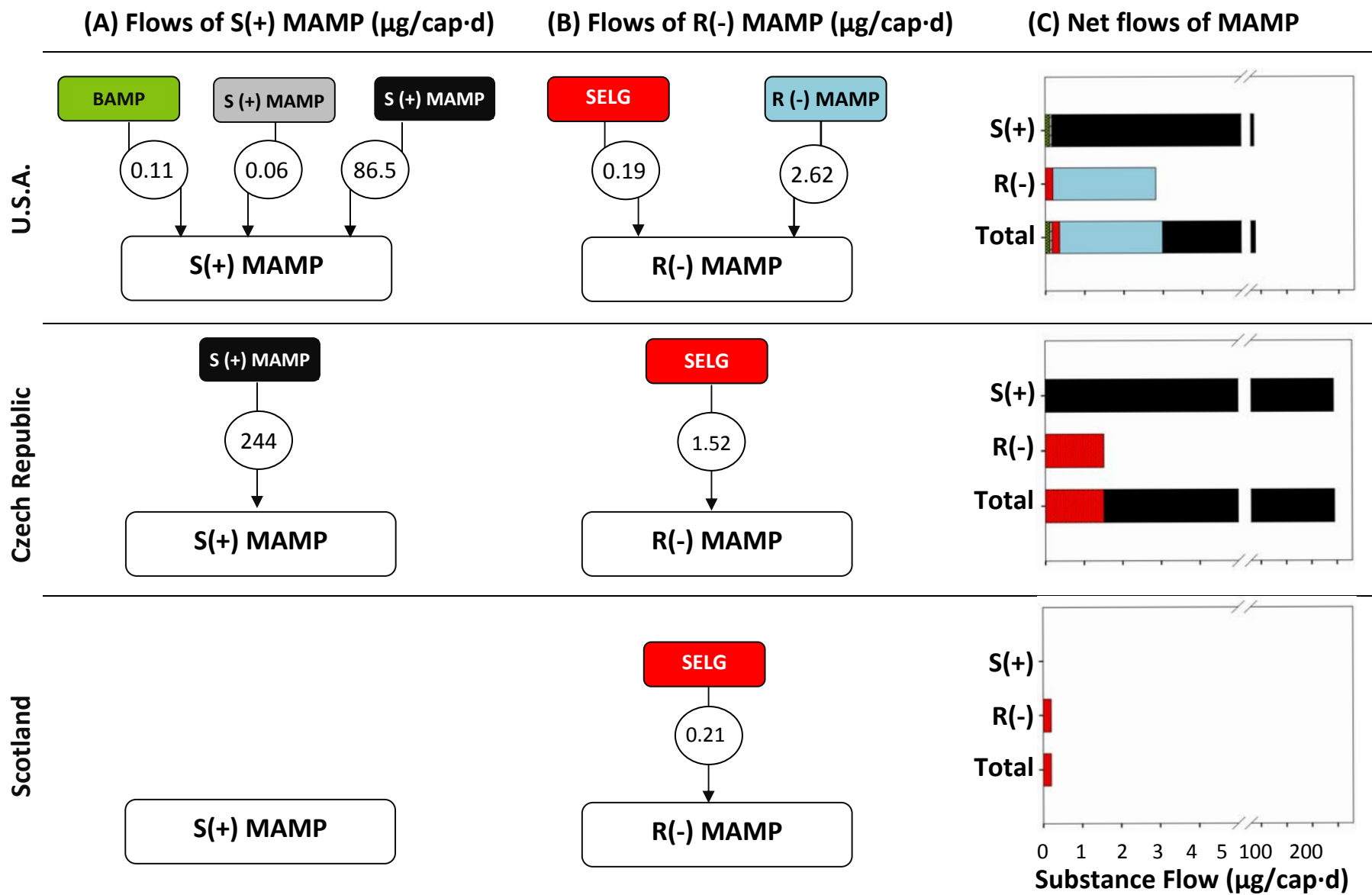


Figure 7.1 Substance flows of (A) the S(+) enantiomer of MAMP, (B) the R(-) enantiomer of MAMP, and (C) the cumulative flows of S(+) MAMP, R(-) MAMP and total MAMP. All units are expressed in μg of MAMP/cap·d. Individual contributions for Fig 1(C): () BAMP, () Licit S(+) MAMP, () SELG, () Licit R(-) MAMP and () Illicit S(+) MAMP.

For details on how substance flows were estimated and the data sources required in the process, see Appendix E.

Very little evidence exists to suggest that illicit use of MAMP was of significance in Scotland circa 2006 (see Appendix C). Hence, around 2006, the sewer loads of MAMP to Scottish sewers were expected to exclusively arise from the population's use of selegiline (see Figure 7.1). Therefore, the net loads of MAMP released to Scottish sewers were expected to amount to fairly minor levels and, further, expected to be almost exclusively R(-) in enantiomeric nature (see Figure 7.1).

Overall, the substance flow analyses suggest that, in countries/regions where a record of use of illicit MAMP is fairly well established (e.g., U.S.A. and the Czech Republic), almost the entire load of MAMP released to sewers is expected to result from the population's use of illicit MAMP. Furthermore, for such cases, the enantiomeric form of the net MAMP sewer load is largely expected to duplicate the enantiomeric nature of locally-available illicit MAMP. In countries where the levels of illicit MAMP use are low/negligible (e.g., Scotland), the contributions of licit sources could be significant. However, in such populations the net sewer loads of MAMP are expected to be substantially smaller than those realized in populations with an established problem associated with the use of illicit MAMP.

From a sewer epidemiology perspective, there exists particular interest in establishing the importance of MAMP sewer loads expected to arise from licit sources. To study this in further detail, licit contributions to the sewer loads of MAMP were estimated for 18 countries (see Appendix F). The analysis suggests that licit contributions to the net sewer loads of MAMP will only be relevant in those national and/or sub-national populations where minor quantities of illicit MAMP are used. Further, the analysis suggests that the national per capita consumption of SELG, a source of MAMP expected to be present in almost all populations, appears to be declining in most national populations.

Lastly, the relative contribution of illicit MAMP flows to the net sewer flows of MAMP in populations where its record of illicit use is well established may suggest that enantiomeric-specific analysis of MAMP may not be required to better isolate the fraction of the net load that arises exclusively due to the illicit use of MAMP. Nevertheless, an enantiomeric-specific analysis in these populations could serve to establish the relative enantiomeric composition of illicit MAMP available to the upstream population. Such an analysis is of value since higher the fraction of S(+) MAMP enantiomer in the net loads of MAMP, the more potent is the illicit MAMP available to the population of interest. Moreover, the relative enantiomeric composition could indirectly serve to establish the nature of precursor chemicals used to manufacture the illicit MAMP available to the monitored population. For example, an enantiomeric ratio of close to 1:1 of MAMP sewer loads would suggest that most illicitly-available MAMP within population was manufactured from 1-phenyl-2-propanone (Lee et al., 2007; UNODC, 2008). On the other

hand, a predominantly S(+) sewer load of MAMP would suggest that most of the illicitly available MAMP was manufactured from (+)pseudoephedrine or (-)ephedrine (Lee et al., 2007; UNODC, 2008). An additional utility of performing enantiomeric-specific analysis of MAMP in populations with established levels of illicit MAMP use would be that such an analysis could directly serve to establish the sewer loads and, hence, the environmental loads and relevance of the two enantiomers.

7.3.1.6 SEEB to track the illicit use of MAMP

As indicated above, MAMP is not expected to degrade appreciably (i.e., $k_{d-MAMP} \approx 0$) or sorb on to influent suspended solids (i.e., $x_{s-MAMP} \approx 0$). Additionally, at present, there is no evidence to suggest that MAMP is likely to be generated due to the degradation of other contaminant loads (i.e., $J_{G,MAMP} \approx 0$). Taken together, these simplifications allow one to adapt the general SEEB expression, Eq. (9), to the following expression specifically tailored to MAMP:

$$p_{r-mMAMP} = \frac{\left(\frac{C_{in-MAMP} \cdot Q_{in}}{P} \right) - J_{L,MAMP} - J_{I,O}}{xr_{15-64} \cdot \sum_{m=1}^M x_{m,MAMP} \cdot d_{m,MAMP}} \cdot \frac{100}{(0.42 \pm 0.17) \cdot x_{non-smoking} + (0.27 \pm 0.08) \cdot x_{smoking}} \quad (10)$$

In Eq. (10), a distinction is only made between the mass fraction of MAMP that is smoked (i.e., x_{smoke}) and the mass fraction that is administered through other routes-of-administration (i.e., $x_{non-smoke}$). This is due to the analysis presented in section 7.3.1.2 above that suggests that the effects of route-of-administration are only expected to be statistically significant when MAMP is smoked.

Further, in Eq. (10), $J_{L,MAMP}$ can be expanded with the aid of Eq. (5) to the following:

$$J_{L,MAMP} = J_{L,MAMP-m} + J_{L,MAMP-c} + J_{L,MAMP-end} \quad (10a)$$

MAMP is not endogenously produced and hence $J_{L,MAMP-end} = 0$. The contributions $J_{L,MAMP-m}$ and $J_{L,MAMP-c}$ can themselves be expanded using Eq. (2) and (3) along with the general source model for MAMP (see Appendix B) to yield:

$$J_{L,MAMP-c} = L_{MAMP} \cdot ((1 - Y_{n,MAMP}) \cdot (0.40 \pm 0.16) + Y_{n,MAMP} \cdot Y_{f,MAMP}) \quad (10b)$$

$$J_{L,MAMP-m} = L_{BAMP} \cdot (1 - Y_{n,BAMP}) \cdot (0.013 \pm 0.004) + L_{FAMP} \cdot (1 - Y_{n,FAMP}) \cdot (0.05 \pm 0.02) + L_{SELG-oral} \cdot (1 - Y_{n,SELG-ORAL}) \cdot (0.24 \pm 0.06) \\ + L_{SELG-TD} \cdot (1 - Y_{n,SELG-TD}) \cdot (0.14 \pm 0.06) \quad (10c)$$

In Eq. (10c), only those contributions have been included for which there was evidence to suggest that they are still in clinical use somewhere in the world. Hence, the equation does not account for licit

contributions from the consumption of DMAMP, FENC and FURF since no clinical use of these formulations could be identified (INCB, 2010; Sweetman, 2009).

The general source model (see Appendix B) suggests that the only illicit contribution that needs to be accounted for other than use of illicit MAMP is the one that arises from the population's use of DMAMP. Such a contribution can be modeled by simplifying Eq. (7) to the following:

$$J_{I,o} = N_{DMAMP-oral} \cdot (0.103) \quad (10d)$$

In its most general form, when the total concentrations of MAMP are measured, the suggested SEEB is Eqs. (10) to (10d). However, as suggested earlier, the licit contributions described by Eqs. (10b) and (10c) at present are only expected to be of significance in populations where minor levels of illicit MAMP are used. Further, presently Eq. (10d) will likely only be relevant in some Asian countries where the illicit use of DMAMP is observed.

7.3.2 Amphetamine (AMP)

Globally, amphetamine's illicit use is of significance in a number of European and Middle/Near-Eastern countries (Kilmer and Pacula, 2009; UNODC, 2008).

7.3.2.1 Route-of-administration trends for AMP

Typically, one or more of the following routes are used to administer illicit amphetamine: nasal insufflation, injection or oral ingestion (EMCDDA, 2010a). Furthermore, since amphetamine sulphate, which is the common salt form of illicit amphetamine, is insufficiently volatile when heated, the smoking of AMP is rarely observed (EMCDDA, 2010a).

7.3.2.2 Excretion profiling of AMP

The urinary profiling of the various relevant enantiomeric forms of orally-administered amphetamine is summarized in Table 7.3. The two drug residues of interest for which data is summarized and pooled in Table 7.3 include unchanged amphetamine (AMP) and the metabolite hydroxyamphetamine (HO-AMP). Fecal disposition data of AMP in animals and chemical analogues in humans suggest that only minor to trace levels of AMP would be expected to be eliminated via the fecal route (Caldwell, 1976; Dring et al., 1970, 1975; Krishnan et al., 2008; Yamamoto et al., 1979).

The meta-analysis of compiled data (see Table 7.3) for the urinary disposition of orally administered AMP suggests that, irrespective of its enantiomeric nature, the major urinary drug residue is unchanged AMP whereas HO-AMP is released in only minor amounts.

Unfortunately, the effect of route-of-administration could not be assessed since, to our knowledge, the excretory profiles for intravenously- and nasally-administered amphetamine have not been reported under uncontrolled urinary conditions. However, similar excretion profiles have been reported for orally- and intravenously- administered amphetamine in studies where urine was deliberately controlled to be acidic (Beckett and Rowland, 1965a; Beckett et al., 1965c; Davis et al., 1971). Further, excretion profiling of methamphetamine, which itself is metabolized *in vivo* to amphetamine suggests that route-of-administration effects of intravenously- and nasally-administered AMP are likely to be masked by the expected variations in the metabolic capacity of its users (see Table 7.1). Hence, in the absence of better data, the available excreted fractions for orally-administered AMP (see Table 7.3) are used here as surrogates for other relevant routes of using illicit AMP (i.e. nasal insufflation and I.V. injection).

The analysis of the compiled data in Table 7.3 further suggests that the enantiomeric nature of parent AMP in most instances is not expected to result in statistically significant effects on the urinary profile of AMP. Only when AMP is administered as the R(-) enantiomer are the statistically higher levels of unchanged AMP to be expected compared to those released had the AMP been administered as the S(+) enantiomer (see Table 7.3).

7.3.2.3 Sewer epidemiology metabolite for AMP

Both AMP and HO-AMP are potential SEMs that can be used to track a population's use of illicit AMP. Neither is expected to appreciably adsorb onto influent suspended solids (see Appendix A, Baker and Kasprzyk-Hordern (2011-b) and Metcalfe et al. (2010)). To-date, conflicting data has been reported on the stability of AMP in wastewater. For example, Bisceglia (2010) reported AMP to slowly degrade with a half-life of 44 hours. In contrast, Baker and Kasprzyk-Hordern (2011-a) observed an increase in the concentration of AMP in a single grab sample. Note that in the latter case, no explanation is apparent to indicate how AMP was generated in stored wastewater influent samples. Overall, recognizing the limited scope of the two studies, it is concluded that further work is required to confidently describe the degradation behaviour of sewer-borne AMP loads.

Table 7.3 Urinary profile of orally-administered amphetamine (AMP).

Reference ^(a)	Dose (mg)	n	Age (yrs)	Duration (hr)	Fraction of administered dose (%)					
					AMP			HO-AMP		
					Total ^(d)	S (+) ^(e)	R(-) ^(f)	Total ^(d)	S (+) ^(e)	R(-) ^(f)
Racemic AMP										
^(c) Caldwell et al., 1972b	14.6	2		24	18, 20			2.4,4.4		
^(c) Dring et al., 1970	0.07 ^(b)	3		24	30 ± 6.3			2.8 ± 2.9		
Gunne et al., 1967	3.6-7.3	4		48	39.4 ± 13.1	18.8 ± 6.0	20.6 ± 7.2			
				Pooled data ^(h)	39.4 ± 13.1	18.8 ± 6.0	20.6 ± 7.2	3.0 ± 2.2		
Adderall[®] (S(+)/R(-) of 3:1 AMP)										
Cody et al., 2003	12.7	5		120	40.3 ± 7.4	28.8 ± 5.0	11.5 ± 2.4			
S (+) AMP										
^(c) Dring et al., 1970	0.07 ^(b)	3		24	33.7 ± 7.6	33.7 ± 7.6	n.a. ^(g)	1.1 ± 1.2	1.1 ± 1.2	n.a.
Beckett & Rowland, 1965b	3.6-10.9	11	23-33	48	29.4 ± 8.4	29.4 ± 8.4	n.a.			
Rowland, 1969	7.3	3		144	45.3 ± 3.0	45.3 ± 3.0	n.a.			
Vree & van Rossum, 1969	3.6	2		60	35, 38	35, 38	n.a.			
Sever et al., 1973	1.4	2	46-51	48	40, 44	40, 44	n.a.	1.1, 2.4	1.1, 2.4	n.a.
^(c) Ellison et al., 1970	3.6	4	25-28	24	24.3 ± 3.1	24.3 ± 3.1	n.a.	5.4 ± 0.6	5.4 ± 0.6	n.a.
				Pooled data ⁽ⁱ⁾	34.2 ± 9.4 ^(h)	34.2 ± 9.4	n.a.	3.2 ± 0.9	3.2 ± 0.9	n.a.
R(-) AMP										
Beckett & Rowland, 1965b	3.6-10.9	6	23-33	48	49.7 ± 14.4	n.a.	49.7 ± 14.4			
^(c) Dring et al., 1970	0.07 ^(b)	3		24	33.7 ± 10.2	n.a.	33.7 ± 10.2	3.9 ± 4.7	n.a.	3.9 ± 4.7
				Pooled data ⁽ⁱ⁾	49.7 ± 14.4	n.a.	49.7 ± 14.4	3.9 ± 4.7	n.a.	3.9 ± 4.7

(a) Since the excretion of amphetamine is highly dependent on the pH of urine (Beckett et al., 1965c), only those studies where the urinary pH was not deliberately controlled were considered for inclusion; (b) Dose administered was reported as mg/kg; (c) Since the elimination half-life of unchanged AMP is reported to be 12-13 hours (Rowland, 1969), all studies that monitored their subjects for a duration less than 48 hours were not included when pooling the excreted fractions of unchanged AMP. However, for the excretion of HO-AMP such a restriction on the monitoring duration of the study was not imposed since this metabolite is primarily eliminated within 24 hours of use (Sever et al., 1973); (d) Total fraction of the administered dose excreted as the metabolite (%); (e) Fraction of the administered dose that is excreted as the S(+) enantiomer of the metabolite (%); (f) Fraction of the administered dose that is excreted as the R(-) enantiomer of the metabolite (%); (g) n.a. = Not applicable; (h) Based on the pooling of individual data points; (i) Data pooled by number of subjects studied (i.e., n), unless otherwise indicated.

Drug residue abbreviations: amphetamine (AMP); hydroxyamphetamine (HO-AMP).

No data have been reported with respect to the degradation potential of HO-AMP, but this compound is expected to be predominantly excreted as its sulphate conjugates (Sever et al., 1976) and such conjugates are known to be fairly stable during the sewer transmission process (D'Ascenzo et al., 2003). Hence, both the free and sulphate-conjugated forms of HO-AMP would need to be monitored if HO-AMP is selected as the SEM of choice. The sewer loads of both AMP and HO-AMP must be corrected for a number of licit contributions due to the upstream population's consumption of relevant clinical formulations and other illicit drugs (see Table 7.2). Furthermore, HO-AMP itself is used clinically (US FDA, 2010) and, hence, its sewer loads will be influenced by such use, since HO-AMP is not metabolized to AMP (Sever et al., 1976). Nevertheless, at present, clinical use of HO-AMP is primarily limited to ophthalmic preparations (e.g., Paremyd[®] (US FDA, 2010)) and, hence, the contribution to the sewer loads of HO-AMP arising from such licit use should be of negligible importance. The presence of HO-AMP in sewers could also be ascribed to an upstream population's use of the illicit designer drug *para*-methoxyamphetamine (PMA) and/or *para*-methoxymethamphetamine (PMMA) (Kitchen et al., 1979; Staack et al., 2003). However, these illicit designer drugs are not metabolized to AMP. Perhaps most importantly, the sewer loads of HO-AMP are expected to be not only substantially smaller than those of unchanged AMP, but also extremely variable (see Table 7.3). The only major limitation of using AMP would be that observed sewer loads would be susceptible to the direct dumping events; nevertheless, as mentioned before, influent sampling campaigns could be designed to account for such contributions. Overall, it is concluded that unchanged AMP is the most suitable SEM to track the use of amphetamine within a population of interest.

7.3.2.4 General source model for AMP

In theory, licit loads of S(+) and/or R(-) AMP could be released to sewers due to an upstream population's consumption of the following precursors: Amphetaminil (AMPIL); Benzphetamine (BAMP); Clobenzorex (CLOB); Dimethylamphetamine (DMAMP); Ethylamphetamine (EAMP); Famprofazone (FAMP); Fencamine (FENC), Fenethylamine (FENE); Fenproporex (FENP); Furfenorex (FURF); Lis-dexamfetamine (LDAMP); Mefenorex (MEF); Mesocarb (MES), Prenylamine (PRE) and Selegiline (SELG) (Cody, 2002, 2007; Krishnan et al., 2008). Among these, AMPIL, DMAMP, EAMP, FENC, FURF, MEF, MES and PRE are presently not in clinical use (INCB, 2010; Sweetman, 2009). However, as mentioned earlier, illicit use of DMAMP has been documented in Asia (Sato et al., 2002). Among the precursor formulations that are still in clinical use, BAMP is exclusively prescribed in the U.S.A. (INCB, 2010; Sweetman, 2009). CLOB remains in use in Mexico (PLM, 2009) and was previously available over-the-counter in Panama (Cody and Valtier, 1999) but it remains unclear if this still remains the case. FAMP is currently available over-the-counter in Taiwan (Chan et al., 2010). At

present, FENE may only be clinically used in Belgium (Sweetman, 2009). FENP is extensively used in Brazil as a dietary aid (INCB, 2010). Other countries that report the medicinal use of this particular precursor include Chile, Mexico and Argentina (Sweetman, 2009). LDAMP is a recently-approved drug with expanding use for the treatment of attention deficit hyperactivity disorder (ADHD) in both U.S.A. and Canada (US FDA, 2010; Health Canada, 2010). At present, the use of this formulation is limited in Europe. Finally, SELG is used in most countries (Sweetman, 2009).

AMP loads are also expected to be released to sewers due to a population's licit consumption of S(+) MAMP and R(-) MAMP. At present, R(-) MAMP is exclusively available to the American population in the form of Vicks inhalers[®], while the clinical use of S(+) MAMP has been reported in Chile and the U.S.A. (INCB, 2010; Sweetman, 2009).

AMP will be released to sewers due to the clinical use of AMP itself. The S(+) enantiomer of AMP is used clinically in U.S.A., United Kingdom, Canada, Australia, Belgium, Norway, Sweden, New Zealand, Finland, Denmark, Switzerland, Germany and the Netherlands (GIP, 2010; INCB, 2010). In Denmark, Iceland, Norway and Sweden, enantiomeric mixtures of AMP are also clinically used (Apoteket AB., 2009, DKMA, 2010; IMA, 2010; NIPH, 2010). Furthermore, in the U.S.A. and Canada, AMP is also clinically used as a unique formulation called Adderall^(R) consisting of a 3:1 mixture of the S(+) enantiomer to the R(-) enantiomer (Health Canada, 2010; US FDA, 2010).

Illicit loads of AMP will also be released due to the illicit use of AMP and MAMP within a population (see Tables 7.1 and 7.4). Typically, illicitly-produced AMP is racemic in nature (George and Braithwaite, 2000) and the relevant isomeric forms of illicitly-produced MAMP include S(+) MAMP and a racemic mixture (Lee et al., 2007; UNODC, 2008). Furthermore, in certain populations an illicit load of AMP may be released to sewers due to the population's use of DMAMP (Sato et al., 2002).

Noting the aforementioned licit and illicit source, the excretion profiling of AMP precursors summarized in Table 7.2 and the excretion profiling of the relevant enantiomeric forms of MAMP and AMP detailed in Tables 7.1 and 7.3, one can produce a general source model for the release of the two enantiomeric forms of AMP to sewers (see Appendix H).

7.3.2.5 Substance flow analysis for AMP

The general source model derived for AMP (see Appendix H) can be used along with consumption of relevant licit and illicit sources, summarized in Appendices C, D and G, to establish estimates of national

substance flows of the two enantiomers of AMP. The national flows of AMP to American, Czech and Scottish sewers are depicted in Figure 7.2.

Based on data collected circa 2006, AMP was expected to be predominantly released to American sewers as the S(+) enantiomer (see Figure 7.2). Specifically, $\approx 60\%$ of S(+) AMP's net sewer loads was expected to arise due to the American population's consumption of licitly-dispensed S(+) AMP and R/S(3:1) AMP (i.e., Adderall^(R)), while the remainder was almost entirely expected to be arise from the population's use of illicit MAMP. All other contributions were of negligible to minor significance to the net sewer loads of S(+) AMP. The net sewer loads of R(-) AMP, circa 2006, were expected to amount to only minor levels when compared to those for the S(+) enantiomer. Furthermore, almost all contributions to the net sewer load of R(-) AMP were expected to arise from licit sources, with the largest source being the population's consumption of licitly-dispensed R/S(3:1) AMP. Presently, however, R(-) AMP is also expected to be released to American sewers due to the population's use of illicit MAMP since, unlike in 2006, a significant fraction of illicit MAMP currently available is expected to be enantiomerically-mixed in nature (NDIC, 2010). Hence, currently, the relative proportion of R(-) AMP with respect to the net sewer loads of AMP are expected to be higher than those predicted in Figure 7.2 for the year 2006.

Although the use of illicitly-produced AMP in the United States is expected to be of minor importance, the illicit use of this drug is in fact observed (SAMHSA, 2009). This has been suggested to largely be due to the diversion of licitly-dispensed S(+) AMP and R/S(3:1) AMP (SAMHSA, 2009; Wilens et al., 2008). Hence, a potential application of sewer epidemiology would be to gain insight into the level of diversion of such formulations by monitoring the influent loads of AMP. This would particularly be an interesting possibility in those states of the U.S.A. where the levels of illicit MAMP use are fairly minor (i.e., in most north-eastern states), since in such cases only minor contributions to the sewer load of AMP would be expected to arise from the population's use of illicit MAMP. However, in states where a record of use of illicit MAMP is well established (i.e., in most western and southwestern states), a correction amounting to a significant fraction of the measured AMP load would need to be made. Hence, in populations where a record of use of illicit MAMP is well established, the use of measured AMP loads to monitor an upstream population's consumption of relevant AMP formulations, and hence possibly their diversion patterns, should be interpreted with caution.

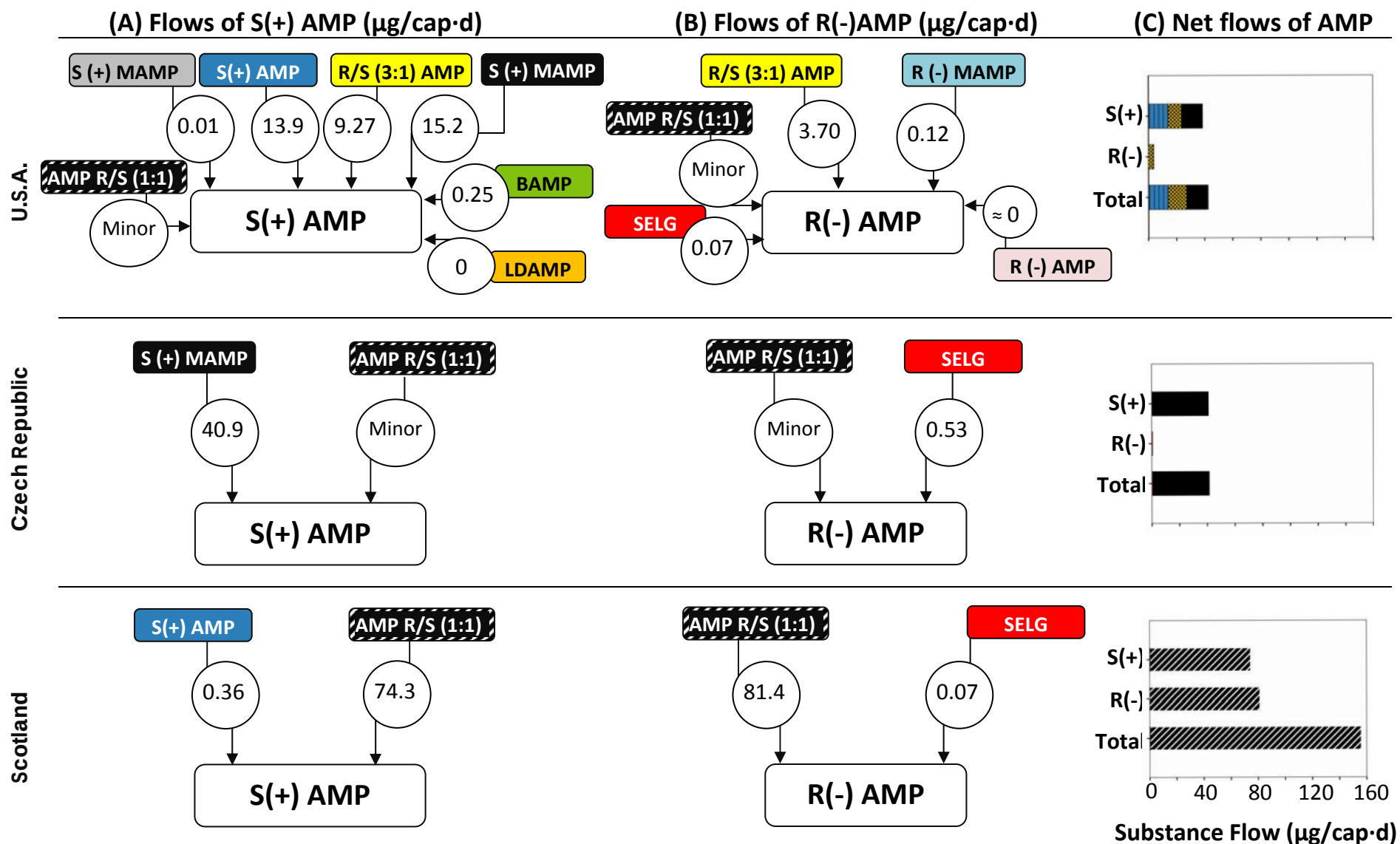


Figure 7.2 Substance flows of (A) the S(+) enantiomer of AMP, (B) the R(-) enantiomer of AMP, and (C) the cumulative flows of S(+) AMP, R(-) AMP and total AMP. All units are expressed in μg of AMP/cap·d. **Individual contributions for Fig 2(C):** (▨) BAMP, (▨) Licit S(+) MAMP, (▨) SELG, (▨) Licit R(-) MAMP, (▨) Licit S(+) AMP, (▨) Licit R/S(3:1) AMP, (▨) Illicit S(+) MAMP and (▨) Illicit R/S (1:1) AMP.

Footnote: For details on how substance flows were estimated and the data sources required in the process, see Appendix I.

Overall the substance flow analysis for the U.S.A. suggests that in populations where a record of use of illicit MAMP is well established, the use of illicitly-produced AMP is low and the treatment of ADHD through clinical formulations of AMP is widely accepted, the use of MAMP and the use of clinical AMP formulations are both expected to be important contributors to the sewer loads of AMP.

AMP was largely expected to be released to Czech sewers, circa 2006, due to the population's use of illicit MAMP (see Figure 7.2). Hence, the net load of AMP released to Czech sewers was expected to largely replicate the S(+) enantiomeric nature of illicit MAMP available, circa 2006. The sewer loads of R(-) AMP were expected to be comparatively minor to those released for the S(+) enantiomer and mainly expected to result from the population's licit consumption of SELG. Overall, the substance flow analysis for the Czech Republic suggests that in populations where a record of use of illicit MAMP is well established and further where the levels of illicit AMP use and the use of relevant licit formulation of AMP are low or non-existent, almost the entire load is expected to arise from the population's use of illicit MAMP. Furthermore, due to the relative contribution of illicit MAMP substance flows to the net sewer loads of AMP in such populations, the enantiomeric nature of the net sewer loads of AMP is largely expected to replicate the nature of illicit MAMP available to the population. Lastly, it is interesting to note that in such populations, the sewer loads of AMP could be used as a secondary SEM to establish an upstream population's use of illicit MAMP. The utility of AMP as the secondary SEM in such populations will be that its sewer loads are not expected to be susceptible to influence by direct dumping of MAMP.

Of the populations studied, Scotland was the only one where a record of use of illicitly-produced AMP was well established (see Appendix G). The substance flow analysis suggests that, circa 2006, the population's use of illicitly-produced AMP was expected to be the single most important source of AMP to Scottish sewers (see Figure 7.2). Furthermore, given that illicitly-produced AMP available in Scotland was expected to be racemic in nature (George and Braithwaite, 2000; UNODC, 2008), and also recognizing the relative contribution of such an illicit source to AMP's net sewer loads, the net sewer loads of AMP were expected to be racemic in nature. Licit contributions to the sewer loads of S(+) and R(-) AMP due to the population's clinical consumption of S(+) AMP and SELG, respectively, were expected to be of negligible importance (see Figure 7.2). Overall, the substance flow analysis for Scotland suggests that in populations where a record of use of illicitly-produced AMP is well established and the use of illicit MAMP is either non-existent or minor, almost the entire sewer load of AMP would be expected to arise from the population's use of illicitly-produced AMP. Further, due to the relative contribution of illicit AMP substance flows to the net sewer loads of AMP in such populations, the

enantiomeric nature of the net sewer loads of AMP is largely expected to replicate the nature of illicit AMP available for use.

Since clinical formulations of AMP and/or its precursor SELG are expected to yield licit sewer loads of AMP for a number of populations, it is of interest from a sewer epidemiology perspective to better grasp the importance of such contributions. Such an analysis is detailed in Appendix J for 17 countries. The analysis therein suggests that in most populations a sewer load of less than $1 \mu\text{g}/\text{cap}\cdot\text{d}$ would be expected to arise from all licit sources of AMP with the notable exception to this being the consumption patterns of clinical AMP formulations within U.S.A., Canada and Australia. In these populations, substantial contributions to the sewer loads of AMP would be expected to arise from such licit sources. However, it worth noting that in the U.S.A. and Australia, since the use of illicitly-produced AMP has largely been replaced by the use of illicit MAMP, very little interest may presently exist in using influent loads of AMP to estimate the level of use of illicitly-produced AMP. Overall, the analysis suggests that in populations where the use of illicitly-produced AMP is currently of relevance (i.e., a number of European populations) the contribution of licit sources of AMP to sewers are expected to amount to minor levels (i.e., less than $1 \mu\text{g}/\text{cap}\cdot\text{d}$). However, it is worth noting that the national per capita consumption of clinical formulations of AMP is rapidly increasing in certain European populations (see Appendix J).

Since 2006 when it was not yet approved for sale, the use of LDAMP has expanded significantly in the U.S.A.. Furthermore, the use of this formulation is expected to substantially expand in Europe (Schlander, 2007). Overall, the analysis detailed in Appendix K suggests that the current consumption levels of LDAMP in the U.S.A. and the predicted levels in Germany and England could be a significant licit source of S(+) AMP to sewers – particularly so if the use of LDAMP expands significantly beyond the currently observed or predicted levels.

7.3.2.6 SEEB to track the illicit use of AMP

AMP is not expected to sorb onto influent suspended solids ($x_{s-AMP} \approx 0$). Further, at present there is no conclusive evidence to suggest that AMP is likely to be generated due to the degradation of other contaminant loads (i.e., $J_{G,AMP} \approx 0$). Given these considerations, the general expression Eq. (9) can be simplified to the following expression for AMP:

$$p_{r-AMP} = \frac{\left(\frac{C_{in-AMP} \cdot Q_{in}}{P} \right) - J_{L,AMP} - J_{I,o}}{\text{EXP}(-k_{d,AMP} \cdot t_s) \cdot x_{I_{5-64}} \cdot \sum_{m=1}^M x_{m,AMP} \cdot d_{m,AMP}} \cdot \frac{100}{(0.39 \pm 0.13)} \quad (11)$$

Since illicitly-produced AMP tends to be racemic in nature (George and Braithwaite, 2000), the dataset reported by Gunne (1967) for the excreted fractions of unchanged AMP (i.e., $39 \pm 13\%$) was selected from the values available in Table 7.3 for Eq. (11).

In light of conflicting data currently available with respect to the degradation potential of AMP in wastewater influents $k_{d,AMP}$ has been retained as an unknown in the Eq. (11).

In Eq. (9), $J_{L,AMP}$ can be expanded with the aid of Eq. (5) to the following:

$$J_{L,AMP} = J_{L,AMP-m} + J_{L,AMP-c} + J_{L,AMP-end} \quad (11a)$$

AMP is not endogenously produced and hence $J_{L,AMP-end} = 0$. The contributions $J_{L,AMP-m}$ and $J_{L,AMP-c}$ can be expanded using Eq. (2) and (3) along with the general source model for AMP (Appendix H) to yield:

$$J_{L,AMP-c} = L_{S(+),AMP} \cdot [(1 - Y_{n,S(+),AMP}) \cdot (0.34 \pm 0.09) + Y_{n,S(+),AMP} \cdot Y_{f,S(+),AMP}] \\ + L_{S(+),R(-),3:1AMP} \cdot [(1 - Y_{n,S(+),R(-),3:1AMP}) \cdot (0.40 \pm 0.07) + Y_{n,S(+),R(-),3:1AMP} \cdot Y_{f,S(+),R(-),3:1AMP}] \quad (11b)$$

$$J_{L,AMP-m} = L_{BAMP} \cdot (1 - Y_{n,BAMP}) \cdot (0.03 \pm 0.01) + L_{CLOB} \cdot (1 - Y_{n,CLOB}) \cdot (0.05 \pm 0.02) + L_{FAMP} \cdot (1 - Y_{n,FAMP}) \cdot (0.004 \pm 0.003) \\ + L_{FENP} \cdot (1 - Y_{n,FENP}) \cdot (0.22 \pm 0.02) + L_{FENE} \cdot (1 - Y_{n,FENE}) \cdot (0.08 \pm 0.02) + L_{LDAMP} \cdot (1 - Y_{n,LDAMP}) \cdot (0.21 \pm 0.06) \\ + L_{SELG-T.D.} \cdot (1 - Y_{n,SELG-T.D.}) \cdot (0.05 \pm 0.02) + L_{SELG-oral} \cdot (1 - Y_{n,SELG-oral}) \cdot (0.08 \pm 0.02) + L_{S(+),MAMP} \cdot (1 - Y_{n,S(+),MAMP}) \cdot (0.09 \pm 0.03) \\ + L_{R(-),MAMPnasal} \cdot (1 - Y_{n,R(-),MAMPnasal}) \cdot (0.02 \pm 0.01) \quad (11c)$$

In Eq. (11c), only those contributions have been included for which there was evidence to suggest that these compounds are still in clinical use somewhere in the world. Thus, the equation does not account for licit contributions from the consumption of AMPIL, DMAMP, EAMP, FENC, FURF, MEF, MES and PRE since no present clinical use of these formulations could be identified (INCB, 2010; Sweetman, 2009).

In order to establish illicit contributions to the sewer load of AMP ($J_{I,o}$), potential contributions from the use of MAMP and DMAMP must be accounted for (see Appendix H). Such an expression can be developed by expanding Eq. (7) with the aid of Appendix H to the following (note: this equation assumes that illicit MAMP is available in its S(+) enantiomeric form):

$$J_{I,o} = N_{DMAMP-oral} \cdot (0.01) + N_{MAMP} \cdot [(0.08 \pm 0.03) \cdot x_{non-smoke} + (0.05 \pm 0.01) \cdot x_{smoke}] \quad (11d)$$

In summary, in its most general form, when the total concentrations of AMP are measured in an influent wastewater, the suggested SEEB for this compound is represented by Eq. (11) to (11d).

7.3.3 Tetrahydrocannabinol (THC)

Globally, cannabis and, hence, its primary active ingredient tetrahydrocannabinol (THC), tend to be the most widely used illicit drug (Leggett, 2006).

7.3.3.1. Routes-of-administration trends for THC

Most commonly, THC is smoked in cigarettes by mixing it with tobacco (Atha, 2005; EMCDDA, 2010a). Other significant routes-of-administration of THC includes smoking it through water pipes and smoking it “neat” in cigarettes without mixing it with tobacco (Atha, 2005).

7.3.3.2 Excretion Profiling and SEM selection for THC

In total, nineteen suitable studies were identified that reported on the various relevant aspects of THC disposition (see Table 7.4). The three drug residues of interest for which data is summarized and pooled in Table 7.4 include: unchanged tetrahydrocannabinol (THC), 11-hydroxy-tetrahydrocannabinol (11OH-THC) and 11-*nor*-9-carboxy- tetrahydrocannabinol (THC-COOH).

The excretion profile summarized in Table 7.4 suggests that only trace to minor levels of unchanged THC are expected to be excreted unchanged via the urinary route. For the commonly-used route of smoking THC, only trace levels of 11OH-THC are expected to be released via the urinary excretions of THC users. Conversely, THC-COOH is the major urinary metabolite of smoked THC. Significant fractions of urinary THC-COOH is conjugated to glucuronic moieties (Wall et al., 1983; Williams and Moffat, 1980), however, such conjugates are expected to largely revert to the free form during the sewer-transit process (D’Ascenzo et al., 2003). Fecal THC-COOH, in contrast, is primarily released as the free compound (Wall et al., 1983). For smoked THC, Huestis et al. (1996) reported that frequent users (2.3

cigarettes/week) of the drug excreted $0.54 \pm 0.12\%$ of the THC dose placed in cigarettes as urinary THC-COOH. However, infrequent users (0 to <1 cigarettes/month) of the drug have been reported to excrete in their urinary excretions $0.03 \pm 0.02\%$ of the initial dose of THC placed in the cigarettes as THC-COOH (Brenneisen et al., personal communication). Although discrepancies between the two studies are expected due to differences in methodology, such inconsistency is also not entirely surprising since, in comparison with those who use THC infrequently, frequent users have been reported to excrete a larger fraction of the administered dose via their urine (Lemberger et al., 1971a; Lemberger et al., 1971b; Johansson et al., 1990). Of the two data sets, the data of Huestis et al., (1996) is likely more relevant for sewer epidemiology investigations. This is because frequent users of THC, despite amounting to only 50-60% of the THC-using population (Clements and Zhao, 2009; Hakkarainen et al., 2008; Kilmer and Pacula, 2009; UNODC, 2006), are estimated to consume between 85-96% of the net mass of THC consumed within a population (Bouchard, 2008; Clements and Zhao, 2009; Hakkarainen et al., 2008; Kilmer and Pacula, 2009; Leggett, 2006; Legleye et al., 2008; UNODC, 2006). Such mass considerations are of critical importance to sewer epidemiology investigations, since it is the mass load of an appropriate SEM that is measured at the influents of sewage treatment plants.

The dataset of Huestis et al. (1996) only accounts for the levels of THC-COOH released via the urinary excretions of users and, hence, does not consider the fraction that is released to the sewer via the user's fecal excretions. This is of importance since, irrespective of the route with it is administered, THC is primarily eliminated via the fecal route (see Table 7.4). To our knowledge, the cumulative level of a smoked THC dose that is eliminated as fecal THC-COOH has not been reported to-date. In addition, the cumulative fraction of a smoked THC dose that is expected to be eliminated via the fecal route also currently remains unreported. However, Wall and Perez-Reyes (1981) observed that of the net levels of smoked THC eliminated via the fecal route within the first 24 hrs, 31% was in the form of THC-COOH. Unfortunately, the authors did not report the net levels of the smoked THC dose that was eliminated via the fecal route. Nevertheless, theoretically plausible attempts can be made to estimate the net fraction of a smoked THC dose that can be expected to be eliminated via the fecal route. For this to be done, it is essential to first note that, once systemically bioavailable, the metabolic disposition of smoked THC has been reported to be similar to that observed for intravenously-administered THC (Wall et al., 1976). Hence, the net fecal-to-urinary ratio of approximately 2 (estimated from relevant data presented in Table 7.4) for the disposition of intravenously-administered THC can be multiplied by the available net urinary

Table 7.4 Excretory profile of tetrahydrocannabinol (THC) upon various routes of administration.

Reference	Dose (mg)	n	Age (yrs)	Freq. of use ^(a)	Duration (hr)	Fraction of administered dose (%)							
						Urine				Fecal			
						Total ^(b)	THC	11OH-THC	THC-COOH	Total ^(b)	THC	11OH-THC	THC-COOH
I.V. Administered THC													
Wall et al., 1983	2.2, 4.0	12	23 ± 3	Past users	72	15.5 ± 3.5			4.0 ± 1.7 ^(o)	31.0 ± 15.0 ^(c)	2.1 ± 1.2 ^{(c),(p)}	6.9 ± 4.4 ^{(c),(p)}	6.1 ± 4.1 ^{(c),(p)}
Wall et al., 1976	4.6	7-10			72	12							
Hunt and Jones, 1980	2	6	22-30	11-40	96	23.2 ± 3.2 ^(d)				66.3 ± 6.7 ^(d)			
Hunt and Jones, 1980	2	6	22-30	11-40	96	17.5 ± 3.3 ^(e)				64.6 ± 7.7 ^(e)			
Hunt et al., 1981	2	4	22-30	4-10	96	23.3 ± 5.8							
Lemberger et al., 1971a	0.5	4		Non-users	168	21.7 ± 3.0				45.0 ± 5.0			
Lemberger et al., 1971a	0.5	5	21-27	Daily-users	168	30.2 ± 1.7				40.0 ± 5.0			
Lemberger et al., 1970	0.5	3	18-22	Non-users	240	33.3	< 1			52.2	Minor ^(q)	20 ^(o)	
Lemberger, 1973		4		Heavy	72	26.7 ± 4.2		5 ^(o)		39.6 ± 4.1 ^(f)		20 ^(o)	
Oral THC													
Wall et al., 1983	15, 20	12	22 ± 4	Past users	72	14.7 ± 2.9			3.8 ± 1.1 ^(o)	50.7 ± 14.0 ^(g)	5.0 ± 1.8 ^{(g),(p)}	3.8 ± 0.9 ^{(g),(p)}	9.7 ± 3.9 ^{(g),(p)}
Gustafson et al., 2004	0.4 -14.8	7x4	36.3	2.0 -7.0 (mean 4.5)					1.9 ± 1.7 ^(o)				
Wall and Perez-Reyes, 1981	20	6			72					35			
Cone et al., 1988	22-45	5x2	27-38	Daily to weekly	Up to 246				1.3 ± 0.2 ^(o)				
Johansson et al., 1990	20	4		Light + Heavy ^(h)	120	8-14							
Halldin et al., 1982	20-30	3			48	10	n.d. ^(r)		2.7 ^(o)				
Kanter et al., 1978	30	3			24		0.006 ± 0.002 ^(o)						
Hollister et al., 1974	30	4		Light?	24 -48		0.005-0.01 ^(o)						
Lemberger, 1973		5		Heavy?	72	19.5 ± 2.7				39.6 ± 5.2			
Perez-Reyes et al., 1972	35	40		< 1	72	20 ± 5	0.1 ± 0.1 ^(t)	0.07 ± 0.02 ^(t)		57 ± 7 ^(u)	20 ? ^(u)		
Smoked THC													
Stillman et al., 1976	10	9		Past Users	24	8							
Wall & Perez-Reyes, 1981	17			Heavy	24					Major ⁽ⁱ⁾	6 ^(j)	26 ^(j)	31 ^(j)
Johansson et al., 1990	19	2		<1 ^(k)	120	2							
Johansson et al., 1990	19	2		>1 ^(l)	120	5							
Brenneisen et al., Unpublished ⁽ⁿ⁾	70	12	26 ± 3	0-<1 ^(s)	264		0.001 ± 0.001 ^{(m),(o)}	0.012 ± 0.009 ^{(m),(o)}	0.026 ± 0.018 ^{(m),(o)}				
Huestis et al., 1996	16,34	6x2	28-36	0.4 -7.9 (mean 2.3)	168				0.54 ± 0.12 ^{(m),(o)}				
Galanter et al., 1972	10	3	21-26	Heavy	24	5.1 ± 2.8 ^(m)							
Lemberger, 1973	10	3		Heavy	24	4.8 ± 2.6 ^(m)							

Footnotes Table 7.4

(a) Where available, the average number of marijuana cigarettes consumed per week by the subjects was compiled; (b) Total fraction of the administered dose eliminated via urine or fecal matter (%); (c) $n = 9$; (d) Before tolerance was induced by authors through the chronic administration of oral THC; (e) After tolerance was induced by authors through the chronic administration of oral THC; (f) $n = 3$; (g) $n = 11$; (h) Light users were defined by the authors as those who smoked less than one cigarette per week, while chronic/heavy users were defined as those who smoked the drug more than once a week; (i) The exact fraction of the smoked dose that is eliminated via the fecal route was not reported by the authors, however the authors asserted that their data (albeit not specifically reported in the paper) suggested that the fecal excretions were the major elimination route for smoked THC; (j) Fraction of 24-hour fecal collections (i.e., not relative to the administered dose of THC); (k) Defined to be light users by the authors; (l) Defined to be heavy users by the authors; (m) Based on the mass of the THC dose initially placed in the respective smoking devices (i.e., cigarettes and etc.); (n) Although the cumulative fractions as listed in the table remain unpublished and were obtained through a personal communication with Dr. Brenneisen at the University of Bern, the associated urinary concentration data have been published by the group (Brenneisen et al., 2010); (o) Includes fraction of the metabolite conjugated to glucuronic moieties; (p) Free metabolites, however conjugated fraction of these metabolites in fecal excretions is of minor importance (Wall et al., 1983); (q) Not explicitly quantified; (r) Below detection limit; (s) Frequency of use on a per month basis; (t) $n=5$; (u) $n=3$.

Drug residue abbreviations: tetrahydrocannabinol (THC); 11-hydroxy-tetrahydrocannabinol (11OH-THC); 11-*nor*-9-carboxy-tetrahydrocannabinol (THC-COOH).

levels for smoked THC of 5-8% (see Table 7.4 for heavy smokers of the drug) to produce an estimate that 10-16% of a smoked THC dose is expected to be eliminated via the fecal route. Encouragingly, similar values are arrived at for the net fecal elimination of a smoked THC dose if instead of net urinary data, the bioavailability of smoked THC in frequent/heavy users of the drug (Lindgren et al., 1981; Ohlsson et al., 1982) is used for estimation purposes. The estimated net fecal elimination of 10-16% can be used along with observations of Wall and Perez-Reyes (1981) with respect to the fraction of fecal THC that is approximately THC-COOH (i.e., 31%), to estimate that 3.1 to 5.0% of a smoked THC dose can be expected to be eliminated via the fecal route as THC-COOH. Overall, theoretically plausible calculations described above suggest that the predominant fraction of THC-COOH is expected to be released to sewers via the fecal route. The potential importance of such a contribution has largely gone unrecognized in the field of sewer epidemiology.

At the typical pH value of 7.5 for fecal matter and the surrounding wastewater (Tietz, 1995; Qasim, 1999), THC-COOH, unlike THC and 11OH-THC, is expected to be fully ionized (see Appendix L). The tendency for an ionic chemical to adsorb onto organic carbon, and hence solid matrices, can be assessed by estimating its organic carbon–water distribution coefficient (D_{oc}). Specifically, for THC-COOH at a pH of 7.5, D_{oc} values of 147 L/kg and 174 L/kg are predicted by ACD Lab’s property prediction software (2011) and the model of Franco and co-workers (Franco and Trapp, 2008; Franco et al., 2009), respectively. In an approach similar to that shown in Appendix A, such D_{oc} values can be used in the model of Deo and Halden (2010) to estimate that at equilibrium only 1.1 to 1.3% of the sewer load of THC-COOH is expected to remain adsorbed to sewer-borne solids. Hence, if sewer-transit conditions were such that equilibrium is established between the solid and liquid phases, then almost the entire fecal load of THC-COOH would be expected to partition out into the aqueous phase. While it remains to be confirmed whether under typical sewer-transit conditions equilibrium will be achieved, it is important to note that appreciable dissolution and breakage of fecal matter is expected to occur in sewers since they are typically designed to at the very least maintain a self-cleansing velocity of 0.6 m/s (for example see GLUMRB, 2004).

Overall, it would be of particular interest to establish the exact levels of THC-COOH that are expected to be released via the fecal excretions of THC smokers and to subsequently study the aqueous “availability” of this excreted load under typical sewer-transit conditions. Until such studies are done, any back extrapolations based only on the urinary values reported by Huestis et al. (1996) should be considered to possibly over-estimate the mass of THC used within an upstream population.

7.3.3.3 SEEB to track THC use

Once in the aqueous phase, THC-COOH is not expected sorb onto influent suspended solids (i.e., $x_{s-THC-COOH} \approx 0$, see Appendix A). Further, at present there is no evidence to suggest that THC-COOH is likely to be generated due to the degradation of other contaminant loads (i.e., $J_{G, THC-COOH} \approx 0$). The current consumption levels (INCB, 2010) of dronabinol, a synthetic form of THC that is clinically-used in a few national populations as an anti-emetic, are such that negligible loads would be expected to arise from such a source. Licit loads of THC-COOH are also expected to be released to sewers due to a population's consumption of hemp-seed based food products; however, the current consumption levels of such food products (Fortenbery and Bennett, 2004; Karus and Vogt, 2004; Kruse, 2011) and their associated THC content (EFSA, 2011; Holler et al., 2008) is such that negligibly minor loads of THC-COOH are expected to result from their consumption. Overall, at present, $J_{L, THC-COOH}$ can be approximated to be of negligible importance. Lastly, THC-COOH is not expected to be released to sewers due to the consumption of other illicit drugs (i.e., $J_{I, THC-COOH} \approx 0$). Given these considerations, Eq. (9) can be simplified to the following for THC-COOH:

$$P_{r-THC} = \frac{\left(\frac{C_{in-THC-COOH} \cdot Q_{in}}{P} \right)}{\text{EXP}(-k_{d, THC-COOH} \cdot t_s) \cdot x_{f_{15-64}} \cdot \sum_{m=1}^M x_{m, THC} \cdot d_{m, THC}} \cdot \frac{100 \times 0.91}{(0.005 \pm 0.001 + F_{smoked, THC-COOH})} \quad (12)$$

Although stability studies in urine at room temperature suggest that excreted loads of THC-COOH are expected to be fairly stable (Abraham et al., 2007), there is a need to concretely establish this under relevant sewer-transit conditions. Hence, $k_{d-THC-COOH}$ has been retained as an unknown in Eq. (12).

Furthermore, due to the considerations discussed above, the fraction of a smoked THC dose that is expected to be eliminated via the fecal route as THC-COOH (i.e., $F_{smoked, THC-COOH}$) has been retained as a parameter in Eq. (12) because further study is required before it can be quantified with confidence.

7.4 LIMITATIONS AND OPPORTUNITIES FOR FURTHER DEVELOPMENT

The general SEEB expression (Eq. (9)) is a tool that can be used to back-extrapolate measurable concentrations of selected SEMs into prevalence measures of parent illicit drugs. However, the full use of such equations requires that its various variables be parameterized using four lines of information. First,

the concentrations of the selected SEM would need to be measured in a representative manner. Further, the selected SEM's sewer transit behaviour would need to be accurately understood. Additionally, in certain cases, the level of use of relevant licit formulations and other illicit drugs in the upstream population would need to be accounted for. Lastly, some prior knowledge is also required of the relevant characteristics of the upstream illicit drug-using population. The limitations and difficulties of accurately parameterizing variables of Eq. (9) using these lines of information, particularly the last one, have been discussed at length previously by Khan and Nicell (2011). However, an aspect that has not been discussed previously is the suitability of the metabolic disposition data currently available. Specifically, there is some concern about the suitability of disposition data available thus far from pharmacokinetics studies where the smoking of an illicit drug is studied. Typically, such studies modify the smoking devices used and/or the manner in which they allow subjects to smoke the drug in ways that ensure that reproducible pharmacokinetic data is generated from a route-of-administration that is expected to be inherently variable. Hence, the excretory profiles from these studies may not be fully representative of real-life use of the drug. For example, consider the most relevant data for the urinary disposition of smoked THC as reported by Huestis et al. (1996). In their smoking protocol section the authors write: "Marijuana smoking was computer paced. The number of cigarettes puffs, the length of time for each inhalation, the time between puffs and puff hold time were controlled to reduce intersubject variability...". The computer-paced administration and the artificial control on the intersubject variability are two aspects of this study that would suggest that the reported excretory profiles may not be fully representative of real-life smokers of THC. Similar concerns can be raised for the smoking device and administration protocol used by Cook et al. (1993), the most relevant study on the disposition of smoked MAMP (see Appendix M for an extended examination of this study's smoking device and administration protocol).

Overall, these considerations suggest that there should be renewed interest in establishing "real-life" excretory profiles for all illicit drugs for which smoking is a relevant route-of-administration. Until such data becomes available, the sewer epidemiologist must resort to using the data arising from studies such as those of Huestis et al. (1996) for THC and Cook et al. (1993) for MAMP, but it is necessary to recognize the possibly significant limitations of the available data.

7.5 CONCLUSIONS

The conclusions arising from this study are summarized as follows:

- *SEM selection:* A multi-criteria evaluation was used to select unchanged MAMP, unchanged AMP and THC-COOH as the most appropriate SEMs to track an upstream population's use of illicit methamphetamine, amphetamine and THC, respectively.
- *General source model development:* Since sewer loads of MAMP and AMP may result from multiple licit and illicit sources other than through the use of the illicit drug-of-interest, comprehensive general source models were developed for their enantiomeric-specific release to sewers.
 - The relative importance of all sources identified in the general source model was gauged by performing national substance flow analyses. The results of these analyses suggested that licit contributions to the sewer loads of MAMP are only expected to be of relevance in populations where minor levels of illicit MAMP are used. Similarly, in populations where the use of illicitly-produced AMP is currently of relevance (e.g., a number of European populations) the licit contributions to AMP's sewer loads appear to be of negligible importance.
 - Further, the developed general source models also suggest that in certain instances enantiomeric-specific analyses of influent samples for AMP and/or MAMP could serve to minimize the relative importance of contributions from sources other than the population's use of illicit amphetamine and methamphetamine, respectively.
- *SEEB development:* For each selected SEM, sewer epidemiology extrapolation mass balances (SEEBs) were developed by considering relevant aspects of the parent illicit drug's use and the developed general source models. The developed SEEBs for the first time utilize all suitable disposition data available in literature for all the various sources of a given SEM, incorporate route-of-administration considerations where relevant, and account for variations in the metabolic capacity of users of the various relevant clinical formulations and illicit drugs.

- *Fecal elimination of THC-COOH:* The SEM selection and SEEB development for THC suggested that an important knowledge gap that needs to be addressed is an evaluation of the actual levels of THC-COOH eliminated via the fecal route of THC smokers. Furthermore, there is also a need to understand the aqueous “availability” of this fecal load. Therefore, until these knowledge gaps are addressed, any extrapolations performed with the currently available urinary values should be considered to possibly over-estimate the mass of THC used within an upstream population.

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Chapter 8: Sewer Epidemiology: Whom are We Measuring?

PREFACE

This chapter addresses the objective of the thesis focussed on the need to better understand the environmental presence of certain PhACs so that sewer epidemiology analyses can be performed and interpreted in a meaningful way. In particular, the chapter serves to highlight a very important, yet unrecognized, limitation of the field of sewer epidemiology. That is, measured drug loads of an illicit drug's metabolite are highly sensitive to a small number of users. Therefore, spatial and temporal variations in the measured loads of an illicit drug's metabolite should not be taken by themselves to be indicative of the changes in the number of users of an illicit drug in the upstream population.

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Sewer Epidemiology: Whom are we measuring?

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Sewer epidemiology is a technique in which the influent loads of selected drug residues are used to gauge the level of use of parent illicit drugs in an upstream population. With increasing interest in using the technique to compare drug use patterns over spatial and temporal scales, a fundamental question needs further attention; that is, what is the relationship between the influent loads of a selected drug residue and the “number of users” of the parent illicit drug in the upstream population being monitored? In particular, can we use influent loads measured in a number of distinct geographical locations and/or over temporal scales as a reasonable basis for estimates of the number of users of a particular illicit drug in a given location and/or over time? To shed some light on such questions, it is important to recognize that it is inevitably the mass loads of drug residues that are measured in sewer epidemiology investigations. Hence, the measured downstream concentration of the drug residue in wastewater influents is directly related to the consumption profile of the parent illicit drug in the upstream population. Therefore, to rationalize the variations in influents loads it is important to understand or, at the very least, begin to grasp the consumption profiles of illicit drugs.

Typically, consumption estimates of a given illicit drug for the United States are reported by making a distinction between individuals who used the drug within the past month and those who used the drug within the past year but not the past month. Furthermore, past month users are grossly considered to represent those who use the drug with heavy intensity, while users who have reported drug use in the past year but not past month are generally considered to represent light users of the drug. Using such a classification system, the estimates of Kilmer et al.¹ for the consumption of cannabis in the United States demonstrate that heavy users of cannabis are responsible for using approximately 94% of the drug’s net mass even though they represent only 58% of the overall population of cannabis users. Therefore, 42% of the overall user population, who are light users of the drug, consume only 6% of drug’s net mass. Such estimates suggest that influent loads of cannabis drug residues and, hence, their spatial variability will be highly sensitive to changes in the number, use pattern, and the mobility of heavy users of a drug and largely insensitive to changes in the aforementioned traits of the lighter users. For example, using these

estimates for the United States as a basis, if a drug residue load that is measured in the influent from a community of Population B is twice as high as that measured for Population A, it could imply any of the following general scenarios: (1) twice as many users of cannabis reside in Population B compared to Population A; (2) a slightly higher number of heavy users of cannabis reside in Population B compared to Population A; or (3) a significantly higher number of light users of cannabis reside in Population B compared to Population A.

Which of the above possibilities (or combinations thereof) is the actual situation is difficult to ascertain based solely on measurements of drug residues in wastewaters. The sensitivity of mass loads to a relatively small number of users can be further highlighted by recognizing that the so-called “heavy users” themselves constitute a lumping of a diverse group of users with varying consumption patterns, as do the light users of the drug. For example, consider the estimates furnished by Bouchard² for the consumption of cannabis in the Canadian province of Quebec, in which heavy and light users of the drug are classified further. Specifically, Bouchard² classified the cannabis-consuming population into five distinct groups: those who use the drug with yearly, occasional, monthly, weekly and daily frequencies. The relative proportions of these users as well as the fraction of the net cannabis mass they consume are plotted in Figure 1. In this case, the daily users consume 85% of the net mass of the drug even though they represent only 18% of users. Leggett⁴ also reported a similar use profile for their estimates of the global consumption of cannabis. Even more than the estimates of Kilmer et al.¹ discussed above, such data highlight the sensitivity of the mass flow of drug residue in an influent wastewater to a relatively minor fraction of users who use the drug with a heavy intensity.

This sensitivity is not unique to cannabis. Cocaine and methamphetamine are two additional illicit drugs that demonstrate this behaviour of disproportionate use of the drug by their respective heavy users. For example, consider that heavy users of methamphetamine consume about 74% of the net mass of that drug within the United States during a given year despite only amounting to 39% of the active user population.⁴ Similarly, heavy users of cocaine consume 74% of the net mass of cocaine while they only represent 28% of the active cocaine user population.⁵

Temporal analyses of drug residues in wastewaters downstream of a given population may serve to provide further insight into the fraction of the upstream population that are heavy users as opposed to light users of a drug. That is, it could be surmised that heavy users of the drug would be expected to contribute an omnipresent and reasonably constant background load, while recreational users may be expected to only contribute to the influent loads at distinct times. For example, as an initial working assumption, light users may be expected to use the drug

predominately on weekends and special occasions (i.e., New Year's Eve). If true, this would suggest that drug residue loads measured on such occasions would be less sensitive to a small number of heavy users of the drug.

The above examples serve to illustrate the sensitivity of influents loads of drug residues to the consumption patterns of heavy users of certain illicit drugs. This aspect warrants recognition as the spatial and temporal domains of the field of sewer epidemiology expand and the results are used to gauge the level of drug abuse in upstream populations of varying characteristics.

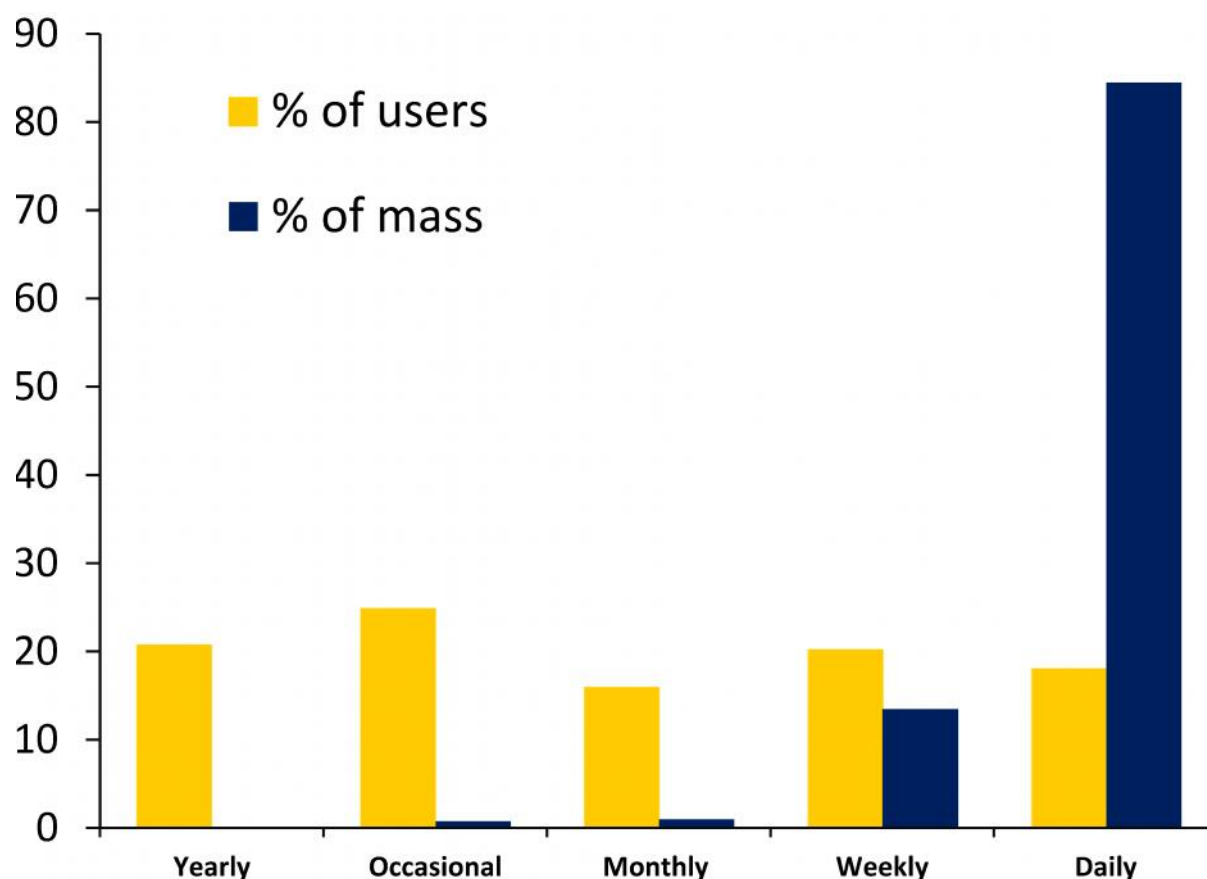


Figure 1 Consumption profile of Cannabis in Quebec during the Year 2003 (plotted from estimates put forth by Bouchard²)

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Chapter 9: Conclusions

The research presented in this thesis aimed to understand the sources, risks, trade-offs and aspects of sewer epidemiology as they relate to the environmental release and presence of PhACs. The relationships between the upstream patterns and level of use or excretion of PhACs and their resulting downstream mass loads in wastes and the environment were explored and modelled. These models were then applied to the Canadian, USA or other geographical contexts and populations to address important human health and eco-toxicological questions, which yielded the main conclusions listed below. Note that this is not intended to be an exhaustive list and, as such, it is left to the reader to refer to the conclusions sections presented in Chapters 2 to 8 for a more complete list of conclusions arising from this work.

- A model for the environmental release of 25 endogenous chemicals including androgens, thyroids and their *in vivo* metabolites was developed. The model was applied in the context of the USA to evaluate the environmental relevance of the selected chemicals, but since only limited eco-toxicological data was available, it was possible to assess the environmental relevance of only 5 of the 25 selected PhACs. Based on available eco-toxicological data, testosterone, dihydrotestosterone, thyroxine and triiodothyronine were deemed unlikely to pose a risk to receiving aquatic ecosystem. However, under a high exposure scenario, the androgen androstenedione was found to carry the potential to yield eco-toxicological impacts on fish. Therefore, the environmental release, the fate and the effects of androstenedione warrant further investigation.
- An approach was developed for the assessment of human-health and eco-toxicological risks posed by PhACs in urine that is applied to agricultural land. The approach was applied to evaluate 25 widely-used PhACs through six routes of exposure. Of the 25 PhACs evaluated, 14 were found to pose possible eco-toxicological or human-health risks. Overall, the approach developed can be used to identify exposure routes and toxicological endpoints that are of greatest concern. The application of the approach also allows one to develop a priority list of PhACs whose presence in collected urine may require pre-treatment.
- A priority list of 335 PhACs of possible environmental or health concern was developed for Canada. In order to estimate the environmental loads of the 335 PhACs to the Canadian environment, a model that accounted for seven possible source terms was developed. Results arising from the application of the model suggested that all identified source terms warranted consideration when trying to accurately estimate the environmental loading of any given PhAC. Hospital contributions to the net load of individual PhACs were found to vary significantly from one case to another. However, for most

PhACs evaluated, hospitals appeared to be a minor source. Nevertheless, certain PhACs and certain drug classes appear to be predominately sourced through hospitals. Overall, it appeared that even if PhACs in the wastewaters of hospitals are successfully treated before their release to municipal sewer systems, the majority of the mass load of most PhACs will still be released into sewer systems for subsequent treatment and/or disposal in the environment.

- Of the 335 PhACs whose environmental loadings to the Canadian environment were estimated, non-clinical sources were found to be particularly relevant for 19. Of these, 13 were estimated to predominately to almost entirely arise from non-clinical sources. Therefore, exposure to such PhACs can only be mitigated by facilitating their removal in drinking and wastewater treatment plants.
- An approach was developed and applied that integrated various points of departure for the evaluation of the potential effects of the 335 selected PhACs on human-health. It was necessary to develop this approach since government-derived health benchmarks were only available for 32 of these. For the remaining 303 PhACs, provisional acceptable daily intake (*ADI*) values were estimated through the approach developed here. Of these, *ADI* values for 133, 164, 3 and 3 of the PhACs were based on *LOTD*, *OEL*, *NSRL* and *LTD₁₀* values, respectively. For 220 PhACs, both *LOTD* and *OEL* values were available and in nearly 70% of these cases an *OEL*-based approach yielded the more conservative provisional *ADI*. The developed *ADIs* were subsequently used to estimate for each PhAC of interest a predicted-no-effect-concentration for potential exposure of humans through drinking waters.
- Due to the fact that only limited monitoring data for PhACs in finished Canadian drinking waters has been reported to date, a human-health risk assessment based on measured data could be performed for only 17 PhACs. The evaluation suggested that all 17 PhACs pose a negligible risk to human-health despite their confirmed presence in Canadian drinking waters. Given the shortage or complete absence of monitoring data for many compounds, human-health risk assessments were also performed for the 335 PhACs in the Canadian context using predicted exposure concentrations. The results of the evaluation suggested that 323 of the PhACs are expected to pose a negligible risk to human-health due to their potential presence in drinking waters. However, the results indicated that the following 14 PhACs warrant further study: triiodothyronine, thyroxine, ramipril and its metabolite ramiprilat, candesartan, lisinopril, atorvastatin, lorazepam, fentanyl, atenolol, metformin, enalaprilat, morphine and irbesartan.

- The sufficiency of the existing monitoring data for PhACs in Canadian surface and drinking waters was also evaluated. The evaluation clearly demonstrated that most PhACs of relevance or potential relevance have yet to be monitored in Canadian surface and drinking waters.
- Clinical, family planning and environmental fate data was compiled and analysed to explore and quantify the relationships and trade-offs involved between the contraceptive choices of a population and the corresponding environmental load of steroidal estrogens. The evaluation suggested that a load of steroidal estrogens can be associated with the use of each contraceptive option. However, when compared to the estrogenic load associated with the use of “no contraception” at all, the use of each and every contraceptive option was found to prevent an estrogenic load from being released to the environment. By extension, contraception collectively was also established to avert a load of steroidal estrogens from being released to the environment. It was also established that those who use ethinylestradiol-based oral contraceptives produce a lower estrogenic load on the environment than those who discontinue the use of such an option. The analysis also identified those contraceptive options that can allow a population to simultaneously meet environmental, public health and family planning objectives. That being said, in the USA, at most 13% of the annual estrogenic load can be averted by fully meeting the contraceptive needs of the population. Therefore, while the issue of estrogen impacts on the environment cannot be addressed solely by meeting the population’s contraceptive needs, a significant fraction of the estrogenic mass released to environment can be averted by improving the level with which their contraceptive needs are met.
- To better understand how best to translate measured loads of selected drug residues in wastewaters to the levels with which the parent illicit drugs are used in their respective upstream populations, sewer epidemiology mass balances were developed for a number of illicit drugs in wide use including amphetamine, cocaine, ecstasy, heroin, methamphetamine and tetrahydrocannabinol. To accomplish this, an appropriate drug residue was selected that could be monitored in wastewaters to track the use of each drug. Then the mass balances were developed that account for the excretion patterns of the illicit drugs for each of their various routes of administration, illicit and licit sources that could lead to the release of the selected drug residue, sorption of the drug residue onto sewer-laden suspended solids, and the potential for the drug residue to degrade during sewer transmission. Overall, through the development of these mass balances, it was established that the extrapolation factors used in the literature that relate drug residue measurements in wastewaters to drug use in a population required significant refinement to improve their reliability and applicability.

- Finally, an important limitation of the field of sewer epidemiology was identified through an analysis that suggested that the influent loads of certain illicit drug residues are expected to be highly sensitive to a small number of users, thereby making it difficult to interpret geographical and temporal variations in the measured influent loads of a relevant drug residue.

Appendices for Chapter 2

APPENDIX

Assessment of the Aquatic Release and Relevance of Selected Endogenous Chemicals: Androgens, Thyroids and their *in vivo* Metabolites

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Table A.I: Total per capita daily urinary (U_t) excretion of 5 α -androstane-3 α 17 β diol and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t					
Chemical	Quantifying U _i											
	I					f _i ^(a)	U _i ·f _i		F _u	G _u	S _u	
	Reference	Age (yr)/status	# of samples	U _i (x ± σ)		x ± σ						Reference
				(μg/cap·d)		(μg/cap·d)			(%)	(%)	(%)	
5α-Androstane-3α17βdiol	Male	(1-3)	Adults	49	155 ± 61	0.5 ^(b)	76 ± 30		minor	53.5	46.5	(8)
		(2-6)	Adults	64	47 ± 37	0.5 ^(b)	24 ± 19		minor	53.5	46.5	(8) ^(g)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=113) ^(c)				100 ± 35	F _u ·U _t ^{(d),(*)} ≈ 0 G _u ·U _t ^{(e),(†)} = 54 S _u ·U _t ^{(f),(§)} = 47				

(a) Based on demographic data for the simulation base year 2005 (7); (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete 5 α -androstane-3 α 17 β diol as adults; (c) Total per capita daily load of 5 α -androstane-3 α 17 β diol excreted in human urine ($\mu\text{g}/\text{cap}\cdot\text{d}$); (d) Total per capita daily load of 5 α -androstane-3 α 17 β diol excreted in human urine in free form ($\mu\text{g}/\text{cap}\cdot\text{d}$); (e) Total per capita daily load of 5 α -androstane-3 α 17 β diol excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap}\cdot\text{d}$); (f) Total per capita daily load of 5 α -androstane-3 α 17 β diol excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap}\cdot\text{d}$); (g) Assumed to be equal to the conjugated and unconjugated proportions of male urinary excretions.

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.II: Total per capita daily urinary excretion (U_i) of etiocholanolone and its conjugated and unconjugated fractions ($F_u \cdot U_i$, $G_u \cdot U_i$, $S_u \cdot U_i$).

Chemical		U _i						Conjugated fraction of U _i				
		Quantifying U _i				f _i ^(a)	U _i ·f _i		F _u (%)	G _u (%)	S _u (%)	Reference
		I	n	U _i (x ± σ)	x ± σ							
		Reference	Age (m/yr)/status	# of samples	(μg/cap·d)		(μg/cap·d)					
Etiocholanolone	Male	(9)	0-<3m	24	87 ± 45	0.00	0.2 ± 0.1	Minor	95	5	(28)	
		(9-11)	3m - <12	46	447 ± 334	0.08	36 ± 27					
		(9-11)	12-<17	92	1379 ± 748	0.04	50 ± 27					
		(9,10,12-17,20,27)	17-<50	136	2495 ± 1336	0.24	594 ± 318					
		(9,19,22)	50-<70	91	1883 ± 755	0.10	186 ± 74					
		(9,19-21)	70+	66	1453 ± 657	0.04	53 ± 24					
	Female	(9)	0-<3m	24	73 ± 37	0.00	0.1 ± 0.1	Minor	95	5	(28) ^(f)	
		(9,11)	3m - <12	42	265 ± 148	0.08	21 ± 12					
		(9,11)	12-<17	49	1175 ± 637	0.03	41 ± 22					
		(4,6,9,12,14,16-18,20,23-26)	17-<50	290	1578 ± 797	0.23	369 ± 187					
		(9,18,24,26)	50-<70	97	1073 ± 544	0.11	114 ± 58					
		(9,20)	70+	32	577 ± 255	0.05	30 ± 14					
	Total (μg/cap·d)		U _i =ΣU _i ·f _i (n=989) ^(b)				1492 ± 384	F _u ·U _t ^{(c),(*)} ≈ 0 G _u ·U _t ^{(d),(†)} = 1417 S _u ·U _t ^{(e),(§)} = 75				

(a) Based on demographic data for the simulation base year 2005 (7); (b) Total per capita daily load of etiocholanolone excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (c) Total per capita daily load of etiocholanolone excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of etiocholanolone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of etiocholanolone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Assumed to be equal to the conjugated and unconjugated proportions of male urinary excretions.

$$* F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$† G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$§ S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.III: Total per capita daily urinary excretion (U_t) of epitestosterone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t					
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u		G _u	S _u	Reference
		I		n	U _i (x ± σ)		x ± σ					
		Reference	Age (yr)/status	# of samples	(µg/cap·d)		(µg/cap·d)	(%)	(%)	(%)		
Epitestosterone	Male	(29-31)	0-<10	14	2.2 ± 1.9	0.07	0.2 ± 0.1	0.3	81.3	18.3	(40)	
		(29,30,32,33)	10-<15	114	9.0 ± 6.0	0.04	0.3 ± 0.2					
		(30,31,33-39)	15-<30	125	51 ± 39	0.11	5.5 ± 4.1					
		(27,31,32,34-37)	30-<50	94	38 ± 15	0.15	5.5 ± 2.2					
		(32,35,37)	50+	46	23 ± 9	0.13	3.1 ± 1.1					
	Female	(29,31)	0-<10	5	3.0 ± 2.7	0.07	0.2 ± 0.2	2.0	94.3	3.7	(40)	
		(29,31,39)	10-<20	11	8.8 ± 3.1	0.07	0.6 ± 0.2					
		(4,31,32,34,35,38,39,41,42)	20-<40	114	6.0 ± 3.6	0.14	0.8 ± 0.5					
		(31,34,35,39)	40+	44	2.6 ± 2.4	0.24	0.6 ± 0.6					
	Total (µg/cap·d)		U _t =ΣU _i ·f _i (n=567) ^(b)				16.7 ± 4.9		F _u ·U _t ^{(c),(*)} = 0.1 G _u ·U _t ^{(d),(†)} = 13.9 S _u ·U _t ^{(e),(§)} = 2.7			

(a) Based on demophaic data for the simulation base year 2005 (7); (b) Total per capita daily load of epitestosterone excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (c) Total per capita daily load of epitestosterone excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of epitestosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of epitestosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$\begin{aligned}
 * \quad F_u U_t &= (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}} \\
 † \quad G_u U_t &= (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}} \\
 § \quad S_u U_t &= (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}
 \end{aligned}$$

Table A.IV: Total per capita daily urinary excretion (U_t) of dehydroepiandrosterone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U _t						Conjugated fraction of U _t				
		Quantifying U _i				f _i ^(a)	U _i ·f _i		F _u	G _u	S _u	Reference
		I	n	U _i (x ± σ)	x ± σ							
		Reference	Age (m/yr)/status	# of samples	(μg/cap·d)		(μg/cap·d)					
Dehydroepiandrosterone	Male	(9)	0-<3m	24	58 ± 29	0.00	0.1 ± 0.1	Minor	7.0	93.0	(8)	
		(9-11)	3m - <12	46	78 ± 63	0.08	6.4 ± 5.1					
		(9-11)	12-<17	92	157 ± 109	0.04	5.7 ± 3.9					
		(9,10,12,14-17)	17-<50	84	909 ± 375	0.24	216 ± 89					
		(9,19)	50-<70	72	303 ± 361	0.10	30 ± 36					
		(9,19)	70+	37	207 ± 113	0.04	7.5 ± 4.1					
	Female	(9)	0-<3m	24	43 ± 22	0.00	0.1 ± 0.0	Minor	7.0	93.0	(8) ^(f)	
		(9,11)	3m - <12	42	96 ± 61	0.08	7.5 ± 4.8					
		(9,11)	12-<17	49	197 ± 139	0.03	6.8 ± 4.8					
		(6,9,12,14,16-18,23-25,43)	17-<50	259	360 ± 416	0.23	84 ± 97					
		(9,22,24,43)	50-<70	92	243 ± 45	0.11	26 ± 4.8					
		(9)	70+	24	87 ± 29	0.05	4.7 ± 1.6					
	Total (μg/cap·d)		U _t =ΣU _i f _i (845) ^(b)				395 ± 137		F _u ·U _t ^{(c),(*)} = 0 G _u ·U _t ^{(d),(†)} = 28 S _u ·U _t ^{(e),(§)} = 367			

(a) Based on demographic data for the simulation base year 2005 (7); (b) Total per capita daily load of dehydroepiandrosterone excreted in human urine ($\mu\text{g}/\text{cap}\cdot\text{d}$); (c) Total per capita daily load of dehydroepiandrosterone excreted in human urine in free form ($\mu\text{g}/\text{cap}\cdot\text{d}$); (d) Total per capita daily load of dehydroepiandrosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap}\cdot\text{d}$); (e) Total per capita daily load of dehydroepiandrosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap}\cdot\text{d}$); (f) Assumed to be equal to the conjugated and unconjugated proportions of male urinary excretions.

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$† \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$§ \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.V: Total per capita daily urinary excretion (U_t) of androstane-3,11,17-trione, (5. α) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U_t						Conjugated fraction of U_t			
		Quantifying U_i				$f_i^{(a)}$	$U_i \cdot f_i$	F_u	G_u	S_u	Reference
		Reference	I	n	$U_i (x \pm \sigma)$		$x \pm \sigma$				
			Age (yr)/status	# of samples	($\mu\text{g}/\text{cap} \cdot \text{d}$)		($\mu\text{g}/\text{cap} \cdot \text{d}$)	(%)	(%)	(%)	
Androstane-3,11,17-trione, (5 α)-	Male	(44)	Adults	9	299 $\pm$ 47	0.5 ^(b)	149 $\pm$ 23	Minor	55.0	45.0	(44)
	Female	(44)	Adults	6	305 $\pm$ 55	0.5 ^(b)	153 $\pm$ 28	Minor	55.9	44.1	(44)
	Total ($\mu\text{g}/\text{cap} \cdot \text{d}$)		$U_t = \sum U_i \cdot f_i$ (n=15) ^(c)				302 $\pm$ 36	$F_u \cdot U_t^{(d),(*)} = 0.0$ $G_u \cdot U_t^{(e),(\dagger)} = 168$ $S_u \cdot U_t^{(f),(\S)} = 135$			

(a) US Census Bureau (7) for the simulation year 2005; (b) Due to lack of data is is conservatively assumed here that the whole male and female populations excrete androstane-3,11,17-trione, (5. α) as adults; (c) Total per capita daily load of androstane-3,11,17-trione, (5. α) excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of androstane-3,11,17-trione, (5. α) excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of androstane-3,11,17-trione, (5. α) excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of androstane-3,11,17-trione, (5. α) excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$* F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.VI: Total per capita daily urinary excretion (U_t) of androstenetriol and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t				
Chemical		Quantifying U _i			f _i ^(a)	U _i ·f _i	F _u	G _u	S _u	Reference	
		I	n	U _i (x ± σ)							x ± σ
		Reference	Age (yr)/status	# of samples	(μg/cap·d)	(μg/cap·d)	(%)	(%)	(%)		
Androstenetriol	Male	(12)	20-<50	16	460 ± 43	0.5 ^(b)	225 ± 21	minor	100.00	0.00	Assumed ^(g)
		(6,12,24)	20-<50	40	330 ± 195	0.5 ^(b)	168 ± 99	minor	100.00	0.00	Assumed ^(g)
	Female										
		Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=56) ^(c)			393 ± 101	F _u ·U _t ^{(d),(*)} ≈ 0 G _u ·U _t ^{(e),(†)} = 393 S _u ·U _t ^{(f),(§)} = 0			

(a) Based on demographic data for the simulation base year 2005 (7); (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete androstenetriol as adults; (c) Total per capita daily load of androstenetriol excreted in human urine ($\mu\text{g}/\text{cap}\cdot\text{d}$); (d) Total per capita daily load of androstenetriol excreted in human urine in free form ($\mu\text{g}/\text{cap}\cdot\text{d}$); (e) Total per capita daily load of androstenetriol excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap}\cdot\text{d}$); (f) Total per capita daily load of androstenetriol excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap}\cdot\text{d}$); (g) Assumed to be all conjugated to glucuronic acid.

$$\begin{aligned}
 * \quad F_u U_t &= (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}} \\
 † \quad G_u U_t &= (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}} \\
 § \quad S_u U_t &= (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}
 \end{aligned}$$

Table A.VII: Total per capita daily urinary excretion (U_t) of androstane-3,17-dione, (5 β) and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U_t						Conjugated fraction of U_t			
		Quantifying U_i				$f_i^{(a)}$	$U_i \cdot f_i$	F_u	G_u	S_u	Reference
		Reference	I	n	$U_i (x \pm \sigma)$		$x \pm \sigma$				
			Age (yr)/status	# of samples	($\mu\text{g}/\text{cap} \cdot \text{d}$)		($\mu\text{g}/\text{cap} \cdot \text{d}$)	(%)	(%)	(%)	
Androstane-3,17-dione, (5 β)-	Male	(44)	Adults	9	1686 $\pm$ 432	0.5 ^(b)	840 $\pm$ 215	Minor	78	23	(44)
	Female	(44)	Adults	6	1468 $\pm$ 322	0.5 ^(b)	737 $\pm$ 162	Minor	69	32	(44)
	Total ($\mu\text{g}/\text{cap} \cdot \text{d}$)		$U_t = \sum U_i \cdot f_i (n=15)^{(c)}$				1577 $\pm$ 269	$F_u \cdot U_t^{(d),(*)} \approx 0$ $G_u \cdot U_t^{(e),(\dagger)} = 1157$ $S_u \cdot U_t^{(f),(\S)} = 419$			

(a) US Census Bureau (7) for the simulation base year 2005; (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete as adults; (c) Total per capita daily load of androstane-3,17-dione, (5 β) excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of androstane-3,17-dione, (5 β) excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of androstane-3,17-dione, (5 β) excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of androstane-3,17-dione, (5 β) excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.VIII: Total per capita daily urinary excretion (U_t) of 11 β -hydroxyandrosterone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t								Conjugated fraction of U _t			
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u	G _u	S _u	Reference
		I	n	U _i (x ± σ)	x ± σ						
		Reference	Age (m/yr)/status	# of samples	(μg/cap.d)	(μg/cap.d)	(%)	(%)	(%)		
11β-Hydroxyandrosterone	Male	(9)	0-<3m	24	123 ± 63	0.00	0.2 ± 0.1	Minor	100	0	Assumed ^(f)
		(9,10)	3m - <12yr	28	523 ± 251	0.08	43 ± 21				
		(9, 10)	12-<17	67	815 ± 383	0.04	30 ± 14				
		(9,12,14,16,17,20)	17-<50	106	1025 ± 389	0.24	244 ± 93				
		(9)	50-<70	24	1456 ± 429	0.10	143 ± 42				
		(9,20,21)	70+	53	1101 ± 418	0.04	40 ± 15				
	Female	(9)	0-<3m	24	30 ± 16	0.00	0.1 ± 0.0	Minor	100	0	Assumed ^(f)
		(9)	3m - <12yr	24	137 ± 55	0.08	11 ± 4.2				
		(9)	12-<17	24	304 ± 109	0.03	11 ± 3.7				
		(4, 6, 9, 12, 14, 16, 17, 20, 23, 26)	17-<50	132	553 ± 254	0.23	129 ± 59				
		(9,26)	50-<70	39	381 ± 163	0.11	40 ± 17				
		(9,20)	70+	32	363 ± 320	0.05	20 ± 17				
	Total (μg/cap.d)		U _t =ΣU _i ·f _i (577) ^(b)				710 ± 124	F _u ·U _t ^{(c),(*)} ≈ 0.0 G _u ·U _t ^{(d),(†)} = 710 S _u ·U _t ^{(e),(§)} ≈ 0.0			

(a) US Census Bureau (7) for the simulation base year 2005; (b) Total per capita daily load of 11 β -hydroxyandrosterone excreted in human urine ($\mu\text{g}/\text{cap.d}$); (c) Total per capita daily load of 11 β -hydroxyandrosterone excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of 11 β -hydroxyandrosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of 11 β -hydroxyandrosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$); (f) Assumed to be primarily conjugated to glucuronide ions based on observations of (45).

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.IX: Total per capita daily urinary excretion (U_t) of 11 β -hydroxyetiocholanolone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U _t						Conjugated fraction of U _t				
		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u	G _u	S _u	Reference	
		Reference	I	n	U _i (x ± σ)							x ± σ
			Age (m/yr)/status	# of samples	(μg/cap·d)							(μg/cap·d)
11β-Hydroxyetiocholanolone	Male	(9)	0-<3m	24	61 ± 31	0.00	0.1 ± 0.1	Minor	100	0	Assumed ^(f)	
		(9,10)	3m - <12yr	28	282 ± 126	0.08	23 ± 10					
		(9, 10)	12-<17	67	410 ± 201	0.04	15 ± 7.3					
		(9,12,14,16,17,20)	17-<50	106	364 ± 161	0.24	87 ± 38					
		(9)	50-<70	24	444 ± 148	0.10	44 ± 15					
		(9,20,21)	70+	53	490 ± 281	0.04	18 ± 10					
	Female	(9)	0-<3m	24	30 ± 16	0.00	0.1 ± 0.0	Minor	100	0	Assumed ^(f)	
		(9)	3m - <12yr	24	152 ± 62	0.08	12 ± 4.8					
		(9)	12-<17	24	289 ± 117	0.03	10 ± 5.0					
		(4, 6, 9, 12, 14, 16, 17, 20, 23, 26)	17-<50	132	328 ± 184	0.23	77 ± 43					
		(9,26)	50-<70	39	305 ± 153	0.11	32 ± 16					
		(9,20)	70+	32	363 ± 320	0.05	20 ± 17					
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (577) ^(b)				336 ± 66	F _u ·U _t ^{(c),(*)} ≈ 0 G _u ·U _t ^{(d),(†)} = 336 S _u ·U _t ^{(e),(§)} ≈ 0				

(a) US Census Bureau (7) for the simulation base year 2005; (b) Total per capita daily load of 11 β -hydroxyetiocholanolone excreted in human urine (μg/cap·d); (c) Total per capita daily load of 11 β -hydroxyetiocholanolone excreted in human urine in free form (μg/cap·d); (d) Total per capita daily load of 11 β -hydroxyetiocholanolone excreted in human urine conjugated to glucuronide (μg/cap·d); (e) Total per capita daily load of 11 β -hydroxyetiocholanolone excreted in human urine conjugated to sulphate ions (μg/cap·d); (f) Assumed to be primarily conjugated to glucuronide ions based on observations of (45).

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{males} + (F_u \sum U_i \cdot f_i)_{females}$$

$$† \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{males} + (G_u \sum U_i \cdot f_i)_{females}$$

$$§ \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{males} + (S_u \sum U_i \cdot f_i)_{females}$$

Table A.X: Total per capita daily urinary excretion (U_t) of androsterone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U _t						Conjugated fraction of U _t				
		Quantifying U _i				f _i ^(a)	U _i ·f _i		F _u	G _u	S _u	Reference
		Reference	I	n	U _i (x ± σ)		x ± σ					
			Age (m/yr)/status	# of samples	(μg/cap·d)		(μg/cap·d)					
Androsterone	Male	(9)	0-<3m	24	102 ± 52	0.00	0.2 ± 0.1	Minor	93	7	(28)	
		(9-11)	3m - <12	46	442 ± 305	0.08	36 ± 25					
		(9-11)	12-<17	92	1397 ± 705	0.04	51 ± 26					
		(9,10,12-17,20,27)	17-<50	136	2490 ± 913	0.24	593 ± 217					
		(9,19,22)	50-<70	91	2039 ± 919	0.10	201 ± 91					
		(9,19-21)	70+	66	1295 ± 557	0.04	47 ± 20					
	Female	(9)	0-<3m	24	44 ± 22	0.00	0.1 ± 0.0	Minor	93	7	(28) ^(f)	
		(9,11)	3m - <12	42	383 ± 244	0.08	30 ± 19					
		(9,11)	12-<17	49	1352 ± 733	0.03	47 ± 25					
		(4,6,9,12,14,16-18,20,23-26)	17-<50	290	1427 ± 675	0.23	334 ± 158					
		(9,18,24,26)	50-<70	97	963 ± 405	0.11	102 ± 43					
		(9,20)	70+	32	447 ± 278	0.05	24 ± 15					
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=989) ^(b)				1463 ± 292		F _u ·U _t ^{(c),(*)} ≈ 0.0 G _u ·U _t ^{(d),(†)} = 1361 S _u ·U _t ^{(e),(§)} = 102			

(a) Based on demographic data for the simulation base year 2005 (7); (b) Total per capita daily load of androsterone excreted in human urine ($\mu\text{g}/\text{cap-d}$); (c) Total per capita daily load of androsterone excreted in human urine in free form ($\mu\text{g}/\text{cap-d}$); (d) Total per capita daily load of androsterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap-d}$); (e) Total per capita daily load of androsterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap-d}$); (f) Assumed to be equal to the conjugated and unconjugated proportions as for male urinary excretions.

$$* F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$† G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$§ S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.XI: Total per capita daily urinary excretion (U_t) of 5 α -androstanedione and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

		U _t						Conjugated fraction of U _t			
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u	G _u	S _u	Reference
		I	n	U _i (x ± σ)	x ± σ						
		Reference	Age (yr)/status	# of samples	(μg/cap·d)	(μg/cap·d)					
5α-Androstanedione	Male	(44)	Adults	9	2780 ± 500	0.5 ^(b)	1384 ± 249	Minor	62.5	37.5	(44)
	Female	(44)	Adults	6	1882 ± 551	0.5 ^(b)	945 ± 277	Minor	68.0	32.0	(44)
	Total (μg/cap.d)		U _t =ΣU _i ·f _i (n=15) ^(c)				F _u ·U _t ^{(d),(*)} ≈ 0 G _u ·U _t ^{(e),(†)} = 1508 S _u ·U _t ^{(f),(§)} = 821				

(a) US Census Bureau (7) for the simulation base year 2005; (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete 5 α -androstanedione as adults; (c) Total per capita daily load of 5 α -androstanedione excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of 5 α -androstanedione excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of 5 α -androstanedione excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of 5 α -androstanedione excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$\begin{aligned}
 * \quad F_u U_t &= (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}} \\
 \dagger \quad G_u U_t &= (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}} \\
 \S \quad S_u U_t &= (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}
 \end{aligned}$$

Table A.XII: Total per capita daily urinary excretion (U_t) of 11-ketoandrosterone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U _t						Conjugated fraction of U _t (µg/cap.d)			
		Quantifying U _i			f _i ^(a)	U _i ·f _i	F _u	G _u	S _u	Reference	
		I	n	U _i (x ± σ)		x ± σ					
		Reference	Age (m/yr)/status	# of samples		(µg/cap·d)					(µg/cap·d)
11-Ketoandrosterone	Male	(9)	0-3m	24	91 ± 31	0.00	0.2 ± 0.1	Minor	100	0	Assumed ^(f)
		(9,10)	3m - <12yr	28	232 ± 110	0.08	19 ± 8.9				
		(9,10)	12-<17	67	223 ± 127	0.04	8.1 ± 4.6				
		(9,10,17)	17-<50	38	405 ± 164	0.24	96 ± 39				
		(9)	50-<70	24	380 ± 179	0.10	37 ± 18				
		(9,21)	70+	35	239 ± 128	0.04	8.6 ± 4.6				
	Female	(9)	0-3m	24	30 ± 16	0.00	0.1 ± 0.0	Minor	100	0	Assumed ^(f)
		(9)	3m - <12yr	24	152 ± 62	0.08	12 ± 4.8				
		(9)	12-<17	24	289 ± 116	0.03	10 ± 4.0				
		(6,9,17)	17-<50	51	395 ± 200	0.23	92 ± 47				
		(9)	50-<70	24	335 ± 124	0.11	36 ± 13				
		(9)	70+	24	259 ± 85	0.05	14 ± 4.6				
	Total (µg/cap·d)		U _t =ΣU _i ·f _i (387) ^(b)				333 ± 66	F _u ·U _t ^{(c),(*)} ≈ 0.0 G _u ·U _t ^{(d),(f)} = 333.0 S _u ·U _t ^{(e),(§)} ≈ 0.0			

(a) US Census Bureau (7) for the year 2005; (b) Total per capita daily load of 11-ketoandrosterone excreted in human urine ($\mu\text{g}/\text{cap.d}$); (c) Total per capita daily load of 11-ketoandrosterone excreted in human urine in free form ($\mu\text{g}/\text{cap.d}$); (d) Total per capita daily load of 11-ketoandrosterone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap.d}$); (e) Total per capita daily load of 11-ketoandrosterone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap.d}$); (f) Assumed to be primarily conjugated to glucuronide ions.

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.XIII: Total per capita daily urinary excretion (U_t) of 11-ketoetiocholanolone and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t (μg/cap.d)				
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i				
		Reference	I	n	U _i (x ± σ)	x ± σ	Reference	F _u	G _u	S _u	
			Age (m/yr)/status	# of samples	(μg/cap·d)						
11-Ketoetiocholanolone	Male	(9)	0-3m	24	61 ± 31	0.00	0.1 ± 0.1	Minor	100	0	Assumed ^(f)
		(9,10)	3m - <12yr	28	236 ± 96	0.08	19 ± 8				
		(9,10)	12-<17	67	580 ± 458	0.04	21 ± 17				
		(9,10,14,17)	17-<50	45	536 ± 208	0.24	128 ± 49				
		(9)	50-<70	24	381 ± 132	0.10	38 ± 13				
		(9,21)	70+	35	310 ± 237	0.04	11 ± 9				
	Female	(9)	0-3m	24	30 ±16	0.00	0.1 ± 0.0	Minor	100	0	Assumed ^(f)
		(9)	3m - <12yr	24	137 ± 54	0.08	11 ± 4				
		(9)	12-<17	24	304 ± 109	0.03	11 ± 4				
		(9,14,16,17,23,26)	17-<50	81	361 ± 168	0.23	85 ± 39				
		(9,26)	50-<70	39	302 ± 107	0.11	32 ± 11				
		(9)	70+	24	198 ± 70	0.05	11 ± 4				
	Total (μg/cap.d)		U _t =ΣU _i ·f _i (439) ^(b)				365 ± 69	F _u ·U _t ^{(c),(*)} ≈ 0.0 G _u ·U _t ^{(d),(†)} = 365 S _u ·U _t ^{(e),(§)} ≈ 0.0			

(a) US Census Bureau (7) for the year 2005; (b) Total per capita daily load of 11-ketoetiocholanolone excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (c) Total per capita daily load of 11-ketoetiocholanolone excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of 11-ketoetiocholanolone excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of 11-ketoetiocholanolone excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Assumed to be primarily conjugated to glucuronide ions.

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.XIV: Total per capita daily urinary excretion (U_t) of 5 β -androstane-3-11-17-trione and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t					
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u		G _u	S _u	Reference
		I	n	U _i (x ± σ)		x ± σ						
		Reference	Age (yr)/status	# of samples	μg/cap·d		μg/cap·d	(%)	(%)	(%)		
5β-Androstane-3-11-17-trione	Male	(44)	Adults	9	356 ± 110	0.5 ^(b)	177 ± 55	Minor	44.4	55.6	(44)	
	Female	(44)	Adults	6	346 ± 191	0.5 ^(b)	174 ± 96	Minor	29.2	70.8	(44)	
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=15) ^(c)				351 ± 110	F _u ·U _t ^{(d),(*)} ≈ 0 G _u ·U _t ^{(e),(†)} = 129 S _u ·U _t ^{(f),(§)} = 222				

(a) US Census Bureau (7) for the simulation base year 2005; (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete as adults; (c) Total per capita daily load of 5 β -androstane-3-11-17-trione excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of 5 β -androstane-3-11-17-trione excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of 5 β -androstane-3-11-17-trione excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of 5 β -androstane-3-11-17-trione excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.XV: Total per capita daily urinary excretion (U_t) of androst-4-ene-3,6,17-trione and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t								Conjugated fraction of U _t			
Chemical		Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u F _u	G _u G _u	S _u S _u	Reference
		Reference	I	n	U _i (x ± σ)	x ± σ					
			Age (yr)/status	# of samples	(μg/cap·d)	(μg/cap·d)					
Androst-4-ene-3,6,17-trione	Male	(44)	Adults	9	1890 ± 805	0.5 ^(b)	941 ± 401	Minor	4.3	95.7	(44)
	Female	(44)	Adults	6	778 ± 336	0.5 ^(b)	391 ± 169	Minor	9.7	90.3	(44)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=15) ^(c)				1332 ± 435		F _u ·U _t ^{(d),(*)} ≈ 0.0 G _u ·U _t ^{(e),(†)} = 79 S _u ·U _t ^{(f),(§)} = 1253		

(a) Based on demographic data for the simulation base year 2005 (7); (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete androst-4-ene-3,6,17-trione as adults; (c) Total per capita daily load of androst-4-ene-3,6,17-trione excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of androst-4-ene-3,6,17-trione excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of androst-4-ene-3,6,17-trione excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of androst-4-ene-3,6,17-trione excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

Table A.XVI: Total per capita daily urinary excretion (U_t) of 5 β -androstane-3 α 17 β diol and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

Chemical		U_t						Conjugated fraction of U_t			
		Quantifying U_i			$f_i^{(a)}$	$U_i \cdot f_i$		F_u	G_u	S_u	Reference
		Reference	I	n		$U_i (x \pm \sigma)$	$x \pm \sigma$				
			Age (yr)/status	# of samples		($\mu\text{g}/\text{cap}\cdot\text{d}$)	($\mu\text{g}/\text{cap}\cdot\text{d}$)	(%)	(%)	(%)	
5 β -Androstane-3 α 17 β diol	Male	(2,3)	Adults	36		617 $\pm$ 171	0.5 ^(b)	minor	62.4	37.6	(8)
	Female	(2-4)	Adults	36		182 $\pm$ 119	0.5 ^(b)	minor	62.4	37.6	(8) ^(g)
		Total ($\mu\text{g}/\text{cap}\cdot\text{d}$)		$U_t = \sum U_i \cdot f_i (n=72)^{(c)}$			396 $\pm$ 104	$F_u \cdot U_t^{(d),(*)} \approx 0$ $G_u \cdot U_t^{(e),(f)} = 247$ $S_u \cdot U_t^{(f),(g)} = 149$			

(a) US Census Bureau (7) for the year 2005; (b) Due to the lack of data it is conservatively assumed here that the whole male and female populations excrete 5 β -androstane-3 α 17 β diol as adults; (c) Total per capita daily load of 5 β -androstane-3 α 17 β diol excreted in human urine ($\mu\text{g}/\text{cap}\cdot\text{d}$); (d) Total per capita daily load of 5 β -androstane-3 α 17 β diol excreted in human urine in free form ($\mu\text{g}/\text{cap}\cdot\text{d}$); (e) Total per capita daily load of 5 β -androstane-3 α 17 β diol excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap}\cdot\text{d}$); (f) Total per capita daily load of 5 β -androstane-3 α 17 β diol excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap}\cdot\text{d}$); (g) Assumed to be equal to the conjugated and unconjugated proportions as reported for male urinary excretion.

$$* \quad F_u U_t = (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\dagger \quad G_u U_t = (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}}$$

$$\S \quad S_u U_t = (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}$$

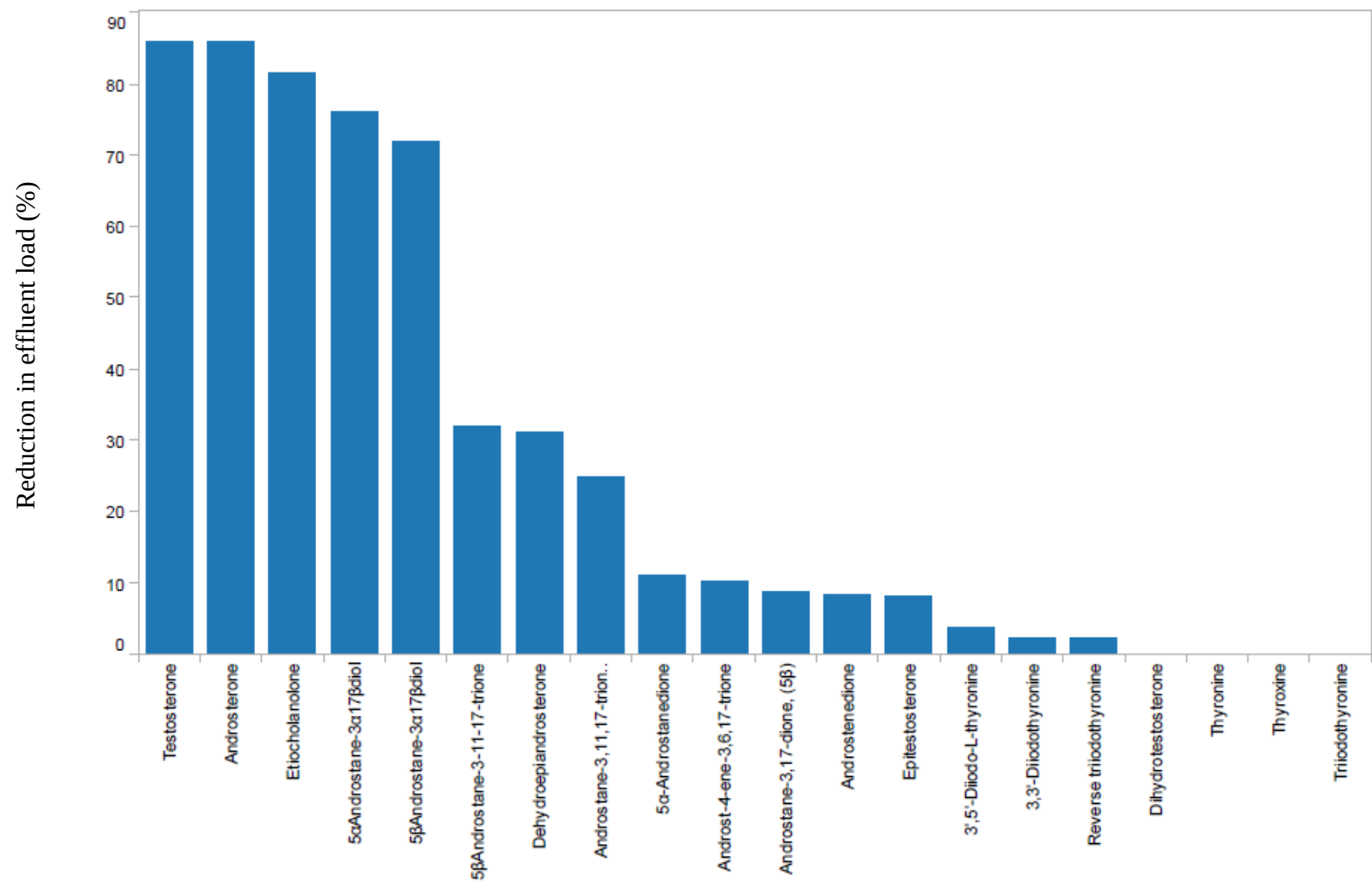
Table A.XVII: Total per capita daily urinary excretion (U_t) of reverse triiodothyronine (rT_3), 3',5'-diiodo-L-thyronine ($3',5'T_2$), 3,3'-diiodothyronine ($3',3'T_2$) and thyronine (T_0). and its conjugated and unconjugated fractions ($F_u \cdot U_t$, $G_u \cdot U_t$, $S_u \cdot U_t$).

U _t							Conjugated fraction of U _t				
Chemical	Quantifying U _i				f _i ^(a)	U _i ·f _i	F _u		G _u	S _u	Reference
	Reference	I	n	U _i (x ± σ)		x ± σ					
		Age (yr)/status	# of samples	(μg/cap·d)		(μg/cap·d)					
rT ₃	All	(55)	21-82	15-25	0.5 ± 0.1	1.0 ^(b)	0.5 ± 0.1	9.7	23.2	67.1	(46)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n= 15-25) ^(c)				0.5 ± 0.1	F _u ·U _t ^{(d),(*)} = 0.1 G _u ·U _t ^{(e),(†)} = 0.1 S _u ·U _t ^{(e),(§)} = 0.3			
3',5'T ₂	All	(55)	21-82	16-34	0.4 ± 0.1	1.0 ^(b)	0.4 ± 0.1	1.8	44.6	53.5	(46)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n= 16-34) ^(c)				0.4 ± 0.1	F _u ·U _t ^{(d),(*)} ≈ 0.0 G _u ·U _t ^{(e),(†)} = 0.2 S _u ·U _t ^{(e),(§)} = 0.2			
3',3'T ₂	All	(55)	21-82	16-34	1.3 ± 0.6	1.0 ^(b)	1.3 ± 0.6	26.6	33.5	39.9	(46)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n= 16-34) ^(c)				1.3 ± 0.6	F _u ·U _t ^{(d),(*)} = 0.4 G _u ·U _t ^{(e),(†)} = 0.5 S _u ·U _t ^{(e),(§)} = 0.5			
T ₀	All	(56)	Adults?	22	4.1 ± 1.3	1.0 ^(b)	4.1 ± 1.3	100	0.0	0.0	(47)
	Total (μg/cap·d)		U _t =ΣU _i ·f _i (n=22) ^(c)				4.1 ± 1.3	F _u ·U _t ^{(d),(*)} = 4.1 G _u ·U _t ^{(e),(†)} = 0.0 S _u ·U _t ^{(e),(§)} = 0.0			

(a) Based on demographic data for the simulation base year 2005 (7); (b) Age cohorted data for triiodothyronine and thyroxine (Table IV and V) suggests age isn't a huge factor with respect to the excretion of endogenous thyroids therefore it is assumed here that population age cohorts not studied (<20 for reference 46 and non-adults for reference 47) excrete as age cohorts studied; (c) Total per capita daily load of thyroids excreted in human urine ($\mu\text{g}/\text{cap} \cdot \text{d}$); (d) Total per capita daily load of thyroids excreted in human urine in free form ($\mu\text{g}/\text{cap} \cdot \text{d}$); (e) Total per capita daily load of thyroids excreted in human urine conjugated to glucuronide ($\mu\text{g}/\text{cap} \cdot \text{d}$); (f) Total per capita daily load of thyroids excreted in human urine conjugated to sulphate ions ($\mu\text{g}/\text{cap} \cdot \text{d}$).

$$\begin{aligned}
 * \quad F_u U_t &= (F_u \sum U_i \cdot f_i)_{\text{males}} + (F_u \sum U_i \cdot f_i)_{\text{females}} \\
 \dagger \quad G_u U_t &= (G_u \sum U_i \cdot f_i)_{\text{males}} + (G_u \sum U_i \cdot f_i)_{\text{females}} \\
 \S \quad S_u U_t &= (S_u \sum U_i \cdot f_i)_{\text{males}} + (S_u \sum U_i \cdot f_i)_{\text{females}}
 \end{aligned}$$

Figure A.1: Percent reduction in effluent loads if sulphate conjugates are made available for treatment.



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Appendices for Chapter 4

Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water

Usman Khan and Jim A. Nicell

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Appendix A: List of references that report on presence of pharmaceutically active compounds in Canadian surface waters

The following list of 34 references report on the presence of pharmaceutically active compounds (PhACs) in Canadian surface waters:

Boyd et al., 2003; Brun et al., 2006; Comeau et al., 2008; Crouse et al., 2012; Csiszar et al., 2011; Evans et al., 2012; Garcia-Ac A et al., 2009a, 2009b; Gillis et al., 2014; Hebben, 2012; Helm et al., 2012; Hua et al., 2006; Jeffries et al., 2010; Kleywegt et al., 2011; Lajeunesse and Gagnon, 2007; Lajeunesse et al., 2008; Lee et al., 2009; Li et al., 2010; Lissemore et al., 2006; MacLeod et al., 2007; MDDEP, 2011; Metcalfe et al., 2003, 2010; Miao et al., 2003a, 2003b, 2003c; Rahman et al., 2010; Robinson et al., 2009; Servos et al., 2007; Sosiak and Hebben, 2005; Tabe et al., 2010; Viglino et al., 2008a, 2008b; Viglino et al., 2009; Yargeau et al., 2007.

Appendix B: Evaluation set

1	Acarbose	86	Codeine	171	Ibuprofen	256	Perphenazine
2	Acebutolol	87	Cortisone	172	Idarubicin	257	Phenobarbital
3	Acetaminophen	88	Cromolyn	173	Ifosfamide	258	Phenyltoloxamine
4	Acetylcysteine	89	Cyclophosphamide	174	Imipramine	259	Phenytoin
5	Acetylsalicylic Acid	90	Cyproterone	175	Indomethacin	260	Piperacillin
6	Acyclovir	91	Cytarabine	176	Ipratropium	261	Piroxicam
7	Alendronate	92	Daclinomycin	177	Irbesartan	262	Pravastatin
8	Allopurinol	93	Daunorubicin	178	Isoniazid	263	Prednisolone
9	Alprazolam	94	Desloratadine	179	Isosorbide Dinitrate	264	Prednisone
10	Amantadine	95	Desogestrel	180	Isosorbide-5-Mononitrate	265	Primidone
11	Amiloride	96	Dexamethasone	181	Ketamine	266	Procainamide
12	Aminosalicylic Acid	97	Dextroamphetamine	182	Ketoconazole	267	Prochlorperazine
13	Amiodarone	98	Dextropropoxyphene	183	Ketoprofen	268	Promethazine
14	Amiripityline	99	Diazepam	184	Labetalol	269	Propafenone
15	Amlodipine	100	Diclofenac	185	Lamotrigine	270	Propofol
16	Amoxicillin	101	Didanosine	186	Lansoprazole	271	Propranolol
17	Amphetamine	102	Digoxin	187	Letrozole	272	Propylthiouracil
18	Amphotericin B	103	Dihydrotestosterone	188	Leuprolide	273	Quetiapine
19	Ampicillin	104	Diltiazem	189	Levodopa	274	Quinapril
20	Anastrozole	105	Diphenoxylate	190	Levofloxacin	275	Quinine
21	Androstenedione	106	Dipyridamole	191	Lidocaine	276	Rabeprazole
22	Atenolol	107	Disulfiram	192	Lisinopril	277	Ramipril
23	Atorvastatin	108	Docusate	193	Loratadine	278	Ranitidine
24	Atropine	109	Domperidone	194	Lorazepam	279	Risperidone
25	Azathioprine	110	Doxepin	195	Losartan	280	Rifampin
26	Azithromycin	111	Doxorubicin	196	Loxapine	281	Rizatriptan
27	Baclofen	112	Doxycycline	197	MDMA	282	Rosuvastatin
28	Beclomethasone	113	Drosiprenone	198	Mefenamic Acid	283	Roxithromycin
29	Benserazide	114	Enalapril	199	Melphalan	284	Salbutamol
30	Benztrapine	115	Enalaprilat	200	Meprobamate	285	Salmeterol
31	Benzylamine	116	Epirubicin	201	Metformin	286	Selegiline
32	Betamethasone	117	Eprosartan	202	Methadone	287	Sertraline
33	Betaxolol	118	Erythromycin	203	Methamphetamine	288	Sildenafil
34	Bezafibrate	119	Escitalopram	204	Methotrexate	289	Simvastatin
35	Bicalutamide	120	Esomeprazole	205	Methylphenidate	290	Sinacalcin
36	Bisoprolol	121	Estradiol	206	Methylprednisolone	291	Sotalol
37	Bleomycin	122	Ethacrynic acid	207	Metoprolol	292	Spiramycin
38	Bromazepam	123	Ethambutol	208	Miconazole	293	Spirolactone
39	Bromocriptine	124	Ethinyl estradiol	209	Midazolam	294	Sulfacetamide
40	Budesonide	125	Ethynodiol	210	Minocycline	295	Sulfamethoxazole
41	Buprenorphine	126	Etodolac	211	Misoprostol	296	Sulfapyridine
42	Bupropion	127	Etonogestrel	212	Mitomycin	297	Sulfasalazine
43	Buserelin	128	Etoposide	213	Mometasone	298	Sulfisoxazole
44	Butalbital	129	Exemestane	214	Morphine	299	Sulindac
45	Candesartan	130	Famciclovir	215	Mupirocin	300	Sumatriptan
46	Capecitabine	131	Famotidine	216	Nabumetone	301	Tamoxifen
47	Captopril	132	Felodipine	217	Nadolol	302	Tamsulosin
48	Carbamazepine	133	Fenofibrate	218	Naloxone	303	Tazobactam
49	Carbidopa	134	Fenofibric Acid	219	Naltrexone	304	Telithromycin
50	Carboplatin	135	Fenoprofen	220	Naproxen	305	Temazepam
51	Carmustine	136	Fenoterol	221	Neomycin	306	Terbutaline
52	Carvedilol	137	Finasteride	222	Nifedipine	307	Testosterone
53	Cefaclor	138	Fluconazole	223	Nilutamide	308	Tetracycline
54	Cefadroxil	139	Fluocinonide	224	Nimodipine	309	Tetrahydrocannabinol
55	Cefazolin	140	Fluorouracil	225	Nitrazepam	310	Theophylline
56	Cefixime	141	Fluoxetine	226	Nitrofurantoin	311	Thyroxine
57	Cefprozil	142	Fluphenazine	227	Nizatidine	312	Tiaprofenic Acid
58	Ceftazidime	143	Flurazepam	228	Norethindrone	313	Ticarcillin
59	Ceftriaxone	144	Flutamide	229	Norfloxacin	314	Ticlopidine
60	Cefuroxime	145	Fluticasone	230	Norgestimate	315	Timolol
61	Celecoxib	146	Fluvoxamine	231	Nortriptyline	316	Tolbutamide
62	Cephalexin	147	Formoterol	232	Nystatin	317	Tramadol
63	Cetirizine	148	Fosfomycin	233	Ofloxacin	318	Trazodone
64	Chloral Hydrate	149	Fosphenytoin	234	Omeprazole	319	Triamterene
65	Chloramphenicol	150	Fulvestrant	235	Ondansetron	320	Trihexyphenidyl
66	Chlorhexidine	151	Furosemide	236	Orlistat	321	Triiodothyronine
67	Chloroquine	152	Gabapentin	237	Orphenadrine	322	Trimethoprim
68	Chlorpromazine	153	Gemfibrozil	238	Osetamivir	323	Trimipramine
69	Cimetidine	154	Gentamicin	239	Osetamivir carboxylate	324	Valacyclovir
70	Ciprofloxacin	155	Gliclazide	240	Oxapropin	325	Valproic Acid
71	Cisplatin	156	Glyburide	241	Oxazepam	326	Valsartan
72	Citalopram	157	Goserelin	242	Oxprenolol	327	Vancocin
73	Clarithromycin	158	Haloperidol	243	Oxydnone	328	Venlafaxine
74	Clavulanic Acid	159	Heroin	244	Pamidronate	329	Verapamil
75	Clindamycin	160	Hydrochlorothiazide	245	Pantoprazole	330	Warfarin
76	Clodronic Acid	161	Hydrocodone	246	Paroxetine	331	Xylometazoline
77	Clofibrate	162	Hydrocortisone	247	Penicillin G	332	Zidovudine
78	Clofibrilic Acid	163	Hydromorphone	248	Penicillin V	333	Zopiclone
79	Clonazepam	164	Hydroxychloroquine	249	Perindopril		
80	Clonidine	165	Cocaine	250			
81	Clopidogrel	166		251			
82	Clorazepate	167		252			
83	Clotrimazole	168		253			
84	Clozapine	169		254			
85		170		255			

Appendix C: Arriving at $N_{i,c} \cdot S_{i,c}$ estimates for the use of acetaminophen, acetylsalicylic acid, clotrimazole and ibuprofen

The methods and data inputs detailed below were used to arrive at estimates of $N_{i,c} \cdot S_{i,c}$ for the general population use of acetaminophen, acetylsalicylic acid, clotrimazole and ibuprofen.

Acetaminophen and acetylsalicylic acid

Estimated using the Canadian market evaluations for acetaminophen and Aspirin as estimated by A.C. Nielsen (2004) and the per unit cost with which the province of Quebec reimburses the prescription of these PhACs (RAMQ, 2012). The resultant estimates are likely conservative but similar in magnitude to what has been reported for other countries.

Clotrimazole

Since Clotrimazole is also available over-the-counter in Canada, instead of using the prescription only estimates, the net consumption of the PhAC was estimated from German and British consumption data as reported in OSPAR (2005). Specifically, OSPAR reported the consumption of this PhAC at levels of between 93 -170 $\mu\text{g}/\text{cap}\cdot\text{d}$ for the national German and British populations, respectively. Here the British per capita consumption is used along with the Canadian national population to conservatively estimate the use of Clotrimazole through all channels at 2000 kg/yr.

Ibuprofen

Estimated from a leading manufacturer's estimate of their annual supply of ibuprofen to the Canadian market and the share this supply represents of the net market for the PhAC within Canada (confidential personal communication).

Appendix D: Metabolic disposition of selected PhACs

A database of urinary plus fecal excretion (i.e., $U_{ex} + F_{ex}$) values for the selected PhACs was developed by firstly identifying the relevant routes through which each selected PhAC is administered. Then, for each identified route of administration (ROA), suitable metabolic disposition literature that reported on the urinary and/or fecal excretions of the PhAC were reviewed. Subsequently, from all identified studies, the reported fractions of the dose for each route of administration that are eliminated as the unchanged parent compound and/or as glucuronic and sulphate conjugates of the parent compound was compiled.

Overall, the database presented in its entirety as Table D.1 reports route-of-administered-specific disposition data for 318 PhACs. This represents the outcome of data from more than 500 literature sources. All drug monographs referenced in Table D.1 were obtained from Health Canada's Drug Product Database (2013).

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Acarbose	O	0.4-1.7	16-51	16-53	Ahr et al., 1989; Muller, 1988; Pütter, 1982
Acebutolol	O	11.6	27.4	39	Gabriel et al., 1981
Acetaminophen	O	92 ^(b)	1.2 ^(o)	93	Prescott, 1980; Siegers et al., 1984
Acetylcysteine	P	29	Minor ^(c)	29	Borgstrom et al., 1986
	O	7-10	5	12-15	
Acetylsalicylic acid	O	1.9	0	1.9 ^(p)	Elliot Cham et al., 1982
Acyclovir	O	12-22	80 ^(d)	92-100	de Miranda and Blum, 1983; Vergin et al., 1995
Alendronate	O	0.4-0.9	99.3 ^(d)	100	Gertz et al., 1995
Allopurinol	O	9.5	20	29.5	Day et al., 2007
Alprazolam	O	21.4	7 ^(e)	28.4	Fraser, 1987
Amantadine	O	86	1 ^(e)	87	Bleidner et al., 1965; Uchiyama and Shibuya, 1969
Amiloride	O	40	52	92	Weiss et al., 1969
5-Aminosalicylic acid	O	8	9-27	17-38	De Vos, 2000
	RE	1	30	100 ^(f)	Jacobsen et al., 1991
	RS	0	45	100 ^(f)	Jacobsen et al., 1991
Amiodarone	O	<1	66-75 ^(e)	66-75	Harris et al., 1983; Padmanabhan, 2010; Vassallo and Trohman, 2007
Amitriptyline	O	27.3 ^(b)	8	35	Vandel et al., 1983
Amlodipine	O	4-5	2.3	6.3-7.3	Beresford et al., 1988; Stopher et al., 1988
Amoxicillin	O	41-85	10 ^(e)	51-95	Arancibia et al., 1980; Lee et al., 1979; Welling et al., 1977
Amphetamine (3:1 of S(+):R(-))	O	40.3		40.3 ^(p)	Cody et al., 2003
Amphetamine (S(+))	O	34.2		34.2 ^(p)	Khan and Nicell, 2012
Amphotericin B	P	4.5 ^(g)	4 ^(g)	8.5	Beresford et al., 1988
	P	20.6	42.5	63.1	
Ampicillin	P	77-80	Minor	77-80	Ali et al., 1983; Bergan, 1978
	O	21-49	39 ^(d)	60-88	Bergan, 1978; Swahn, 1976
Anastrozole	O	10	13-15 ^(d)	23-25	Plourde et al., 1995

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Atenolol	O	42	46	88	Reeves et al., 1978
Atorvastatin	O	1.2	70 – 98 ^(e)	100	Lennernas, 2003; Stern et al., 1997; White, 2002
Atropine	P	40-60	Traces	40-60 ^(p)	Hinderling et al., 1985; Van der Meer et al., 1986
	O	30-50	Traces	30-50 ^(p)	Drug Monograph
Azathioprine	O	10	12	22	Dollery et al., 1991; Elion, 1972; Elion, 1993
Azithromycin	O	4.5	>50	> 54.5	Foulds et al., 1990; Moffat et al., 2004
	P	12.2	>50	> 62.2	
Baclofen	O	70	20	90	Dollery, 1991; Faigle and Keberle, 1972
Butalbital	O	3-7		3-7 ^(p)	Gilbert et al., 1997
Beclometasone	?			90 ^(q)	Cunningham et al., 2009
Benserazide	O			100 ⁽ⁱ⁾	
Benztropine	O			100 ⁽ⁱ⁾	
Benzydamine	OR			100 ^(j)	
Betamethasone	D	0.7 ^(k)		86.7 ^(k)	Petersen et al., 1983
	P	4.8		4.8 ^(p)	Petersen et al., 1983
	O	5	30 ^(d)	35	Drug Monograph
Betaxolol	Opth			100 ⁽ⁱ⁾	
	O	15-18	1-3	16-18	Fernandes, 1983; Ludden et al., 1988
Bezafibrate	O	74.1	1.3 ^(e)	75.7	Abshagen et al., 1979
Bicalutamide	O	17 ^(b)	31	48	McKillop et al., 1993
Bisoprolol	O	50-60	2 ^(e)	52-62	Buhring et al., 1986; Leopold, 1986
Bleomycin	P	45-70	?	45-70	Alberts et al., 1978; Hall et al., 1982; Oken et al., 1981
Bromazepam	O	1.1-2.3	2-6 ^(e)	3.1-8.3	Kaplan et al., 1976; Schwartz et al., 1973
Bromocriptine	O	0.02	82 ^(e)	82	Maurer et al., 1983
Budesonide	N	0	15-34 ^(e)	15-34	Dilger et al., 2006; Szeffler, 1999
Bupropion	O	0.23	10 ^(e)	10.2	Findlay et al., 1981
Buserelin	P	17-32		66 ^(m)	Moffat, 2004; Stanova et al., 2010
Candesartan	O	25.7	54	79.7	van Lier et al., 1997
Capecitabine	O	3	2.6 ^(e)	5.6	Judson et al., 1999

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Captopril	O	25-38	18-34	43-72	Drummer and Jarrott, 1986; Duchin et al., 1982; Kripalani et al., 1980
Carbamazepine	O	12	13	25	Bahlmann et al., 2014
Carbidopa	O	8-17	41-54 ^(e)	49-71	Vickers et al., 1974
Carboplatin	P	70-90		70-90 ^(p)	van Warmerdam et al., 1995
Carmustine	P	0	0.4-0.9 ^(e)	0.4-0.9	DeVita et al., 1967
Carvedilol	P	5.5 ^(b)	56-61 ^(e)	61.5-66.5	Neugebauer et al., 1987; Neugebauer and Neubert, 1991
Cefadroxil	O	90-93		90-93 ^(p)	Humbert et al., 1979; Swahn, 1976
Cefazolin	P	82-100		82-100 ^(p)	Kirby and Regamey, 1973; Nicholas et al., 1973; Nishida et al., 1969
Cefaclor	O	45-75		45-75 ^(p)	Bloch et al., 1977; Glynne et al., 1978; Korzeniowski et al., 1977; Meyers et al., 1978
Cefixime	O	18-21		100	Faulkner et al., 1988;
Cefprozil	O	60-70	25 ^(e)	85-95	Shyu et al., 1992
Ceftazidime	P	84-90		84-90	Armstrong et al., 1981; Leroy et al., 1984; Saito, 1983
Ceftriaxone	P	48-56	4-5	52-61	Patel et al., 1981
Cefuroxime	P	93-100		93-100 ^(p)	Foord, 1976; Gower and Dash, 1977
Celecoxib	O	2	2.6	4.6	Davies et al., 2000
Cephalexin	O	85-100		85-100 ^(p)	Finkelstein et al., 1978; Korzeniowski et al., 1977; Welling et al., 1979
Cetirizine	O	50-60	10	60-70	Curran et al., 2004; Wood et al., 1987
Chloral hydrate	O	0.05	0	0.05	Health Canada, 2008; Merdink et al., 2008
Chloramphenicol	P	65-100 ^(b)	1 ^(e)	96-100	Ambrose, 1984; Kauffman et al., 1981
Chlorhexidine	OR	0.3	82	93 ⁽ⁿ⁾	Winrow, 1973
	D			100 ^(r)	
Chloroquine	O	46	10	56	Dollery, 1991; Gustafsson et al., 1983
Chlorpromazine	O	1	5-6 ^(e)	6-7	Dollery, 1991; Whitfield et al., 1978, West et al., 1974
Cimetidine	O	40-53	9.4	56.4-62.4	Grahnen, 1979; Mitchell et al., 1982

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Ciprofloxacin	O	45	25	70	Drug Monograph
	P	50-70	15	65-85	Drug Monograph
Cisplatin	P	15-50 (Maybe as high as 80%)	minor	15-50 (As high as 80%)	McEvoy, 2011; Reece et al., 1989; Reece et al., 1987
Citalopram	O	38 ^(b)	10.5 ^(e)	48.5	Dalgaard and Larsen, 1999
Clarithromycin	O	18-29	4-11	23-40	Ferrero et al., 1990
Clavulanic acid	O	33-46	8 ^(e)	41-53	Bolton et al., 1986; Haginaka et al., 1981
	P	49		49 ^(p)	Bolton et al., 1986
Clindamycin	O	8.9-10.9 ^(s)	2.7 ^(s)	11.6-13.6	Drug Monograph; DeHaan et al., 1973;
	D	0.06-0.34		95.3 ^(t)	Wagner et al., 1968
Clodronic acid	O	1.7	50	100 ^(u)	Hurst and Noble, 1999; Yakatan et al., 1982
Clofibrate	O	0	0	0	Houin et al., 1975; Sedaghat and Ahrens, 1975
Clofibric acid	O	Up to 100	<1	100	Houin et al., 1975; Sedaghat and Ahrens, 1975
Clonazepam	O	0.5 -2	0	0.5 -2	Eschenhof, 1973; Kaplan et al., 1974; Sjo et al., 1975
Clonidine	O	62	22 ^(e)	84	Arndts et al., 1983
Clopidogrel	O	<5	51	56	Lins et al., 1999
Clorazepate	O	1.3	15-19 ^(e)	16-20	Abruzzo et al., 1977; Tranxene Monograph
Clotrimazole	T	0.05 -0.5		100 ^(v)	Duhm, 1972
	V			90-97 ^(w)	Duhm, 1972; Mendling and Plempel, 1982; Ritter, 1985; Ritter et al., 1982
Clozapine	O	2.5 ^(b)	7.3 ^(b)	10	Dain et al., 1997
Cocaine	D			100 ^(x)	Baselt et al., 1990
	Inh			8.2 ^(be)	
	Smoking			4.0 ^(be)	
Codeine	O	64 ^(b)	≈ 0	63.8	Khan and Nicell, 2011
Cortisone	O	0.1-0.3	0	0.1-0.3	Brouillet and Mattox, 1966; Burstein et al., 1953; Peterson et al., 1957
Cromolyn	O	0.4	82	82	Neale et al., 1986; Walker et al., 1971

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
	I	43-44	35	78-79	
	N	2-6.4	84	86-91	
Cyclophosphamide	O/P	3-30 Typically (<20)	1.8 ^(e)	<22	Bagley et al., 1973; Boddy and Yule, 2000; de Jonge et al., 2005
Cyproterone	O	5	58 ^(e)	63	Humpel et al., 1977
Cytarabine	P	4-20	0	4-20	Talley et al., 1967
Dactinomycin	P	10	50	60	Drug Monograph; Moffat, 2004
Daunorubicin	P	12-29	20 ^(e)	32-49	Drug Monograph
Desloratadine	O	1.7	6.7	8.4	Ramanathan et al., 2007a
Desogestrel	O	0	<2	<2	Verhoeven et al., 2001
Dexamethasone	P/O	2-31	36 ^(v)	38-67	Minagawa et al., 1986; Tsuei et al., 1979
Dextropropoxyphene	O	0.6-5	18 ^(e)	19-23	Dollery, 1991; Karkkainen and Neuvonen, 1985; Moffat, 2004
Diatrizoate	O	94-100	0	94-100	HYPACUE Monograph
Diazepam	O	Trace-0.5 ^(b)	9-10 ^(e)	10-12	Arnold, 1975; Chiba et al., 1995; Kaplan et al., 1973a; Schwartz et al., 1965
Diclofenac	O	6-11.5 ^(b)	15	21-27	Degen et al., 1988, Stierlin and Faigle, 1979
	T	<4		97 ⁽ⁱ⁾	Hui et al., 1998
Didanosine	O	12-20	62 ^(d)	74-82	Knupp et al., 1991; Singlas et al., 1992
Digoxin	O	37-55	29	66-84	Gault et al., 1979; Hui et al., 1994; Magnusson, 1983; Roman et al., 2005
Diltiazem	O	2.6-4.6	15-16 ^(e)	18-23	Hoglund and Nilsson, 1989; Sugihara et al., 1984; Tawashi et al., 1991; Yeung et al., 1990
Dipyridamole	O	<5	95	100 ^(z)	Drug Monograph
Diphenoxylate	O	< 1	40	<41	Drug Monograph
Disulfiram	O	0	20	20	Johansson, 1992
Divalproex	O	Converted rapidly to valproic acid in the stomach (Drug Monograph).			
Docusate	O			100 ⁽ⁱ⁾	
Domperidone	O	0.4	7	7.4	Meuldermans et al., 1981
Doxepin	O	0.3-1	0	0.3-1	Ghabrial et al., 1991; Kimura, 1972

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Doxorubicin	P	4-9	20-25	24-29	Camaggi et al., 1988; Drug Monograph
Doxycycline	O	55	32-38	87-93	Schach von Wittenau and Twomey, 1971; Steigbigel et al., 1968
Drospirenone	O			100 ⁽ⁱ⁾	
Enalapril	O	18	6	24	Ulm et al., 1982
Enalaprilat	P	90		90 ^(p)	Drug Monograph
Epirubicin	P	9-15 ^(b)	21-32 ^(aa)	30-46.7	Camaggi et al., 1986; Mross et al., 1988; Weenen et al., 1984
Eprosartan	O	7 ^(b)	90	97	Cox et al., 1996; Drug Monograph
Erythromycin	O	4-9	15	19-24 ^(o)	Austin et al., 1980; Griffith and Black, 1970; Josefsson et al., 1982
	P	11-14	15	26-29 ^(o)	
Escitalopram	O	8-10	10 ^(e)	18-20	Dalgaard and Larsen, 1999; Rao, 2007; Sogaard et al., 2005
Estradiol	O	10 ^(b)		10 ^(p)	Friel et al., 2005
	T	0.64		83.2 ^(av)	Longcope et al., 1985; Walters et al., 1998
	TD			100 ^(ag)	
Esomeprazole	O	1	0	1	Andersson et al., 2001; Cederberg et al., 1989
Estrone	T			100 ⁽ⁱ⁾	
Ethacrynic acid	P/O			100 ⁽ⁱ⁾	
Ethambutol	O	67-79	12-22	79-98	Lee and Wang, 1980; Place et al., 1966
Ethinodiol	O	0	0	0	Kishimoto et al., 1972
Ethinyl estradiol	O	23.1	18.6	41.7	Reed et al., 1972; Speck et al., 1976
	V			94 ^(bc)	
Ethinodiol	O	0	0	0	Kishimoto et al., 1972; Lewis et al., 1980
Etidronic acid	O	3-3.5	96.5-97	100	Drug Monograph
Etodolac	O	18.2 ^(b)	16 ^(e)	34.2	Ferdinandi et al., 1986
Etonogestrel	V			100 ^(bb)	
Etoposide	P	56 ^(b)	44 ^(e)	100	Drug Monograph; Dollery, 1991; Perdaems et al., 1999

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Exemestane	O	0.1-1	42 ^(e)	42-43	Drug Monograph
Famciclovir	O	0	0	0	Filer et al., 1994
Famotidine	O	25	51 ^(e)	76-81	Yeh et al., 1987
	P	71-72		100 ^(ax)	Morgan et al., 1990; Takabatake et al., 1985
Felodipine	O	0-0.5	9.8	10.3	Edgar et al., 1985; Weidolf et al., 1984
Fenofibrate	O	0	15.7	15.7	Weil et al., 1990
Fenofibric Acid	O	40.2	1.9	42.1	Weil et al., 1990
Fenoprofen	O	39 ^(b)	2 ^(e)	41	Rubin et al., 1972
Fenoterol	Inh	≈3 ^(b)	40 ^(e)	43	Drug Monograph
Fentanyl	P	6-10	1.2	7.2-11.2	McClain and Hug, 1980; Muijsers and Wagstaff, 2001
	TD			59-61 ^(ac)	
Finasteride	O	0.044	<0.02	0.06	Carlin et al., 1992
Fluconazole	O	94.3 ^(b)	2.3 ^(e)	96.6	Brammer et al., 1991
Fluocinonide	D			100 ^(ax)	
Fluorouracil	D			100 ^(ad)	
	P	5 - 20	<2 ^(ae)	7 - 22	Beumer et al., 2006; Heggie et al., 1987
Fluoxetine	O	7.7-19	10-15 ^(e)	17.7-34	Neuwoehner et al., 2009
Fluphenazine	P/O			100 ⁽ⁱ⁾	
Flurazepam	O	0.3-1.2 ^(b)	10 ^(e)	10.3-11.2	de Silva and Strojny, 1971; Schwartz and Postma, 1970
Flutamide	O	<1	4.2 ^(e)	5.2	Katchen and Buxbaum, 1975
Fluticasone	?			5 ^(q)	Cunningham et al., 2009
Fluvoxamine	O	0-4	0	0-4	De Bree, 1983; Overmars et al., 1983
Formoterol	Inh (O/P)	37 ^(b)	15.8	52.8	Rosenborg et al., 1999
Fosfomycin	O	30-50	18	48-68	Drug Monograph; Janknegt et al., 1994
Fosphenytoin	P	0-4	?	0-4	Stella, 2004
Fulvestrant	P	<1	19	<19	US FDA, 2002c
Furosemide	O	43 ^(b)	34.7 ^(e)	77.7	Beermann et al., 1975; Smith et al., 1980
	P	80 ^(b)	6-9 ^(e)	86-89	
Gabapentin	O	78	18	96	Vollmer et al., 1986
Gemfibrozil	O	30-33 ^(b)	6 ^(e)	36-39	Nakagawa et al., 1991; Okerholm et al.,

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Gentamicin	P	30-100		30-100	1976 Wood and Farrell, 1976
Gliclazide	O	0-1.4	0	0-1.4 ^(p)	Campbell, 1980; Moffat et al., 2004; Oida et al., 1985; Taylor et al., 1996
Glyburide	O	0	4-6	4-6	Fuccella et al., 1973; Peart et al., 1989
Goserelin	Imp	20		20 ^(p)	Cockshott, 2000
Haloperidol	O	19 ^(b)	15 ^(e)	34	Oida et al., 1989
Heroin	P	0.025		0.025	Khan and Nicell, 2011
Hydrochlorothiazide	O	68-95	Up to 24	100	Alton et al., 1986; Wagstaff, 2006
Hydrocodone	O	11.6	30 ^(b)	41.6	Cone et al., 1978
Hydrocortisone	D			90-99 ^(af)	Fukushima et al., 1960
	P	<1		<1	Peterson et al., 1957
Hydromorphone	O	42.4 ^(b)	1	44	Cone et al., 1977
Hydroxychloroquine	O	23-25	25 ^(b)	48-50	MHRA, 2007; Moffat et al., 2004
Hydroxyzine	O	0.8		0.8 ^(p)	Atarax Drug Monograph
Ibuprofen	O	11-14	10-20	21-34	Lockwood et al., 1983
Idarubicin	P	2-7	39 ^(e)	41-46	Drug Monograph
	O	1-2	61 ^(e)	61-62	
Ifosfamide	P	5-53	2 ^(e)	17-55	Lewis et al., 1991; Zhang et al., 2006
Imipramine	O	1.8-6.4	2 ^(ah)	3.8-8.4	Crammer et al., 1969; Crammer et al., 1968
Indomethacin	O	27.4	1.4	28.8	Kwan et al., 1976a
	R	24	1.3	25.3	
Ipratropium	Inh	0.4-3.1	72	69.8-72.5	Adlung et al., 1976; Wahl, 1975; Wood et al., 1995
	N	4-6	72 ^(h)	74-76	
Irbesartan	O	10.4 ^(b)	30.4 ^(b)	40.8	Chando et al., 1998
Isoniazid	O	7-30	10 ^(e)	30-40	Becker et al., 2007; Ellard and Gammon, 1976
Isosorbide-dinitrate	O	0.2-0.4	0.8 ^(e)	1.2-1.4	Down et al., 1974
Isosorbide-5-mononitrate	O	19-25 ^(b)	1 ^(e)	20-26	Abshagen, 1992; Wood et al., 1984
Ketamine	P	2.3	3-5 ^(e)	5-7	Chang and Glazko, 1974; Dollery, 1991; Wieber et al., 1975

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Ketoconazole	D			100	
	O	0.3-0.5	11-37	11-38	Daneshmend and Warnock, 1988
Ketoprofen	O	76 ^(b)	1-8 ^(e)	77-84	Drug Monograph; Delbarre et al., 1976;
	R	70	1-8 ^(ba)	71-79	Ishizaki et al., 1980
Labetalol	O	55-60 ^(b)	12-27	67-80	Dollery et al., 1991
Lamotrigine	O	90.4 ^(b)	2 ^(e)	93	Posner et al., 1989
Lansoprazole	O	0	1	1	Aoki et al., 1991, Drug Monograph
Loratadine	O	<1	5.4	6.4	Ramanathan et al., 2007b
Levodopa	O	0.8 (Up to 6% when administered with Carbidopa)	2 ^(e)	2.8- 8	Morgan et al., 1971
Levofloxacin	O	85-92	3.9	89-96	Nakashima et al., 1992
Letrozole	O	5-6	4 ^(e)	9-10	Pfister et al., 2001; Requena et al., 2008
Leuprolide	P			100 ⁽ⁱ⁾	
Levobunolol	Oph			100 ⁽ⁱ⁾	
Levothyroxine	O	0	30	30	Drug Monograph; Moffat et al., 2004
Liothyronine	O			100 ⁽ⁱ⁾	
Lisinopril	O	30	70	100	Tomlinson et al., 2000
Lorazepam	O	75 ^(b)	7 ^(e)	82	Elliott, 1976; Kyriakopoulos et al., 1978
Losartan	O	5	60 ^(e)	65	Drug Monograph
Loxapine	O	Trace	0	Assume 0.5% conservatively	Cooper et al., 1979
Lidocaine	P	3-<10	0	3-<10	Keenaghan and Boyes, 1972
	D			100	
MDMA	O			20	Abraham et al., 2009
Mefenamic acid	O	6 ^(b)	0	6	Pentikainen et al., 1981
Melfalan	P	10-34	0	10-34	Alberts et al., 1979; Bosanquet and Gilby, 1982; Reece et al., 1988;
	O	30	37	67	Tattersall et al., 1978
Meprobamate	O	20 ^(b)	10 ^(e)	30	Berger, 1954
Metformin	O	37.9-51.6	26.9-32.9	64.8-82.5	Pentikainen et al., 1979; Tucker et al., 1981
Methadone	O	33	1-5	34-38	Kreek, 1976b

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Methotrexate	O	53.1	4.6 ^(e)	57.7	Wan et al., 1974
	P	80	1.1 ^(e)	81.1	
Methotrimeprazine	O	1	Typically <6	7	Allgen et al., 1963
Methyldopa	O	24-27 ^(b)	49-59	87	Au et al., 1972; Buhs et al., 1964; Kwan et al., 1976; Stenbaek et al., 1977
Methylphenidate	O	<1 – 5.7	3.3 ^(e)	4.3-9.0	Faraj et al., 1974; Wells et al., 1974
Methylprednisolone	P	22-32.1 ^(ai)	9 ^(e)	31.1- 41.1	Lawson et al., 1992; Slaunwhite, and Sandberg 1961; Vree et al., 1999
Metoprolol	O	2.8-11.3	5 ^(e)	7.8 – 16.3	Borg et al., 1975; Quarterman et al., 1981
Metronidazole	O	13.5 ^(b)	14 ^(e)	27.5	Jensen and Gugler, 1983; Loft et al., 1986
	P	16.5 ^(b)	6 ^(e)	22.5	Jensen and Gugler, 1983; Loft et al., 1986
	V/D			100 ^(aj)	
Miconazole	V			100 ^(al)	
	D			100	
Midazolam	P	0.01-0.03	2-10 ^(e)	2-10	Allonen et al., 1981; Smith et al., 1981
Minocycline	O	5-12	20-35	25-47	Agwuh and MacGowan, 2006; Bocker et al., 1991; Steigbigel et al., 1968
Misoprostol	O	<1	0	<1	Karim et al., 1987; Schoenhard et al., 1985
Mitomycin C	P	2-20	0	2-20	den Hartigh et al., 1983; Schilcher et al., 1984; Schwartz and Philips, 1961
Mitotane	O	0	40-60	40-60	BC Cancer Agency Cancer Drug Manual, 2009; Reif et al., 1974
Mometasone Furoate	D			100 ^(ao)	
	N	0.6	41	41.6	Affrime et al., 2000
Morphine	O	69.5	9	77.7	Khan and Nicell, 2011
Mupirocin	D			100 ^(ap)	
Nabumetone	O	0	9.2 ^(e)	9.2	Haddock et al., 1984
Nadolol	O	24.6	76.9	99.5	Dreyfuss et al., 1977
Naloxone	P	38.9 ^(b)		38.9	Fang et al., 2009; Fishman et al., 1973

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Naltrexone	O	8-16 ^(b)	0.2	8.2-16.2	Verebey et al., 1976; Wall et al., 1981
Naproxen	O	59 -70 ^(b)	1-2	60-75	Runkel et al., 1972; Runkel et al., 1973; Segre, 1975; Vree et al., 1993
Neomycin	D			100	
Nifedipine	O	0.1	0	0.1	Kondo et al., 1980; Raemsch and Sommer, 1983
Nimodipine	O	0 - <1	0	0 - <1	Al-Omar, 2004; Gengo et al., 1987; Lettieri et al., 1988
Nitrazepam	O	1.1	8-20 ^(e)	9.1-21.1	Kangas et al., 1979; Sawada and Shinoara, 1971
Nitrofurantoin	O	40		40 ^(p)	Furadantin Drug Monograph
Nizatidine	O	62.5	6 -7 ^(e)	68.5-69.5	Knadler et al., 1986
Norgestimate	O	0	37 ^(e)	37	Alton et al., 1984
Norethindrone	O	2.8-4.5 ^(b)	20-40 ^(e)	23-45	Aygestin Drug Monograph; Sahlberg et al., 1987
Norfloxacin	O	30	28	58	Cofsky et al., 1984; Swanson et al., 1983
Nortriptyline (from the metabolism of amitriptyline)	O	2.1		2.1	Vandel et al., 1983
Nystatin	Various		100	100 ⁽ⁱ⁾	
Nilutamide	O	0.8	1.4-7	2.2-7	Pendyala et al., 1988
Ofloxacin	O	74	4-8	78-82	Lode et al., 1995
	P	77	4-8	71-85	Lode et al., 1995
Omeprazole	O	< 0.1	0	0.1	Cederberg et al., 1989; Lind et al., 1987; Regardh et al., 1990; Regardh et al., 1985
Ondansetron	O/P	<5-10	25 ^(e)	30-35	Saynor and Dixon, 1989
Orlistat	O	0	83.1	83.1	Zhi et al., 1995
Orphenadrine	O	8- 30	11 ^(e)	19-41	Beckett and Khan, 1971; Ellison et al., 1971
Oseltamivir	O	4.75	17 ^(e)	22	EMA, 2011
	P	0	0.3 ^(e)	0.3	
Oseltamivir	O	81	0	81	EMA, 2011

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
carboxylate	P	99.9	0	99.9	
Oxaprozin	O	22-31 ^(b)	0	22.2-30.5	Janssen et al., 1980
Oxazepam	O	61-87 ^(b)	2.4	63.4- 89.4	Alvan et al., 1977; Knowles and Ruelius, 1972; Sonne et al., 1988
Oxycodone	O	9 ^(b)	0.8-2 ^(aq)	10-12	Ishida et al., 1982; Lalovic et al., 2006; Poyhia et al., 1992
Oxprenolol	O	47-52 ^(b)	2.6 – 3.2 ^(e)	57.7- 68.4	Dieterle et al., 1986; Laethem et al., 1995
Pamidronate	P	51	0	100 ^(ar)	Leyvraz et al., 1992; Redalieu et al., 1993; Wingen and Schmahl, 1987
Pantoprazole	O	0	0	0	Peeters, 1993
Paroxetine	O	2	1	3	Cunningham et al., 2004
Penicillin V	O	25.9	32 ^(e)	58	Cole et al., 1973, McEvoy, 2004
Penicillin G	P	66		66	Cole et al., 1973
Pentoxifylline	O	<1	3-5 ^(e)	3-5	Bryce et al., 1989
Perindopril	O	13	0	13	Grislain et al., 1990
Perphenazine	O	31.3 ^(b)	66 ^{(e),(as)}	97	Huang and Kurland, 1964; Symchowicz, 1962
Phenobarbital	O	25-29	0	25-27	Bernus et al., 1994; Tang et al., 1979; Whyte and Dekaban, 1977
Phenytoin	O	1.3	0-33 ^(e)	0.7 – 33	Glazko, 1987; Kadar et al., 1983
Phenyltoloxamine	O			100 ⁽ⁱ⁾	
Piperacillin	P	74-89	<1 ^(e)	75-89	Tjandramaga et al., 1978
Piroxicam	O	5 -10	0	5-10	Ishizaki et al., 1979; Rudy et al., 1994
Pravastatin	O	6.7- 14	33.8	40.5- 41.8	Everett et al., 1991; Singhvi et al., 1990
Prednisolone	O	14	7 ^(e)	21	Chakraborty et al., 1981; Shaffer et al., 1983
	Oph			100 ⁽ⁱ⁾	
Prednisone	O	1.5-5		1.5-5 ^(p)	Garg and Jusko, 1994; Rose et al., 1981
Primidone	O	45.9		46 ^(p)	Martines et al., 1990
Procainamide	O	55		55 ^(p)	Graffner et al., 1975; Karlsson et al., 1975
	P	65		65 ^(p)	
Prochlorperazine	O	0.04		100 ^(at)	Isah et al., 1991

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
	P	0.005		100 ^(at)	
Promethazine	O	0.6		0.6 ^(p)	Drug Monograph, Taylor et al., 1983
Propafenone	O	3-10 ^(b)	0	4-10	Hege et al., 1985; Latini et al., 1992; Vozeh et al., 1990
Propofol	P	42.3 ^(b)	1.6 ^(e)	43.9	Simons et al., 1988
Propranolol	O	14.9-15.4	2.1	17.5	Paterson et al., 1970; Walle et al., 1985; Walle et al., 1984
Propylthiouracil	O	72 ^(b)	0	72	Taurog and Dorris, 1988, Williams et al., 1944
Quinapril	O	3	37 ^(e)	40	Olson et al., 1989
Quetiapine	O	<1 ^(b)	<1.9	2.9	US FDA, 1997a
Quinidine	O	22	0	22	Guentert et al., 1982; Hardy et al., 1983
Quinine	O	23 ^(b)	5 ^(e)	28	Mirghani et al., 2003; Paintaud et al., 1993
Ramipril	O	0.9	40 ^(e)	41	Verho et al., 1995
Ranitidine	O	27-51	26 ^(e)	87	McNeil et al., 1981; van Hecken et al., 1982
	P	69-79	5 ^(e)	84	McNeil et al., 1981; van Hecken et al., 1982
Rabeprazole	O	0	0	0	Setoyama et al., 2006
Rifampin	O	6-15	3-30 ^(e)	9-45	Becker et al., 2009; Ellard and Fourie, 1999; Peloquin et al., 1999
Risperidone	O	4-30	<1	5-31	Mannens et al., 1993
Rizatriptan	O	14	15.2 ^(e)	29.2	Vyas et al., 2000
Rosuvastatin	O	5	76.8	81.8	Martin et al., 2003; Simonson et al., 2003
Roxithromycin	O	4-9	30	34-39	Li et al., 2001; McLean et al., 1988; Puri and Lassman, 1987
Salbutamol	O	80 ^(b)	3.8 ^(e)	83.8	Evans et al., 1973; Morgan et al., 1986
	Inh	84.2	11 ^(e)	95.2	
Salmeterol	Inh	<5	0	<5	Cazzola et al., 2002
Selegiline	O	0.9	14 ^(e)	14.9	Azzaro et al., 2007; Szatmari and Toth, 1992

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Sertraline	O	0	12-14	12-14	US FDA, 1997b
Sildenafil	O	0	0	0	Muirhead et al., 2002; Walker et al., 1999
Simvastatin	O	0	<2	<2	Duggan and Vickers, 1990; Vickers et al., 1990
Sincalide	P			100 ⁽ⁱ⁾	
Sotalol	O	80-90	12.5	90-100	Antonaccio and Gomoll, 1990; Hanyok, 1993
Spiramycin	O	4.4		4.4 ^(p)	Brook, 1998; Drug Monograph
Spirolactone	O	0	0-<2	0-<2	Abshagen et al., 1977; Karim et al., 1976
Sulfacetamide	D	0.08-0.33		96.1-96.3 ^(ab)	Drug Monograph
	Op			100 ⁽ⁱ⁾	
Sulfamethoxazole	O	26-30	0	26-30	Kaplan et al., 1973b
Sulfasalazine	O	3-6	0-43	3-49	Sandborn and Hanauer, 2003
Sulfapyridine (Sulfasalazine metabolite)	O	5.6	< 19.4	< 25	van Hees et al., 1979
Sulfisoxazole	O	51	0	51	Kaplan et al., 1972
Sulindac	O	20	1	21	Dobrinska et al., 1983
Sumatriptan	O	2-3	9	11-12	Dechant and Clissold, 1992; Dixon et al., 1993; Lacey et al., 1995
	N	2-7	9 ^(ak)	11-16	Duquesnoy et al., 1998, Fuseau et al., 2002
	SC	22.2	0.6	22.8	Dixon et al., 1993; Lacey et al., 1995
Tamoxifen	O	0.1	8.9	9.0	Kisanga et al., 2005
Tamsulosin	O	8.7	2 ^(am)	10.7	Soeishi et al., 1996
Tazobactam	P	60-77	0.6 ^(e)	61-78	Sorgel and Kinzig, 1993
Telithromycin	O	7-26	7-20	14-46	Cantalloube et al., 2003; Drug Monograph; Namour et al., 2001,
Temazepam	O	74 ^(b)	11.9 ^(e)	85.9	Schwarz, 1979
Terbutaline	O	20-25	46-60	66-100	Davies et al., 1974; Moffat, 2004
	Inh	2-37 ^(b)	3-35 ^(b)	5-72	Drug Monograph
Testosterone	O	1.5	15 ^(e)	16.5	Peng et al., 2002; Drug Monograph

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex} ^(az)	
	D			90.7 ^(az)	Camacho and Migeon, 1964; Drug Monograph
	P	1	6 ^(e)	7	
	TD			81.4 ^(aw)	
Tetracycline	O	40-60	9-60	100	Agwuh and MacGowan, 2006; Steigbigel et al., 1968
THC	Smoking	Trace	≈ 0.6-1.0	0.6-1.0	Khan and Nicell, 2012
Theophylline	O	13-20		13-20 ^(p)	Beckmann et al., 1987; Morimoto et al., 2004
Tiaprofenic Acid	O	54	40 ^(e)	94	Pottier et al., 1977
Ticarcillin	P	92	3.5 ^(e)	95.5	Davies et al., 1982
Ticlopidine	O	<1	8	< 9	Bruno et al., 1983; Farid et al., 2010
Timolol	O	20	6 ^(e)	26	Tocco et al., 1975
	Ophth			100 ⁽ⁱ⁾	
Tolbutamide	O	<2	9 ^(e)	11	Matin and Rowland, 1973; Thomas and Ikeda, 1966
Tramadol	O	25-32	10 ^(e)	35-42	Lintz et al., 1981
Trazodone	O	0.13-0.39	15 ^(e)	15.1-15.4	Jauch et al., 1976; Nilsen and Dale, 1992; Yamato et al., 1976
Triamterene	O	4-9	Up to 40	44-49	Gundert-Remy et al., 1979; Pruitt et al., 1977
Trifluoperazine	O	<1		100 ^(an)	West et al., 1974
Trihexyphenidyl	O			100 ⁽ⁱ⁾	
Trimethoprim	O	50-75	< 4	54-79	Kasanen et al., 1978; Schwartz et al., 1970; Schwartz and Ziegler, 1969
Trimipramine	O	10	0	10	Drug Monograph
Valacyclovir	O	0 to 0.5	0	0 to 0.5	Soul-Lawton et al., 1995
Valproic Acid	O	22.5 ^(b)	2-3	24.5-25.5	Gugler et al., 1977
Valsartan	O	9.8	70.8	80.6	Waldmeier et al., 1997
Vancomycin	O	0.05	100	100	Griffith, 1957
	P	90	0	90	Geraci et al., 1956
Venlafaxine	O	4.7	1.9 ^(e)	6.6	Howell et al., 1993
Verapamil	O	3-4	9-16 ^(e)	12-20	Eichelbaum et al., 1979

Table D.1 Metabolic disposition of selected PhACs.

PhAC	ROA ^(a)	Metabolic Disposition (% Administered Dose)			Reference
		U _{ex}	F _{ex}	U _{ex} + F _{ex}	
Warfarin	O	1	6	7	Lewis et al., 1974; Toon et al., 1986
Xylometazoline	N			100 ⁽ⁱ⁾	
Zidovudine	O	89	5 ^(e)	91	Cload, 1989; Vuong le et al., 2008
	P	78-91.4	2 ^(o)	80-93.4	
Zopiclone	O	4-5		7-10 ^(au)	Fernandez et al., 1993; Gaillot et al., 1983

Notes:

- (a) Relevant routes-of-administration (ROA); D = Dermatological, Imp = Implant, N = Nasal, O = Oral, OR = Oral Rinse, Oph = Ophthalmic, P = Parenteral, RE = Rectal enema, RS = Rectal suppository, TD= transdermal patches, V= Vaginal.
- (b) Includes the fraction of the PhAC that is conjugated to glucuronide and/or sulphate moieties.
- (c) Expected to be of minor importance.
- (d) Fecal disposition based on the oral absorption of the PhAC.
- (e) In the absence of better fecal disposition data, the net fecal elimination of the PhAC was conservatively assumed to represent unchanged parent compound.
- (f) The urine and fecal fractions do not account for the release of 5-Aminosalicylic acid through fecal water; hence, it was conservatively assumed that the entire mass of the PhAC that is administered via the RE and RS routes is released to sewers as the parent compound.
- (g) Disposition data for Liposomal Amphotericin B.
- (h) Assumed to be similar to the fecal disposition of inhaled Ipratropium.
- (i) No fecal or urinary disposition data could be identified for the PhAC in humans; hence, it was conservatively assumed that the whole mass of the PhAC was released unchanged to sewers.
- (j) Used as an oral rinse and, hence, assumed to enter sewers in its entirety as the parent compound.
- (k) Absorption of topical betamethasone was reported to be 14% (FASS, 2009). Therefore, 86% of the dose is expected to enter sewers un-metabolized. Of the 14% that is absorbed, urinary disposition data of Petersen et al. (1983) can be used to estimate that a further 0.7% of the administered dose would be released to sewers as betamethasone through the user's urinary excretions.

Table D.1 Notes (continued):

- (l) Absorption of topical diclofenac has been reported to be approximately 7% (Hui et al., 1998); hence, it was conservatively assumed that the unabsorbed dose is released to sewers as the parent drug.
- (m) Total fraction excreted in urine and bile as unchanged buserelin (Stanova et al., 2010).
- (n) Only 33% of the oral rinse is retained in the mouth (Winrow et al., 1973), hence the net excreted fraction of Chlorhexidine eliminated to sewers was estimated as follows: un-retained fraction of an oral rinse (0.66) plus the fraction of absorbed Chlorhexidine eliminated in urine and fecal matter (0.823) x fraction retained (0.33).
- (o) Fraction eliminated in bile.
- (p) Fecal elimination of unchanged PhAC has not been reported; however, evidence available suggests that it is expected to be of minor importance.
- (q) Total fraction of the administered dose that is eliminated in fecal matter and urine as the parent compound.
- (r) 96-98% of topically-applied chlorhexidine has been reported to remain on the skin (Denton et al., 1991); hence, the entire mass of dermally-applied chlorhexidine was conservatively assumed to enter sewers as the parent compound.
- (s) Refers to the bioactive fraction; hence, these fractions are likely representative of unchanged clindamycin and its active metabolites (DeHaan et al., 1973). Here it was conservatively assumed that the reported fractions represent parent clindamycin.
- (t) Since, topically-applied clindamycin only demonstrates dermal absorption of 4 to 5%, it was conservatively assumed that unabsorbed clindamycin enters sewers as the parent compound.
- (u) Since a substantial portion of Clodronic acid binds to the patient's bone mass before being slowly eliminated, the actual fractions excreted could be higher than those reported by pharmacokinetics studies available to-date for this PhAC; hence, it was conservatively assumed that the entire mass of Clodronic acid prescribed enters the sewers as the parent drug.
- (v) Topically-applied Clotrimazole is minimal absorbed (Duhm et al., 1972); hence, it was assumed that the entire mass of topically-applied clotrimazole is released to sewers as the parent compound.
- (w) It has been suggested that between 3 and 10% of vaginally-applied clotrimazole reaches systemic circulation (Duhm et al., 1972; Mendling et al., 1982; Ritter et al., 1982; Ritter, 1985); hence, it was conservatively assumed that the remainder enters sewers as the parent drug.
- (x) Topically applied cocaine is poorly absorbed (Baselt, 1990); hence it was conservatively assumed that the entire load enters sewers as the parent drug.
- (y) No data was identified for the fecal disposition of dexamethasone; hence, it was assumed that fecal elimination of unchanged dexamethasone was equal to 1-fraction of dexamethasone's dose that is excreted via urine of 64% as reported by Haque et al. (1972).
- (z) Only very limited disposition data for Dipyrindamole was identified; hence, it was conservatively assumed that the entire mass of this PhAC is released to sewers as the parent compound.

Table D.1 Notes (continued):

- (aa) Fraction eliminated in bile.
- (ab) Only 4% of dermally-applied sulfacetamide is absorbed; hence, the net fraction released to sewer was estimated as the fraction of the absorbed dose that is eliminated as the parent drug via urinary and fecal excretions plus the fraction of dermally-applied sulfacetamide that remains unabsorbed.
- (ac) 57% of Fentanyl remains undelivered in used transdermal patches (Drug Monograph). Of the 43% that is delivered, disposition data of injected fentanyl suggests that a further 3-5% of the administered dose could be released to sewers as fentanyl.
- (ad) Since, fluocinonide is topically applied it was conservatively assumed that the entire mass enters sewers as the parent compound.
- (ae) The fraction released via the bile is expected to be primarily composed of metabolites. Nevertheless, it was conservatively assumed that the entire biliary fraction is composed of unchanged fluorouracil.
- (af) Topical absorption for most relevant sites of application has been reported to be vary between 1 and 10% (Feldmann and Maibach, 1967); hence, for the fraction that is absorbed, it is largely expected to contain little to no unchanged parent hydrocortisone (Fukushima et al., 1960).
- (ag) Since as much as 98% of the estradiol content of transdermally applied patches can remain unused (Castensson, 2008), it was assumed that the entire estradiol content of transdermal patches enters sewers unmetabolized as the parent compound.
- (ah) 20% of administered Imipramine is eliminated via the fecal route; however, unchanged Imipramine was reported to be present in minor amounts therein (Crammer et al., 1969). Such qualitative information was used as a basis to conservatively assume that the unchanged Imipramine in fecal matter amounted to 2% of the administered dose.
- (ai) Includes fraction conjugate to the hemisuccinate and relevant glucuronide conjugates.
- (aj) Topical application of metronidazole shows low absorption (<1%); hence, it was assumed that the entire load of topically-applied metronidazole enters sewers as the parent compound.
- (ak) Assumed to be equal to the fraction eliminated via the fecal route when sumatriptan is administered orally.
- (al) Vaginally applied Miconazole has been reported to have a systemic absorption of 1.4% (Daneshmend, 1986); hence, it was conservatively assumed that the entire mass sold enters sewers as the parent compound.
- (am) Since fecal excretions of tamsulosin primarily originate through biliary excretions, minor amounts of unchanged parent compound are expected to be released via the fecal excretions of users. Nevertheless, it was conservatively assumed that 2% of the administered dose (approx. 1/10th of the entire fecal load) is excreted as unchanged tamsulosin.
- (an) Suitable data was not available concerning the fecal elimination of Trifluoperazine; hence, it was conservatively assumed that the entire mass of this PhAC is released unchanged to sewers.

Table D.1 Notes (continued):

- (ao) Topical absorption of 0.7- 1.4% has been reported for mometasone (Prakash and Benfield, 1998); hence, it was conservatively assumed that entire dose of topically-applied Mometasone is released to the sewers as the parent compound.
- (ap) Topical absorption of Mupirocin has reported to amount to be less than 0.24%; hence, it was conservatively assumed that the entire mass of topically-applied mupirocin enters sewers as the parent compound.
- (aq) Amount found in fecal matter of several mammalian species other than humans.
- (ar) Further to the fraction of the drug reported to be released in urine, the drug is expected to be slowly eliminated from bones; hence, it was conservatively assumed that the entire mass of pamidronate prescribed enters the sewers as the parent drug.
- (as) Total fecal levels reported in rats.
- (at) Expected to be primarily eliminated via the fecal route; hence, in the absence of actual fecal disposition data, it was conservatively assumed that entire load is excreted unchanged to the sewers.
- (au) Total fraction of an administered dose that is eliminated as unchanged zopiclone in the urine and fecal matter of users.
- (av) Absorption of topical estradiol has been reported to be 17.4% (Walters et al., 1998). Therefore, up to 82.6% of the dose is expected to enter sewers as the parent compound. Of the 17.4% that is absorbed, urinary disposition data of Longcope, et al. (1985) can be used to estimate that a further 0.64% of the administered dose would be released to sewers as estradiol through the user's urinary excretions.
- (aw) 80% of the mass of testosterone is retained in used transdermal patches (Androderm monograph); of the 20% that is delivered the assumption is made that it demonstrates disposition similar to intravenous testosterone.
- (ax) Since, the PhAC is topically applied it was assumed that the entire mass prescribed of the PhAC is released to sewers as the parent compound.
- (ay) No data was identified for the fecal disposition of Cefixime; hence, an excreted fraction of 100% was used. This is consistent with the fact that Cefixime is minimally metabolized.
- (az) Absorption of topical testosterone was reported to be 10% (Androgel Drug Monograph). Therefore, up to 90% of the dose is expected to enter sewers as the parent compound. Of the 10% that is absorbed, disposition data of injected testosterone (Camacho and Migeon, 1964) suggests that a further 0.7% of the administered dose could be released to sewers as testosterone.
- (ba) Assumes fecal elimination to be similar to that reported for the oral route.
- (bb) 78% of Etonogestrel remains undelivered in used NuvaRings. Of the 22% that is absorbed, specific metabolic data could not be found hence it was assumed that the entire dose of Etonogestrel that is administered via NuvaRing is released unchanged to the sewers.
- (bc) 88% of Ethinyl estradiol remains behind in used NuvaRings. Of the 12% that is absorbed, it was assumed that, based on the data of Reed et al. (1972), 6% is excreted as Ethinyl estradiol or its conjugates.

Table D.1 Notes (continued):

- (bd) Even though drospirenone is extensively metabolised, it was unclear what fraction of administered dose is excreted as conjugated drospirenone; hence, it was conservatively assumed that entire dose of the PhAC is released to sewers as the parent drug.
- (be) Estimated from the fraction of cocaine that is eliminated as benzoylecgonine and the ratio of cocaine to benzoylecgonine typically observed in wastewater influents.

Appendix E: General source models for PhACs that arise from multiple sources

Forty-one PhACs of the evaluation set were established to be released due to one or more sources over and above their medicinal use and/or their endogenous release. Of these, the precursors of ibuprofen, methylphenidate, salbutamol and zopiclone are not used in Canada (Health Canada, 2013). For the remaining 37, general source models were developed by firstly identifying all exogenous licit and illicit sources that could lead to the release of the PhAC to sewers. Subsequently, the fraction of each of the identified sources expected to be excreted as the PhAC were established. The developed source models are summarized in Table E.1 below.

Table E.1 Source model for 37 PhACs that are released due to one or more sources over and above their respective medicinal uses and endogenous releases.

PhAC	Precursor	Dose metabolized to the PhAC ($U_{ex} + F_{ex}$, % Dose)	References
Acyclovir	Valacyclovir	88	de Miranda and Blum, 1983; Soul-Lawton et al., 1995; Vergin et al., 1995
	Acyclovir	100	
5-Aminosalicylic acid ^{(a),(s)}	5-Aminosalicylic acid	38 (oral), 100 (Rectal)	De Vos, 2000; Jacobsen et al., 1991; Bondesen et al., 1986
	Sulfasalazine	14.8-26.5	
Amphetamine ^(b)	Methamphetamine - (illicit)	5-9.5	Khan and Nicell, 2012
	Selegiline	11.5	
	Lisdexamphetamine ^(t)	41.5	
	Amphetamine	34-40	
Cetirizine ^(v)	Cetirizine	60-70	Atarax Drug Monograph; Curran et al., 2004; Wood et al., 1987
	Hydroxyzine	25	
Clofibric Acid	Clofibrate	100	Houin et al., 1975; Sedaghat and Ahrens, 1975
Cortisone	Hydrocortisone (Oral and Injected)	< 1	Fukushima et al., 1960; Peterson et al., 1955; Brouillet and Mattox, 1966; Burstein et al., 1953; Peterson et al., 1957
	Cortisone	0.1-0.3	
Desloratadine	Desloratadine	8.4	Ramanathan et al., 2007a, 2007b
	Loratadine	3.4	
Dexamphetamine	Methamphetamine - (illicit)	5-9.5	Khan and Nicell, 2012
	Lisdexamphetamine ^(t)	41.5	
	Amphetamine	34-40	
Dihydrotestosterone	Testosterone (Oral)	0.1	Peng et al., 2002
Enalaprilat	Enalaprilat	90	Enalaprilat Drug Monograph; UIm et al., 1982
	Enalapril	70	
Estrone	Estradiol	20-30 (Oral);	Adams et al., 1979; Caldwell et al., 2010; Friel et al., 2005; Johnson et al., 1975; Longcope et al., 1985
	Estropipate, esterified estrogen	15	
	Conjugated estrogen	11	

PhAC	Precursor	Dose metabolized to the PhAC ($U_{ex} + F_{ex}$, % Dose)	References
Estradiol	Estradiol	7-10	Adams et al., 1979; Caldwell et al., 2010; Friel et al., 2005; Johnson et al., 1975; Longcope et al., 1985
	Conjugated estrogen	2	
Estriol	Estradiol	4-6	Friel et al., 2005; Longcope et al., 1985 Paulsen, 1965
	Conjugated estrogen	21 (Estimated)	
Escitalopram	Escitalopram	18-20	Dalgaard and Larsen, 1999; Rao, 2007; Sogaard et al., 2005
	Citalopram	25 ^(m)	
Esomeprazole	Esomeprazole	1	Andersson et al., 2001; Cederberg et al., 1989; Lind et al., 1987; Regardh et al., 1990; Regardh et al., 1985
	Omeprazole	< 0.05 ^(m)	
Etonogestrel	Etonogestrel (Vaginal)	100 ^(p)	
	Desogestrel	100 ^(o)	
Fenofibric Acid	Fenofibrate	42.1	Weil et al., 1990
Fluorouracil	Fluorouracil	7-22	Beumer et al., 2006; Heggie et al., 1987; Judson et al., 1999
	Capecitabine	0.54	
Hydrocodone ^(c)	Hydrocodone	42	Cone et al., 1978; Oyler et al., 2000
	Codeine	< 1 (approx.)	
Hydromorphone	Hydromorphone	44	Cone et al., 1977, 1979, 2008
	Hydrocodone	3.5	
	Morphine	<1 (approx.)	
Isosorbide-mononitrate	Isosorbide-mononitrate	20-26	Abshagen, 1992; Down et al., 1974; Wood et al., 1984
	Isosorbide-dinitrate	8-13	
Levofloxacin	Levofloxacin	89-96	Nakashima et al., 1992 Okazaki et al., 1991
	Ofloxacin	40	
Meprobamate	Meprobamate	30	Berger, 1954; NHTSA, 2011
	Carisoprodol ^(d)	4.7	
Methamphetamine ^(e)	Methamphetamine (<i>illicit</i>)	40-43	Khan and Nicell, 2012
	Selegiline	29.7	
Morphine ^(f)	Morphine	77.7	Khan and Nicell, 2011
	Codeine	6	
	Heroin	71	
Nortriptyline	Amitriptyline	2.1	Vandel et al., 1983
Norethindrone	Norethindrone	25-45 (Oral)	Table E.1 Kishimoto et al., 1972
	Ethinodiol	3.6 ^(k) +22 ^(l)	
Oseltamivir carboxylate	Oseltamivir	81-100	EMA, 2011
Oxazepam ^(g)	Clorazepate	6.2 ^(k) +15-19 ^(l)	Abruzzo et al., 1977; Alvan et al., 1977; Arnold, 1975; Chiba et al., 1995; Kimmel and Walkenstein, 1967; Knowles and Ruelius, 1972; Schwartz et al., 1965; Schwarz, 1979; Sonne et al., 1988; Tranxene Drug Monograph
	Chlordiazepoxide ^(u)	2.4-4.5 ^(j)	
	Diazepam	2.8-8.7 ^(k) + 9-10 ^(l)	
	Oxazepam	63.4- 89.4	
	Temazepam	6.8 ^(k) +11.9 ^(l)	
Prednisone	Prednisone	1.5-5	Garg and Jusko, 1994; Frey et al., 1984; Rose et al., 1981
	Prednisolone	2.3	
Prednisolone	Prednisolone	21	Chakraborty et al., 1981; Frey et al., 1984; Shaffer et al., 1983
	Prednisone	12.8	

PhAC	Precursor	Dose metabolized to the PhAC ($U_{ex} + F_{ex}$, % Dose)	References
Phenobarbital	Phenobarbital	25-27	Bernus et al., 1994; Martinez et al., 1990; Tang et al., 1979; Whyte and Dekaban, 1977
	Primidone	2-5	
Phenytoin	Phenytoin	0.7 – 33	Cerebyx Drug Monograph; Glazko, 1987; Kadar et al., 1983
	Fosphenytoin	1-5	
Sulfapyridine	Sulfasalazine	< 25	van Hees et al., 1979
Theophylline	Theophylline	13-20	Beckmann et al., 1987; Bonati et al., 1982; Morimoto et al., 2004
	Caffeine ^(h)	2.9	
Temazepam ⁽ⁱ⁾	Diazepam	6.4-8.8 ^(k) + 9-10 ^(l)	Arnold, 1975; Chiba et al., 1995; Schwartz et al., 1965; Schwarz et al., 1979
	Temazepam	86	
Valproic Acid	Valproic Acid	24.5-25.5	Gugler et al., 1977
	Divalproex	25 ⁽ⁿ⁾	

Table E.1 Notes:

- (a) Balasalazine is also metabolized to 5-Aminosalicylic acid; however, it is currently not used in Canada (Health Canada, 2013).
- (b) Amphetaminil, benzphetamine, clobenzorex, dimethylamphetamine, ethylamphetamine, famprofazone, fenethylline, fenproporex, fencamine, furfenorex, mefenorex, mesocarb and prenylamine are also metabolized to amphetamine (Khan and Nicell, 2012); however, these formulations are currently not used in Canada (Health Canada, 2013)
- (c) Dihydrocodeine is also metabolized to hydrocodone but this particular PhAC is not currently used in Canada (Health Canada, 2013).
- (d) The clinical use of Carisoprodol was discontinued in Canada in 2003 (Health Canada, 2013).
- (e) Benzphetamine, dimethylamphetamine, famprofazone, fencamine and furfenorex are also metabolized to methamphetamine (Khan and Nicell, 2012) but, these formulations are currently not used in Canada (Health Canada, 2013);
- (f) Ethylmorphine, nicomorphine and pholcodine are also metabolized to morphine (Khan and Nicell, 2011) but these formulations are currently not used in Canada (Health Canada, 2013);
- (g) Demoxepam, Prazepam, Halazepam, Nordiazepam, Medazepam, Ketazolam, Oxazolam, Pinazepam and Camazepam are also metabolized to Oxazepam but these formulations are currently not used in Canada (Health Canada, 2013).
- (h) Caffeine consumption for Canadians has been estimated to amount to 210 mg/cap-d (Heckman et al., 2010).
- (i) Medazepam, Camazepam and Ketazolam are also metabolized to Temazepam but these formulations are currently not used in Canada (Health Canada, 2013).
- (j) Fraction eliminated as oxazepam in urine and fecal excretions of dogs (Kimmel and Walkenstein, 1967).
- (k) Fraction eliminated as the PhAC via the urine.
- (l) In absence of specific data, the net fraction of the precursor that is eliminated via the fecal route is conservatively assumed to be fully composed of the parent PhAC.
- (m) Assumes that the disposition of the two enantiomers of the PhAC is similar.
- (n) Since Divalproex is rapidly converted to Valproic Acid in the stomach, it was assumed that the disposition of Divalproex is similar to that of Valproic Acid.
- (o) From the literature identified for the disposition of desogestrel, it was not possible to establish the net fraction of the administered dose that is excreted as unchanged and conjugated etonogestrel; hence, it was conservatively assumed that the entire administered dose of desogestrel was eliminated as Etonogestrel.
- (p) 78% of Etonogestrel remains undelivered in used NuvaRings. Of the 22% that is absorbed specific metabolic data could not be identified hence it was conservatively assumed that the entire dose of Etonogestrel that is administered via NuvaRing is released unchanged to the sewers.

- (r) Norethynodrel and Lynestrenol are also metabolized to Norethindrone but these drugs are currently not used in Canada (Health Canada, 2013).
- (s) Olsalazine is another precursor of 5-Aminosalicylic acid, which is currently available on the Canadian market. However, its consumption data was not available for this analysis. Nevertheless, its contribution to the net loads of 5-Aminosalicylic acid is expected to be of minor importance.
- (t) Was not approved for sale in Canada until 2009.
- (u) The consumption of this precursor was based on the levels reported in INCB (2007).
- (v) Levocetirizine would also be expected to add to the environmental loading of cetirizine; however this drug is currently not used in Canada (Health Canada, 2013).

Appendix F: Endogenous release of PhACs

Fourteen PhACs of the evaluation set were determined to be endogenously excreted. The endogenous release of these is summarized in Table F.1, along with the sources and methods used to estimate them.

Table F.1 Estimated endogenous release of various PhACs.

PhAC	E _{endo} (Endogenous Excretion) (µg/cap·d)	Notes
Acetylcysteine	8800	(a)
Androstenedione	21.6	(h)
Codeine	0.25	(b)
Cortisone	130	(c)
Cortisol (Hydrocortisone)	118	(d)
Dihydrotestosterone	20	(f)
Estrone	14.9	(j)
Estradiol	6.9	(j)
Estriol	90.6	(k)
Levodopa	37.5	(e)
Thyroxine	20.1	(g)
Triiodothyronine	11.9	(f)
Morphine	0.65	(b)
Testosterone	29.4	(i)

Notes:

- (a) Borgstrom et al. (1986)
- (b) Mikus et al. (1994)
- (c) Finken et al. (1999)
- (d) Shackleton (1993); Finken et al., (1999)
- (e) Armando et al. (1991)
- (f) Estimated by adapting the model of Khan and Nicell (2010) to the Canadian context.
- (g) Endogenous thyroxine is primarily eliminated via the fecal route; however, as highlighted by the analysis of Khan and Nicell (2010) and Svanfelt et al. (2010), only limited information has been published thus far on the endogenous fecal disposition of thyroxine. Hence, as a best approximation, the influent load as measured by Svanfelt et al. (2010) was used to estimate the endogenous release of the chemical as follows:

Endogenous release of thyroxine = [Influent load measured by Svanfelt et al. (2010)] – [Consumption of exogenous levothyroxine prescribed in Finland × Fraction of levothyroxine excreted unchanged]

Endogenous release of thyroxine = 21.4 (Svanfelt et al., 2010) – 4.1 (FIMEA, 2011) × 0.3 = **20.1 µg/cap·d**

Table F.1 Notes (continued)

- (h) Estimated by adapting the model of Khan and Nicell (2010) to the Canadian context as shown in the table below. In addition to the 19 µg/cap-d, an additional 13% is estimated to be eliminated via the fecal excretion of users (Khan and Nicell, 2010). Hence, the net endogenous excretion of Androstenedione can be estimated to amount to **21.6 µg/cap-d**.

Population Cohort		f_i	Urinary excretion of Androstenedione ($\mu\text{g}/\text{cap}\cdot\text{d}$)	
			U_i	$U_i\cdot f_i$
Males				
<10	0.06	0	0.0	
10-15	0.03	6.2	0.2	
15-20	0.03	16	0.6	
20-30	0.07	57	3.9	
30-40	0.07	47	3.3	
40--50	0.08	38	3.2	
50-60	0.07	28	1.8	
61+	0.08	20	1.5	
Females				
<10	0.06	0	0.0	
10-15	0.03	2	0.1	
15-20	0.03	5.3	0.2	
20-40	0.13	16.7	2.2	
40--50	0.07	12.2	0.9	
50-60	0.07	9.0	0.7	
61+	0.09	6.3	0.6	
3 rd Trimester	0.01	6.4	<0.1	
Total Urinary Excretion ($\mu\text{g}/\text{cap}\cdot\text{d}$)			19	

Nomenclature: f_i is the fraction of the population that belongs to each cohort i (Statistics Canada, 2006); U_i is the urinary excretion of Androstenedione by cohort i (Khan and Nicell, 2010).

Table F.1 Notes (continued)

- (i) Estimated by adapting the model of Khan and Nicell (2010) to the Canadian context as shown in the following table. In addition to the 26 $\mu\text{g}/\text{cap}\cdot\text{d}$, an additional 13% is estimated to be eliminated via the fecal excretion of users (Khan and Nicell, 2010). Hence, the net endogenous excretion of Testosterone can be estimated to amount to **29.4 $\mu\text{g}/\text{cap}\cdot\text{d}$** .

Population Cohort	f_i	Urinary excretion of Testosterone ($\mu\text{g}/\text{cap}\cdot\text{d}$)	
		U_i	$U_i \cdot f_i$
Males			
0-5 years	0.03	1.4	0.0
5-10 years	0.03	5.6	0.2
10-15 years	0.03	20	0.7
15-30 years	0.10	85	8.8
30-40 years	0.07	66	4.7
40-50 years	0.08	49	4.1
50+ years	0.14	31	4.4
Females			
0-5 years	0.00	0.0	0.1
5-10 years	0.07	0.2	0.2
10-20 years	0.03	0.4	0.4
20-40 years	0.24	0.8	0.8
40+ years	0.11	1.1	1.1
In 3 rd trimester of pregnancy	0.05	0.1	0.1
Total Urinary Excretion ($\mu\text{g}/\text{cap}\cdot\text{d}$)			26

Nomenclature: f_i is the fraction of the population that belongs to each cohort i (Statistics Canada, 2006); U_i is the urinary excretion of Testosterone by cohort i (Khan and Nicell, 2010).

Table F.1 Notes (continued)

(j) Estimated by adapting the model of Johnson and Williams (2004) to the Canadian context as follows:

Population Cohort	f _i	Estrone			Estradiol			
		U _i	F _i	(U _i +F _i)·f _i	U _i	F _i	(U _i +F _i)·f _i	
		(µg/cap·d)			(µg/cap·d)			
Prepubescent boys	0.09 ⁽¹⁾	0.078	Minor	0.007	0.062	Minor	0.005	
Prepubescent girls	0.08 ⁽²⁾	0.078	Minor	0.006	0.062	Minor	0.005	
Men	0.41 ⁽³⁾	3.2	0.4	1.48	1.5	0.6	0.87	
Non-pregnant menstruating women on oral contraceptives	0.05 ⁽⁴⁾	2.9	0.2	0.15	1.1	0.1	0.06	
Non-pregnant menstruating women not on oral contraceptives	0.22 ⁽⁵⁾	8.2	0.5	1.89	4	0.4	0.95	
Pregnant Women	0.01 ⁽⁶⁾	958	96	11.1	259	200	4.85	
Menopausal Women	0.15 ⁽⁷⁾	1.6	0.1	0.26	0.7	0.1	0.12	
Total Excretion (µg/cap·d)				14.9	Total Excretion (µg/cap·d)			
				6.9				

Nomenclature: f_i is the fraction of the population that belongs to each cohort i (Statistics Canada, 2006); U_i and F_i are the net urinary and fecal excretions of estradiol and estrone by cohort i .

U_i and F_i values for all population cohorts with the exception of pre-pubescent children are from Anderson et al. (2012) and Johnson and Williams (2004). Data for pre-pubescent children are from Shi et al. (2010).

Notes:

- (1) Boys less than the age of 13.5 years (Arim et al., 2007).
- (2) Girls less than the average age of menarche of 12.7 years (Al-Sahab et al., 2010).
- (3) Men above the age of 13.5 years, follows from (1).
- (4) Estimated using the data reported by Statistics Canada (2000).
- (5) Estimated from demographic data as follows: [Women between the average age of menarche (i.e., 12.7 (Al-Sahab et al., 2010)) and the average age of menopause (i.e., 51 (Public Health Agency of Canada, 2003))] - [Item (6)] - [item (4)].
- (6) Estimated from the number of pregnancies reported for 2005 (Statistics Canada, 2006) as follows: Number of pregnancies in the year 2005 $\times$ (40/52). This is likely a conservative estimate since it is assumed that all pregnancies are taken to the full term of 40 weeks (Kieler et al., 1995).
- (7) Estimated from the number of Canadian women above the age of 51, which is the average age of menopause (Public Health Agency of Canada, 2003).

Table F.1 Notes (continued)

(k) Estimated as shown in the following table.

Population Cohort	f_i	Estriol		
		U_i	F_i	$(U_i+F_i) \cdot f_i$
		(µg/cap·d)		
Prepubescent boys	0.09	0.21	Minor	0.019
Prepubescent girls	0.08	0.21	Minor	0.017
Men	0.41	5.3	0.5	2.4
Non-pregnant menstruating women on oral contraceptives	0.05	2.3	0.2	0.1
Non-pregnant menstruating women not on oral contraceptives	0.22	8.7	0.74	2.0
Pregnant Women	0.01	7758	354	85.7
Menopausal Women	0.15	1.8	0.13	0.3
		Total Excretion (µg/cap·d)		
				90.6

Nomenclature: f_i is the fraction of the population that belongs to each cohort i (Statistics Canada, 2006); U_i and F_i are the net urinary and fecal excretions of Estriol, respectively.

Notes:

- f_i were estimated using methods and procedures described in item (j). U_i and F_i values for all population cohorts, with the exception of pregnant women, pre-pubescent children and men, were from Anderson et al. (2012). For pregnant women, prepubescent children and men U_i and F_i values were obtained by pooling data reported in the following studies by the number of subjects studied:
- Men - Adlercreutz and Jarvenpaa, (1982); Dao et al., (1973); Fotsis and Adlercreutz, (1987); Hamalainen et al., (1987); Hill et al., (1979); Morreal et al., (1972); Xiao and McCalley, (2000)
- Pregnant Women- Adlercreutz et al., (1976); Berg and Kuss, (1992)
- Prepubescent Children- Shi et al., (2010)

Appendix G: Consumption/demand for illicit drugs in Canada

Cocaine, heroin, MDMA (3, 4-methylenedioxy-N-methylamphetamine), methamphetamine and cannabis` active ingredient THC (tetrahydrocannabinol) are used illicitly within Canada. The consumption estimates for these drugs as well as the sources used to derive them are summarized in Table G.1. In cases where a range was available for the demand of an illicit drug, the upper end of the range was used to ensure our PEC estimate remain conservative.

Table G.1 Demand estimates for various illicit drugs by the Canadian population.

PhAC	C _{IDU} -Illicit Demand (kg/yr)	Notes
Cocaine	19,800-39,600	(a)
Heroin	800	(b)
MDMA	1,643-2,054	(c)
Methamphetamine	1,201-1,501	(d)
Tetrahydrocannabinol	18,340-85,340	(e)

Notes:

- (a) Kilmer and Pacula's (2009) estimate for the consumption of pure cocaine in Canada in 2005.
- (b) Kilmer and Pacula's (2009) estimate for the consumption of pure heroin in Canada in 2005.
- (c) Bouchard et al. (2012) estimate for the consumption of pure MDMA in Canada in 2009.
- (d) Multiplication of the estimated number of methamphetamine users in Canada in 2009 (Bouchard et al., 2012) by the estimated average per capita consumption of 19.3 grams of pure methamphetamine as per UNODC (2010).
- (e) Multiplication of Kilmer and Pacula's (2009) estimate for the consumption of cannabis in Canada in 2005 by the average THC content of cannabis seized in Canada (UNODC, 2009).

Appendix H: Appendix: Average Production of Wastewater on a Daily Per Capita Basis in Canadian Municipalities

The average daily per capita production of wastewater for 922 municipalities was reported in Environment Canada's MWWS database (Environment Canada, 2010). The analysis of the available data therein (Figure H.1 and H.2) suggests that the median daily wastewater production by Canadian municipalities is 504 L/cap·d.

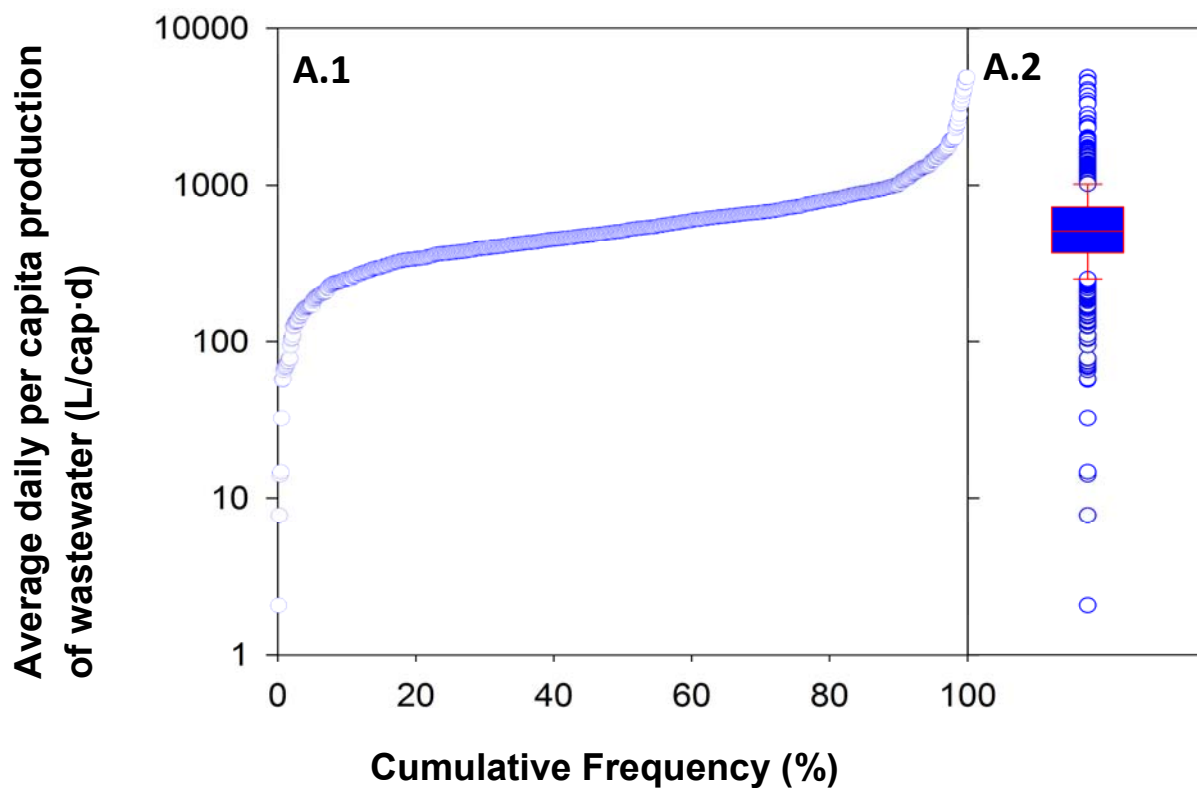


Figure Daily per capita production of wastewater by 922 Canadian municipalities shown as a cumulative frequency (**H.1**) and a box plot (**H.2**).

Appendix I: Removal of PhACs in Secondary WWTPs

In general, when available, preference was given to actual data reported in literature for the removal of selected PhACs in secondary treatment plants (R_{1+2}) over modelled values. A literature survey revealed that for the selected evaluation set of 335 PHACs, removal levels for 166 were reported in literature for one or more full-scale secondary treatment plants. For the remainder, the removal levels were estimated using the SimpleTreat model (RIVM, 2003). The important inputs to the model were established using the following methods/models:

- **Vapour pressure:** The modified grain method as embedded in USEPA's EPI suite program (2011) was used.
- **Degradation constant:** Where specifically not available, the degradation constants of a PhAC was conservatively estimated using the ECHA (2010) guidelines for interpreting results obtained from standardized biodegradability tests (e.g., OECD 301, 302). Further, for PhACs for which the results from such tests were not available, ready biodegradability of the chemical was estimated using the method of Boethling et al. (2004).
- **Sludge sorption coefficients (K_d):** Preference was given to actual measured data for K_d . In cases, where only experimentally-estimated K_{oc} (i.e., organic carbon-water partition coefficient) values were available instead, the respective K_d values were estimated using the following equation:

$$K_d = f_{oc} \cdot K_{oc} \quad (I.1)$$

where: f_{oc} is fraction of sludge that is organic carbon, for which typical values of 0.30 and 0.37 for primary and secondary sludge have been suggested, respectively (Struijs et al., 1991).

In cases, where experimental measured data for the PhACs' K_{oc} and K_d were not available, the following methods/models were used to estimate the respective K_{oc} values:

- **Neutrals** - For neutral PhACs the MCI (Molecular Connectivity Index) methodology (Meylan et al., 1992) was used.

- **Single Acids** - For single acids, the QSPR (quantitative structure–property relationships) of Franco and co-workers (Franco et al., 2009; Franco and Trapp, 2008) was used.
- **Single Bases** - For single bases, the preliminary QSPR of Franco and Gouin (2011) was used to estimate the respective K_{oc} values.
- **All other acid-base characteristics**- Since only QSPRs derived from limited data (i.e., $n = 3$) are currently available for PhACs with such acid-base characteristics as double acidic, double basic and zwitterionic (e.g., Cunningham et al., 2008), no attempt was made to estimate the sorption of PhACs with such acid base characteristics. Hence, for such PhACs it was conservatively assumed that they are not removed in WWTPs via sorption.

The specific values used for estimating the removal of PhACs in secondary treatment plants as well as the rationale behind them are summarized in Table I.1.

Table I.1 Rationale behind and the specific values used when modelling the removal (R_{1+2}) of selected PhACs in secondary wastewater treatment plants.

PhAC	Rationale	R_{1+2} (%)
5-Aminosalicylic acid	Observed removal of 85% (1)	85
Acarbose	Inherently biodegradable (Bayer, 2011). The SimpleTreat model (RIVM, 2003) was run with the following input data: $k_{deg} = 0.1 \text{ hr}^{-1}$ (default value for inherently biodegradable chemicals as per ECHA(2010)) and a predicted vapour pressure of $6.97 \times 10^{-30} \text{ Pa}$ (US EPA, 2011). Since the sorption of the PhAC could not be reliably modeled it was neglected. Nevertheless, the log D of the PhAC is such that minimal absorption of the PhAC onto sludge is expected.	41
Acebutolol	On average, 55% of the PhAC is removed in WWTPs (2,21,36)	55
Acetaminophen	Removals of 97 to 100 % have been observed (2,4,5,7,23)	98
Acetylcysteine	Predicted to be readily biodegradable (Boethling et al., 2004). Since the sorption of the PhAC could not be reliably modeled, it was neglected. The SimpleTreat model (RIVM, 2003) was run with the following data: $k_{deg} = 1 \text{ hr}^{-1}$ (default value for readily biodegradable chemicals as per ECHA (2010)) and a predicted vapour pressure of $1.46 \times 10^{-3} \text{ Pa}$ (US EPA, 2011).	87
Acetylsalicylic acid	On average, 92% of the PhAC is removed in WWTPs (2,9)	92
Acyclovir	On average, 94% of the PhAC is removed in WWTPs (14,30)	94
Alendronate	Not readily biodegradable (US FDA, 2002a). However, Alendronate is expected to bind to divalent ions upon release. Nevertheless, it was conservatively assumed that the PhAC is not removed in WWTPs.	0
Allopurinol	On average, >90% of the PhAC is removed in WWTPs (47)	90
Alprazolam	On average, 38% of the PhAC is removed in WWTPs (5)	38
Amantadine	On average, 30% of the PhAC is removed in WWTPs (28)	30
Amiloride	On average, 33% of the PhAC is removed in WWTPs (23)	33
Amiodarone	Not readily biodegradable (Sanofi, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $5.31 \times 10^{-1} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin for single bases (Franco and Gouin, 2011)) of 4.64 and a $k_{deg} = 0 \text{ hr}^{-1}$.	79
Amitriptyline	Highly variable removal rates varying between -97% and 98 for this PhAC have been reported (1, 5) . Hence, it was conservatively assumed that this PhAC is not removed in WWTPs.	0
Amlodipine	On average, 44% of the PhAC is removed in WWTPs (23)	44
Amoxicillin	On average, 85% of the PhAC is removed in WWTPs (31)	85
Amphetamine	On average, 93% of the PhAC is removed in WWTPs (15,27,42)	93
Amphotericin B	Predicted to be not readily biodegradable (Boethling et al., 2004). Sorption for this PhAC could not be modeled and, hence, was neglected. The SimpleTreat model (RIVM, 2003) was run with the following input data: $k_{deg} = 0 \text{ hr}^{-1}$ and a predicted vapour pressure of $7.21 \times 10^{-39} \text{ Pa}$ (US EPA, 2011).	0
Ampicillin	On average, 75% of the PhAC is removed in WWTPs (22,37)	75
Anastrozole	Not readily biodegradable (AstraZeneca ERAD, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.58 \times 10^{-6} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (mean value of the values reported in AstraZeneca ERAD (2011a) for soils) of 2.68 and a $k_{deg} = 0 \text{ hr}^{-1}$.	6
Androstenedione	On average, 97% of the PhAC is removed in WWTPs (44)	97
Atenolol	On average, 40% removal of the PhAC is reported (2,4,5,7,18-21,36)	40
Atorvastatin	On average, 70% removal of the PhAC is reported (2,5,7,26)	70
Atropine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	4

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 5.98×10^{-6} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin for single bases (Franco and Gouin, 2011)) of 2.53 and a $k_{deg} = 0 \text{ hr}^{-1}$.	
Azathioprine	Neither readily nor inherently biodegradable (GSK, 2006b). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.2×10^{-10} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.10 and a $k_{deg} = 0 \text{ hr}^{-1}$.	13
Azithromycin	Since generation of this PhAC has been reported in more than one study (5,23) it was conservatively assumed to be not removed in WWTPs.	0
Baclofen	Not readily biodegradable (Novartis, 2010). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.7×10^{-6} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Beclometasone	Observed removal rates of > 29% (5)	29
Benserazide	Inherently biodegradable (Roche, 2010a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.8×10^{-11} Pa (US EPA, 2011) and a $k_{deg} = 0.1 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	41
Benzatropine	Not readily biodegradable (Roche, 2005a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.2×10^{-5} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.48 and a $k_{deg} = 0.01 \text{ hr}^{-1}$ (based on hydrolysis data reported in Roche (2005)).	31
Benzydamine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.8×10^{-6} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.33 and a $k_{deg} = 0 \text{ hr}^{-1}$.	21
Betamethasone	Neither readily nor inherently biodegradable (GSK, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.75×10^{-12} Pa (US EPA, 2011), K _d (measured (Cunningham et al., 2009)) of 36 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$.	1.4
Betaxolol	On average, 90% removal of the PhAC is reported (3,10)	90
Bezafibrate	On average, 73% removal of the PhAC is reported (2,4,7)	73
Bicalutamide	Neither readily nor inherently biodegradable (AstraZeneca ERAD, 2011b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.01×10^{-12} Pa (US EPA, 2011), K _d (measured (AstraZeneca ERAD, 2011b)) of 140 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$.	5
Bisoprolol	On average, 37% removal of the PhAC is reported (3,5,10,36)	37
Bleomycin	No data available. Assumed to be not removed in WWTPs.	0
Bromazepam	Neither readily nor inherently biodegradable (Roche, 2009). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.53×10^{-7} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Bromocriptine	On average, >65% removal of the PhAC is reported (5)	65
Budesonide	Not readily biodegradable (AstraZeneca ERAD, 2011c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.17×10^{-12} Pa (US EPA, 2011), K _d (Barron et al., 2009) of 449 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$.	15

PhAC	Rationale	R ₁₊₂ (%)
Buprenorphine	On average, 87% removal of the PhAC is reported (5)	87
Bupropion	On average, 24% removal of the PhAC is reported (5)	24
Buserelin	Readily biodegradable (European Pharmacopoeia, 2008). Since the sorption of the PhAC could not be reliably modeled, it was neglected. The SimpleTreat model (RIVM, 2003) was run with the following input data: $k_{deg} = 1 \text{ hr}^{-1}$ (ECHA (2010) default value for readily biodegradable chemicals) and a predicted vapour pressure of 0 Pa (US EPA, 2011).	87
Butalbital	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $3.42 \times 10^{-8} \text{ Pa}$ (US EPA, 2011) Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.07 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Candesartan	Not readily biodegradable (AstraZeneca ERAD, 2011d). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.39 \times 10^{-18} \text{ Pa}$ (US EPA, 2011), K_d (measured (AstraZeneca ERAD, 2011d)) of 17 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Capecitabine	Inherently biodegradable (Roche, 2010d). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.63 \times 10^{-10} \text{ Pa}$ (US EPA, 2011), K_d (measured (Roche, 2010d)) of 272 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$ (not fulfilling specific criteria of ECHA (2010)).	10
Captopril	Not readily biodegradable (BPCRS, 2010a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $9.67 \times 10^{-4} \text{ Pa}$ (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Carbamazepine	Since generation of the PhAC is often reported (5,6,23), it was assumed that the PhAC is not removed in WWTPs.	0
Carbidopa	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.65 \times 10^{-7} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Carboplatin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.77 \times 10^{-9} \text{ Pa}$ (US EPA, 2011), K_d (measured) of 331 to 2691 L/kg (Lenz et al., 2007) and a $k_{deg} = 0 \text{ hr}^{-1}$.	11-49
Carmustine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $3.91 \times 10^{-2} \text{ Pa}$ (US EPA, 2011) Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.85 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Carvedilol	Removal rates of 56 % have been reported (23)	56
Cefaclor	Removal rates of 96 % have been reported (2)	96
Cefadroxil	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.42 \times 10^{-15} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Cefazolin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.00 \times 10^{-16} \text{ Pa}$ (US EPA, 2011), $K_d \approx 0 \text{ L/kg}$ (Cunningham et al., 2009) and a k_{deg}	0

PhAC	Rationale	R ₁₊₂ (%)
	= 0 hr ⁻¹ .	
Cefixime	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.34x10 ⁻¹⁶ Pa (US EPA, 2011) and a k _{deg} = 0 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Cefprozil	Inherently biodegradable (BMS, 2007). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.60x10 ⁻¹⁶ Pa (US EPA, 2011), and a k _{deg} = 0.1 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	41
Ceftazidime	Neither readily nor inherently biodegradable (GSK, 2011b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.09x10 ⁻¹⁹ Pa (US EPA, 2011), K _d ≈ 0 L/kg (Cunningham et al., 2009) and a k _{deg} = 0 hr ⁻¹ .	0
Ceftriaxone	Neither readily nor inherently biodegradable (Farmaplus, 2011). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.61x10 ⁻²² Pa (US EPA, 2011) and a k _{deg} = 0 hr ⁻¹ . Since sorption of the PhAC could not be reliably modeled it was ignored.	0
Cefuroxime	Inherently biodegradable (GSK, 2007). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.29x10 ⁻¹³ Pa (US EPA, 2011), K _d of 7.9 L/kg (Cunningham et al., 2009) and a k _{deg} = 0.1 hr ⁻¹ .	41
Celecoxib	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.59x10 ⁻⁷ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.5 and a k _{deg} = 0 hr ⁻¹ .	4
Cephalexin	On average, 81% of the PhAC is removed in WWTPs (2,22)	81
Cetirizine	Since generation of the PhAC in WWTPs has been reported (23) it was assumed that the PhAC is not removed by WWTPs.	0
Chloral hydrate	Not readily biodegradable (Merck, 2006a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1230 Pa (US EPA, 2011), Log K _{oc} (estimated using the MCI methodology (US EPA, 2011)) of 0 and a k _{deg} = 0 hr ⁻¹ .	4.2
Chloramphenicol	On average, 93% of the PhAC is removed (1,2)	93
Chlorhexidine	On average, 0% of the PhAC is removed (45)	0
Chloroquine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.66x10 ⁻⁷ Pa (US EPA, 2011), and a k _{deg} = 0 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Chlorpromazine	On average, >34% removal of the PhAC is reported (5)	34
Cimetidine	Removals of 52% have been reported (1,2)	52
Ciprofloxacin	On average, 70% removal of the PhAC is reported (2,3,5,6,7,21)	70
Cisplatin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.42x10 ⁻¹⁸ Pa (US EPA, 2011), K _d (measured) of 1122 to 21379 L/kg (Lenz et al., 2007) and a k _{deg} = 0 hr ⁻¹ .	30-82
Citalopram	Since net generation of this PhAC is often reported (5,6,23) , it was assumed that the PhAC is not removed by WWTPs.	0

PhAC	Rationale	R ₁₊₂ (%)
Clarithromycin	On average, 26% of the PhAC is removed in WWTPs (2,5,31)	26
Clavulanic acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.27×10^{-7} Pa (US EPA, 2011), K_d (measured) of ≈ 0 L/kg (Cunningham et al., 2009) and a $k_{deg} = 0.031 \text{ hr}^{-1}$ (Cunningham et al., 2009).	18
Clindamycin	Since net generation of this PhAC is often reported (5,21) it was assumed that the PhAC is not removed by WWTPs.	0
Clodronic acid	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.66×10^{-10} Pa (US EPA, 2011), K_d of 0 L/kg (Roche, 2004b) and a $k_{deg} = 0 \text{ hr}^{-1}$.	0
Clofibrate	Not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.38×10^{-1} Pa (US EPA, 2011) Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.51 and a $k_{deg} = 0 \text{ hr}^{-1}$.	4
Clofibric acid	On average, 50% of the PhAC is removed in WWTPs (3)	50
Clonazepam	Neither readily nor inherently biodegradable (Roche, 2005b). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 9.76×10^{-9} Pa (US EPA, 2011), K_d for sludge as reported by Hörsing et al. (2011) and a $k_{deg} = 0 \text{ hr}^{-1}$.	18
Clonidine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.49×10^{-3} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.32 and a $k_{deg} = 0 \text{ hr}^{-1}$.	20
Clopidogrel	Not readily biodegradable (US FDA, 2002b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.86×10^{-5} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.62 and a $k_{deg} = 0 \text{ hr}^{-1}$.	33
Clorazepate	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.49×10^{-11} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.77 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Clotrimazole	On average, 30% of the PhAC is removed in WWTPs (5)	30
Clozapine	On average, 39% of this PhAC is removed in WWTPs (23)	39
Cocaine	On average, 96% of this PhAC is removed in WWTPs (15,16)	96
Codeine	On average, 55% of the PhAC is removed in WWTPs (1,2,5,10,16,23,25)	55
Cortisone	On average, 99% of the PhAC is removed in WWTPs (8)	99
Cromolyn	On average, 30% of the PhAC is removed in WWTPs (3)	30
Cyclophosphamide	On average, 46% of the PhAC is removed in WWTPs (23)	46
Cyproterone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.5×10^{-8} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.35 and a $k_{deg} = 0 \text{ hr}^{-1}$.	22
Cytarabine	Inherently biodegradable (Kummerer and Al-Ahmad, 1997). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.17×10^{-9} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 1.0 and a $k_{deg} = 0.1 \text{ hr}^{-1}$.	41
Dactinomycin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	0

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 0 Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	
Daunorubicin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.27 \times 10^{-18} \text{ Pa}$ (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Desloratadine	On average, 15% of the PhAC is removed in WWTPs (5)	15
Desogestrel	On average, 77% of the PhAC is removed in WWTPs (49)	77
Dexamethasone	On average, 99% of the PhAC is removed in WWTPs (8)	99
Dextropropoxyphene	On average, 0% of the PhAC is removed in WWTPs (3)	0
Diphenoxylate	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.84 \times 10^{-10} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 4.14 and a $k_{deg} = 0 \text{ hr}^{-1}$.	60
Dihydrotestosterone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.17 \times 10^{-9} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.34 and a $k_{deg} = 0 \text{ hr}^{-1}$.	21
Diatrizoate	On average, 0% of the PhAC is removed in WWTPs (3)	0
Diazepam	On average, 0% of the PhAC can be approximated to be removed in WWTPs (38)	0
Diclofenac	On average, 42% of the PhAC is removed in WWTPs (2,3)	42
Didanosine	Readily biodegradable (BMS, 2009). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.08 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), and a $k_{deg} = 1 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	87
Digoxin	Inherently biodegradable (GSK, 2008a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $8.30 \times 10^{-27} \text{ Pa}$ (US EPA, 2011), K_d (measured (Cunningham et al., 2009)) of 60 L/kg and a $k_{deg} = 0.1 \text{ hr}^{-1}$.	42
Diltiazem	On average, 36% of the PhAC is removed in WWTPs (1,2,12,13)	36
Dipyridamole	On average, >99% of the PhAC is removed in WWTPs (5)	99
Disulfiram	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $8.8 \times 10^{-4} \text{ Pa}$ (US EPA, 2011) Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.91 and a $k_{deg} = 0 \text{ hr}^{-1}$.	48
Docusate	Inherently biodegradable (Carlsson et al., 2006). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $1.63 \times 10^{-12} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0.1 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	41
Domperidone	On average, 32% of the PhAC is removed in WWTPs (17)	32
Doxepin	On average, 0% of the PhAC is removed in WWTPs (25)	0
Doxorubicin	Removal between 40 to 90% can be expected (47)	40
Doxycycline	On average, 0% of the PhAC is removed in WWTPs (3)	0
Drospirenone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.98 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral	83

PhAC	Rationale	R ₁₊₂ (%)
	chemicals (US EPA, 2011)) of 4.89 and a $k_{deg} = 0 \text{ hr}^{-1}$.	
Enalapril	On average, 87% of the PhAC is removed in WWTPs (3,7,23,31)	87
Enalaprilat	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.4 \times 10^{-10} \text{ Pa}$ (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Epirubicin	Expected to demonstrate high removal via adsorption onto sludge. However, since specific data for its removal has not been reported, it was assumed to be not removed in WWTPs.	0
Eprosartan	On average, 46% of the PhAC is removed in WWTPs (5)	46
Erythromycin	On average, 31% of Erythromycin-H2O is removed in WWTPs (2)	31
Escitalopram	Removal assumed to be similar to that of citalopram due to similarity in structure.	0
Esomeprazole	Not readily biodegradable (US FDA, 2007a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.55 \times 10^{-9} \text{ Pa}$ (US EPA, 2011), $K_d = 48 \text{ L/kg}$ (AstraZeneca ERAD, 2011e) and a $k_{deg} = 0 \text{ hr}^{-1}$.	2
Estradiol	On average, 85% of the PhAC is removed in WWTPs (24)	85
Estriol	On average, 97% of the PhAC is removed in WWTPs (24)	97
Estrone	On average, 67% of the PhAC is removed in WWTPs (24)	67
Ethacrynic acid	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $8.2 \times 10^{-5} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.85 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Ethambutol	Not readily biodegradable (Vaňková and Tuhkanen, 2010). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000236 Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Ethinylestradiol	On average, 84% of the PhAC is removed in WWTPs (24)	84
Ethinodiol	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $3.24 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.43 and a $k_{deg} = 0 \text{ hr}^{-1}$.	25
Etidronic acid	Neither readily nor inherently biodegradable (HERA, 2004). On average, 50 to 90% of the PhAC is removed in WWTPs (Warner Chilcott, 2011).	70
Etodolac	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $2.7 \times 10^{-6} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Etonogestrel	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.68 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 4.124 and a $k_{deg} = 0 \text{ hr}^{-1}$.	59
Etoposide	Readily biodegradable (unclear if 10 d window criterion is met) (BMS, 2008). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $1.2 \times 10^{-19} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.26 and a $k_{deg} = 0.3 \text{ hr}^{-1}$.	67

PhAC	Rationale	R ₁₊₂ (%)
Exemestane	Not readily biodegradable (Ericson, 2010). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.000147 Pa (US EPA, 2011), K _{oc} of 2285 L/kg (Ericson, 2010) and a k _{deg} = 1.8 hr ⁻¹ (Ericsson, 2010).	94
Famciclovir	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.5x10 ⁻⁷ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.78 and a k _{deg} = 0 hr ⁻¹ .	7
Famotidine	On average, 51% of the PhAC is removed in WWTPs (4,7)	51
Felodipine	On average, -2 % of the PhAC is removed in WWTPs (6)	0
Fenofibrate	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.27x10 ⁻⁵ Pa (US EPA, 2011), K _{oc} (using the MCI methodology for neutral chemicals (USEPA, 2011)) of 3862 and a k _{deg} = 0 hr ⁻¹ .	32
Fenofibric Acid	On average, 70% of the PhAC is removed in WWTPs (4,7)	70
Fenoprofen	On average, 85% of the PhAC is removed in WWTPs (9)	85
Fenoterol	Not readily biodegradable (Boehringer Ingelheim, 2010). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.26x10 ⁻⁹ Pa (US EPA, 2011), and a k _{deg} = 0 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Fentanyl	Generation of this PhAC is consistently reported in WWTPs (5), hence it was assumed that it is not removed in WWTPs.	0
Finasteride	Generation of this PhAC has been reported in a number of WWTPs (5), hence it was assumed that it is not removed in WWTPs.	0
Fluconazole	On average, 33% of the PhAC is removed in WWTPs (5)	33
Fluocinonide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.44x10 ⁻¹² Pa (US EPA, 2011), K _{oc} (using the MCI methodology for neutral chemicals (USEPA, 2011)) of 244 and a k _{deg} = 0 hr ⁻¹ .	3
Fluorouracil	Estimated by Straub (2010) using the SimpleTreat model.	41
Fluoxetine	On average, 13% of the PhAC is removed in WWTPs (5)	13
Fluphenazine	On average, 84% of the PhAC is removed in WWTPs (5)	84
Flurazepam	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.05x10 ⁻⁶ Pa (US EPA, 2011), and a k _{deg} = 0 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Flutamide	Not readily biodegradable (Schering Plough, 2009b). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.00015 Pa (US EPA, 2011), K _d for sludge as reported by Hörsing et al. (2011) and a k _{deg} = 0 hr ⁻¹ .	34
Fluticasone	Not readily biodegradable (GSK, 2001a). SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.93x10 ⁻¹¹ Pa (US EPA, 2011), K _d (measured-Cunningham et al., 2009) of 1995 L/kg and a k _{deg} = 0 hr ⁻¹ .	42
Fluvoxamine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.55x10 ⁻³ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.18 and a k _{deg} = 0 hr ⁻¹ .	15

PhAC	Rationale	R ₁₊₂ (%)
Formoterol	Not readily biodegradable (AstraZeneca -fass, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.61×10^{-12} Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Fosfomycin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00221 Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Fosphenytoin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.07×10^{-9} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Fulvestrant	On average, 72% of the PhAC is removed in WWTPs (23)	72
Furosemide	On average, 37% of the PhAC is removed in WWTPs (7,23,31)	37
Gabapentin	On average, 93% of the PhAC is removed in WWTPs (1,3,5)	93
Gemfibrozil	On average, 70% of the PhAC is removed in WWTPs (1,3,5)	70
Gentamicin	Neither readily nor inherently biodegradable (Roche, 2010b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.33×10^{-11} Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was ignored.	0
Gliclazide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.65×10^{-7} Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Glyburide	Since generation of this PhAC has been reported in more than one study (3,23), it was assumed that it is not removed in WWTPs.	0
Goserelin	Readily biodegradable (AstraZeneca ERAD, 2011f). Expected to rapidly biodegrade.	87
Haloperidol	On average, 28% of the PhAC is removed in WWTPs (5)	28
Heroin	On average, 72% of the PhAC is removed in WWTPs (43)	72
Hydrochlorothiazide	High variable removal rates varying from -116 (23) to 34% (31) have been reported. It is conservatively assumed that the PhAC is not removed in WWTPs.	0
Hydrocodone	On average, 89% of the PhAC is removed in WWTPs (3,13)	89
Hydrocortisone	On average, 95% of the PhAC is removed in WWTPs (8,23)	98
Hydromorphone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.56×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.82 and a $k_{deg} = 0 \text{ hr}^{-1}$.	8
Hydroxychloroquine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.32×10^{-7} Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Hydroxyzine	On average, 50% of the PhAC is removed in WWTPs (5)	50
Ibuprofen	On average, 89% of the PhAC is removed in WWTPs (2,4,5-7,23)	89
Idarubicin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	0

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 4.04×10^{-19} Pa (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	
Ifosfamide	On average, 0% of the PhAC is removed in WWTPs (40)	0
Imipramine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.5×10^{-5} Pa (US EPA, 2011), Log K _{oc} 3.99 (Sundstol, 2010) and a $k_{deg} = 0 \text{ hr}^{-1}$.	53
Indomethacin	On average, 70% of the PhAC is removed in WWTPs (2,4)	70
Ipratropium	Not readily biodegradable (Boehringer Ingelheim, 2011). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.23×10^{-14} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Irbesartan	On average, 36% of the PhAC is removed in WWTPs (5)	36
Isoniazid	Not readily biodegradable (Vaňková and Tuhkanen, 2010). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00162 Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (which isoniazid is at circa neutral pH values (US EPA, 2011)) of 1 and a $k_{deg} = 0 \text{ hr}^{-1}$.	0.1
Isosorbide-5-mononitrate	On average, 53% of the PhAC is removed in WWTPs (23)	53
Isosorbide-dinitrate	Readily biodegradable (Kummerer, 2008). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.02×10^{-12} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals) of 1.3 and a $k_{deg} = 1 \text{ hr}^{-1}$.	87
Ketamine	On average, 89% of the PhAC is removed in WWTPs (42)	89
Ketoconazole	On average, 80% of the PhAC is removed in WWTPs (5,17,23)	80
Ketoprofen	On average, 64% of the PhAC is removed in WWTPs (2,4,5,7,23)	64
Labetalol	On average, 7% of the PhAC is removed in WWTPs (36)	7
Lamotrigine	Neither readily nor inherently biodegradable (GSK, 2011c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.25×10^{-6} Pa (US EPA, 2011), K _d (measured (Cunningham et al., 2009)) of 14.1 L/kg and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Lansoprazole	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.23×10^{-9} Pa (US EPA, 2011). Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Letrozole	Not readily biodegradable (Novartis, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.08×10^{-7} Pa (US EPA, 2011), an estimated Log K _{oc} of 3.4 using the QSPR of ECETOC (2014) and a $k_{deg} = 0 \text{ hr}^{-1}$.	24
Leuprolide	The compound is a peptide and is expected to degrade easily. Therefore, assumed to be readily biodegradable.	87
Levobunolol	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.93×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.78 and a $k_{deg} = 0 \text{ hr}^{-1}$.	7
Levodopa	Readily biodegradable (Roche, 2010c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following	68

PhAC	Rationale	R ₁₊₂ (%)
	input data: predicted vapour pressure of 3.41×10^{-8} Pa (US EPA, 2011) and a $k_{deg} = 0.3 \text{ hr}^{-1}$ (Since it is unclear if the window for the readily biodegradable chemicals is met). Since the sorption of the PhAC could not be reliably modeled, it was neglected.	
Levofloxacin	On average, 42% of the PhAC is removed in WWTPs (35)	42
Levothyroxine	On average, 66% of the PhAC is removed in WWTPs (34)	66
Lidocaine	Not readily biodegradable (AstraZeneca-fass, 2011b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.0009 Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Liothyronine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.75×10^{-13} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Lisinopril	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.27×10^{-13} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Lorazepam	On average, 0% of the PhAC is removed in WWTPs (41)	0
Loratadine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.2×10^{-6} Pa (US EPA, 2011) and a measured K_d data of Radjenovic et al. (2009).	49
Losartan	On average, 51% of the PhAC is removed in WWTPs (23)	51
Loxapine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.41×10^{-5} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
MDMA	On average, 58% of the PhAC is removed in WWTPs (15, 29, 42)	58
Mefenamic acid	On average, 39% of the PhAC is removed in WWTPs (2,4)	39
Melphalan	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.05×10^{-8} Pa (US EPA, 2011), K_d (measured (Cunningham et al. (2009)) of 0.2 L/kg and a $k_{deg} = 0.14 \text{ hr}^{-1}$ (hydrolysis half-life (GSK, 2006c)).	49
Meprobamate	On average, 10% of the PhAC is removed in WWTPs (3)	10
Metformin	On average, 65% of the PhAC is removed in WWTPs (5,6)	65
Methadone	On average, 37% of the PhAC is removed in WWTPs (16)	37
Methamphetamine	On average, 40% of the PhAC is removed in WWTPs (15,27,29)	40
Methotrexate	Not readily biodegradable (Henschel et al., 1997). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.78×10^{-17} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Methotrimeprazine	Not readily biodegradable (Sanofi, 2011c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.23×10^{-5} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.76 and a $k_{deg} = 0 \text{ hr}^{-1}$.	41
Methyldopa	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	0

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 9.07×10^{-9} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	
Methylphenidate	Not readily biodegradable (Novartis, 2010c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00786 Pa (US EPA, 2011) Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.89 and a $k_{deg} = 0 \text{ hr}^{-1}$.	8.8
Methylprednisolone SS (Acid)	On average, 100% of the PhAC is removed in WWTPs (8)	100
Metoprolol	On average, 25% of the PhAC is removed in WWTPs (1-5,18-21,23,36)	25
Metronidazole	On average, 42% of the PhAC is removed in WWTPs (1, 23)	42
Miconazole	On average, 57% of the PhAC is removed in WWTPs (5, 17)	57
Midazolam	Inherently biodegradable (Roche, 2011a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.83×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.99 and a $k_{deg} = 0.1 \text{ hr}^{-1}$.	68
Minocycline	On average, 100% of the PhAC is removed in WWTPs (3)	100
Misoprostol	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 6.05×10^{-10} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.2 and a $k_{deg} = 0 \text{ hr}^{-1}$.	2
Mitomycin C	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.93×10^{-9} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Mitotane	Expected to be not readily biodegradable (BMS, 2010). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00225 Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 5.08 and a $k_{deg} = 0 \text{ hr}^{-1}$.	87
Mometasone Furoate	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.66×10^{-13} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 4.30 and a $k_{deg} = 0 \text{ hr}^{-1}$.	67
Mometasone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.46×10^{-11} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.464 and a $k_{deg} = 0 \text{ hr}^{-1}$.	4
Morphine	On average, 88% of the PhAC is removed in WWTPs (10,15,16,29)	88
Mupirocin	Neither readily nor inherently biodegradable (GSK, 2006d). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 2.07×10^{-16} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.95 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Nabumetone	Inherently biodegradable (GSK, 2004a). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00269 Pa (US EPA, 2011), K_d (measured (Cunningham et al., 2009)) of 42 L/kg and a $k_{deg} = 0.0014 \text{ hr}^{-1}$ (Cunningham et al., 2009).	3
Nadolol	On average, 45% of the PhAC is removed in WWTPs (7,36)	45

PhAC	Rationale	R ₁₊₂ (%)
Naloxone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.67×10^{-9} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Naltrexone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.26×10^{-9} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Naproxen	On average, 72% of the PhAC is removed in WWTPs (2,3)	72
Neomycin	Predicted to be readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.14×10^{-26} Pa (US EPA, 2011) and a $k_{deg} = 1 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	87
Nifedipine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.5×10^{-6} Pa (US EPA, 2011), K_d of 27 L/kg (Barron et al., 2009) and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Nilutamide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.84×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.11 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1.6
Nimodipine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.8×10^{-8} Pa (US EPA, 2011), an estimated Log K_{oc} of 4.0 using the QSPR of ECETOC (2014) and a $k_{deg} = 0 \text{ hr}^{-1}$.	53
Nitrazepam	Neither readily nor inherently biodegradable (Roche, 2011c). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 4.1×10^{-8} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals- which Nitrazepam is at circa neutral pH values (US EPA, 2011)) of 3.85 and a $k_{deg} = 0 \text{ hr}^{-1}$.	45
Nizatidine	Not readily biodegradable (Eli Lilly, 2000). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.28×10^{-6} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Nitrofurantoin	Not readily biodegradable (Meda, 2011). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.05×10^{-9} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.5 and a $k_{deg} = 0 \text{ hr}^{-1}$.	0.4
Norfloxacin	On average, 64% of the PhAC is removed in WWTPs (3,7)	64
Norgestimate	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.49×10^{-9} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 6.079 and a $k_{deg} = 0 \text{ hr}^{-1}$.	91
Norethindrone	On average, 100% of the PhAC is removed in WWTPs (50)	100
Nortriptyline	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	19

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 0.000294 Pa (US EPA, 2011), K _d of 600 L/kg (Barron et al., 2009) and a k _{deg} = 0 hr ⁻¹ .	
Nystatin	Predicted to be readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000116 Pa (US EPA, 2011) and a k _{deg} = 1 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	87
Ofloxacin	On average, 69% of the PhAC is removed in WWTPs (2)	69
Omeprazole	Neither readily nor inherently biodegradable (AstraZeneca ERAD, 2011g). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.55x10 ⁻⁹ Pa (US EPA, 2011), K _d = 130 L/kg (Stevens-Garmon et al., 2011) and a k _{deg} = 0 hr ⁻¹ .	5
Ondansetron	Not readily biodegradable (GSK, 2008b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.92x10 ⁻⁸ Pa (US EPA, 2011), K _d = 12303 L/kg (measured (Cunningham et al., 2009)) and a k _{deg} = 3.9x10 ⁻⁴ hr ⁻¹ (Cunningham et al., 2009).	77
Orlistat	Neither readily nor inherently biodegradable (Roche, 2011b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.3x10 ⁻¹¹ Pa (US EPA, 2011), K _d = 3.2x10 ⁴ L/kg (measured (Roche, 2011b)) and a k _{deg} = 0 hr ⁻¹ .	85
Orphenadrine	On average, 44% of the PhAC is removed in WWTPs (5)	44
Oseltamivir	Leknes et al. (39) reported minimal degradation of the compound in a wastewater treatment; hence, it was assumed that PhAC is not removed in WWTPs.	0
Oseltamivir Carboxylate	Leknes et al. (39) reported minimal degradation of the compound in a wastewater treatment; hence, it was assumed that PhAC is not removed in WWTPs.	0
Oxaprozin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 6.77x10 ⁻⁷ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.92 and a k _{deg} = 0 hr ⁻¹ .	1
Oxazepam	Since generation of this PhAC has been reported in more than one study (5,6,23), it was assumed that it is not removed in WWTPs.	0
Oxprenolol	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.16x10 ⁻⁵ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.84 and a k _{deg} = 0 hr ⁻¹ .	8
Oxycodone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.97x10 ⁻⁸ Pa (US EPA, 2011), K _d 14 L/kg (Wick et al., 2009) and a k _{deg} = 0.02625 hr ⁻¹ (Wick et al., 2009).	16
Pamidronate	Not readily biodegradable (Novartis, 2010e). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.74x10 ⁻⁹ Pa (US EPA, 2011) and a k _{deg} = 0 hr ⁻¹ . Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Pantoprazole	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC	36

PhAC	Rationale	R ₁₊₂ (%)
	in WWTPs with the following input data: predicted vapour pressure of 1.67×10^{-10} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals- which Pantoprazole is at circa neutral pH values(US EPA, 2011)) of 3.675 and a $k_{deg} = 0 \text{ hr}^{-1}$.	
Paroxetine	On average, 53% of the PhAC is removed in WWTPs (2,3,5)	53
Penicillin G	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.2×10^{-8} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.75 and a $k_{deg} = 0 \text{ hr}^{-1}$.	0.7
Penicillin V	On average, 40% of the PhAC is removed in WWTPs (2)	40
Pentoxifylline	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.65×10^{-8} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals) of 1.0 and a $k_{deg} = 0 \text{ hr}^{-1}$.	0
Perindopril	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.5×10^{-10} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Perphenazine	On average, 89% of the PhAC is removed in WWTPs (5)	89
Phenobarbital	On average, >99% of the PhAC is removed in WWTPs (2, 3)	99
Phenyltoloxamine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.0158 (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.49 and a $k_{deg} = 0 \text{ hr}^{-1}$.	27
Phenytoin	On average, 44% of the PhAC is removed in WWTPs (2) .	44
Piperacillin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.3×10^{-20} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Absorption is not expected to be of significance for this PhAC.	0
Piroxicam	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.34×10^{-12} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Pravastatin	On average, 55% of the PhAC is removed in WWTPs (1-3, 26)	55
Prednisolone	On average, 78% of the PhAC is removed in WWTPs (8)	78
Prednisone	On average, 99% of the PhAC is removed in WWTPs (8)	99
Primidone	On average, 27% of the PhAC is removed in WWTPs (47)	27
Procainamide	Not readily biodegradable (US FDA, 1995). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.28×10^{-5} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Prochlorperazine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.58×10^{-7} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Promethazine	On average, 51% of the PhAC is removed in WWTPs (23)	51

PhAC	Rationale	R ₁₊₂ (%)
Propafenone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.7×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.24 and a $k_{deg} = 0 \text{ hr}^{-1}$.	16
Propofol	Not readily biodegradable (AstraZeneca ERAD, 2011h). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.3 Pa (AstraZeneca ERAD, 2011h), Log K _{oc} of 2.49 (AstraZeneca ERAD, 2011h), solubility of 172 mg/L (AstraZeneca ERAD, 2011h) and a $k_{deg} = 0 \text{ hr}^{-1}$.	9.5
Propranolol	On average, 7% of this PhAC is removed in WWTPs (1,2,4,10,18,19,20,23,26,36)	7
Propylthiouracil	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.22×10^{-6} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009) - note that pK _{a2} of the PhAC is predicted to be 12.89) of 1.84 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Quetiapine	Not readily biodegradable (AstraZeneca-fass, 2011c). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.66×10^{-6} Pa (USEPA), K _d of 355 L/kg (measured (AstraZeneca-fass, 2011c)) and a $k_{deg} = 0 \text{ hr}^{-1}$.	12
Quinapril	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.44×10^{-12} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since sorption of the PhAC could not be reliably modeled it was ignored.	0
Quinidine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.27×10^{-8} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Quinine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.27×10^{-8} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Rabeprazole	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.23×10^{-11} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Ramipril	On average, 10% of this PhAC is removed in WWTPs (23)	10
Ranitidine	On average, 61% of this PhAC is removed in WWTPs (1,2,5,7,23)	61
Rifampin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.09×10^{-32} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Risperidone	Since generation of this PhAC has been reported in more than one study (5) it was assumed that it is not removed in WWTPs.	0
Rizatriptan	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.41×10^{-6} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC	0

PhAC	Rationale	R ₁₊₂ (%)
	could not be reliably modeled, it was neglected.	
Rosuvastatin	On average, >63% of the PhAC is removed in WWTPs (2)	63
Roxithromycin	On average, 42% of the PhAC is removed in WWTPs (2,5)	42
Salbutamol	On average, 27% of the PhAC is removed in WWTPs (1,7,23,31,36)	27
Salmeterol	Inherently biodegradable (GSK, 2011d). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.57×10^{-13} Pa (US EPA, 2011), K_d of 7943 L/kg (measured (Cunningham et al., 2009)) and a $k_{deg} = 0 \text{ hr}^{-1}$.	70
Selegiline	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.35 Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.54 and a $k_{deg} = 0 \text{ hr}^{-1}$.	30
Sertraline	Highly variables mean removal rates (18% to 71%) have been reported in literature. Here, it is conservatively assumed that 25% (3,6,23) is removed in WWTPs.	25
Sildenafil	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.47×10^{-15} Pa (USEPA), K_d of 165 L/kg (measured (Pfizer-fass, 2011)) and a $k_{deg} = 0 \text{ hr}^{-1}$.	6
Simvastatin	On average, 75% of the PhAC is removed in WWTPs (26)	75
Sinacalide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0 Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Sotalol	On average, 30% of the PhAC is removed in WWTPs (2-4,18,20,21)	30
Spiramycin	Since generation of this PhAC has been reported in more than one study (31,32) it was assumed that it is not removed in WWTPs.	0
Spironolactone	Predicted to be readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 7.32×10^{-9} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.703 and a $k_{deg} = 0 \text{ hr}^{-1}$.	37
Sulfacetamide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.42×10^{-6} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Sulfamethoxazole	On average, 50% of the PhAC is removed in WWTPs (2,3)	50
Sulfasalazine	Since generation of this PhAC has been reported (1) it was assumed that it is not removed in WWTPs.	0
Sulfapyridine	Observed removal of 87% (1)	87
Sulfisoxazole	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.77×10^{-6} Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Sulindac	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.07×10^{-8} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for	1

PhAC	Rationale	R ₁₊₂ (%)
	single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.94 and a $k_{deg} = 0 \text{ hr}^{-1}$.	
Sumatriptan	Inherently biodegradable (GSK, 2011e). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $9.39 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), K_d of 2 L/kg (measured (Cunningham et al., 2009)) and a $k_{deg} = 0.1 \text{ hr}^{-1}$.	41
Tamoxifen	On average, 26% of the PhAC is removed in WWTPs (5)	26
Tamsulosin	Not readily biodegradable (Boehringer Ingelheim, 2005). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $5.28 \times 10^{-9} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Tazobactam	Not readily biodegradable (Wyeth, 2007). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $3.72 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.61 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Telithromycin	Not readily biodegradable (Sanofi, 2011b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $7.6 \times 10^{-29} \text{ Pa}$ (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Temazepam	On average, 0% of the PhAC is removed in WWTPs (25)	0
Terbutaline	Since generation of this PhAC has been reported (23) it was assumed that it is not removed in WWTPs	0
Testosterone	On average, 82% of the PhAC is removed in WWTPs (2)	82
Tetracycline	On average, 76% of the PhAC is removed in WWTPs (2, 5, 7, 23)	76
THC	On average, 99% of the PhAC is removed in WWTPs (15)	99
Theophylline	Readily biodegradable (BASF, 2012). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $7.43 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.11 and a $k_{deg} = 1 \text{ hr}^{-1}$.	87
Tiaprofenic Acid	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000135 Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.83 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Ticarcillin	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $8.74 \times 10^{-13} \text{ Pa}$ (US EPA, 2011), and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Ticlopidine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $6.7 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.77 and a $k_{deg} = 0 \text{ hr}^{-1}$.	41
Timolol	Not readily biodegradable (Merck, 2000). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $6.7 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.63 and a $k_{deg} = 0 \text{ hr}^{-1}$.	5

PhAC	Rationale	R ₁₊₂ (%)
Tolbutamide	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.46×10^{-5} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.80 and a $k_{deg} = 0 \text{ hr}^{-1}$.	1
Tramadol	Since generation of this PhAC has been reported in more than one study (5,23) it was assumed that it is not removed in WWTPs.	0
Trazodone	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.07×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.62 and a $k_{deg} = 0 \text{ hr}^{-1}$.	33
Triamterene	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.45×10^{-5} Pa (US EPA, 2011), K _d of 371 L/kg (measured (Cunningham et al., 2009) and a $k_{deg} = 0 \text{ hr}^{-1}$.	13
Trifluoperazine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.06×10^{-6} Pa (US EPA, 2011), K _d of 1445 L/kg (measured (GSK, 2005)) and a $k_{deg} = 0 \text{ hr}^{-1}$.	35
Trihexyphenidyl	On average, 40% of the PhAC is removed in WWTPs (5)	40
Trimethoprim	On average, 30% of the PhAC is removed in WWTPs (51)	30
Trimipramine	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00153 Pa (US EPA, 2011) and a $k_{deg} = 0 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	0
Valacyclovir	Inherently biodegradable (GSK, 2004b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.28×10^{-11} Pa (US EPA, 2011) and a $k_{deg} = 0.1 \text{ hr}^{-1}$. Since the sorption of the PhAC could not be reliably modeled, it was neglected.	41
Valproic Acid	On average, >99% of the PhAC is removed in WWTPs (2,3)	99
Valsartan	On average, 78% of the PhAC is removed in WWTPs (1)	78
Vancomycin	Since generation of the PhAC has been reported (32) it was assumed that it is not removed in WWTPs.	0
Venlafaxine	On average, 21% of the PhAC is removed in WWTPs (5)	21
Verapamil	On average, 37% of the PhAC is removed in WWTPs (5,25)	37
Warfarin	On average, >99% of the PhAC is removed in WWTPs (3,13)	99
Xylometazoline	Not readily biodegradable (BASF, 2009b). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.75×10^{-5} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.63 and a $k_{deg} = 0 \text{ hr}^{-1}$.	34
Zidovudine	Since generation of this PhAC has been reported (30) it was assumed that it is not removed in WWTPs.	0
Zopiclone	Since generation of this PhAC has been reported (23) it was assumed that it is not removed in WWTPs.	0

Numerical notes in the table above refer to the following references:

(1) Kasprzyk-Hordern et al., 2009; (2) US EPA, 2010; (3) Sadezky et al., 2008; (4) Radjenovic et al., 2009; (5) Fick et al., 2011; (6) SEPA, 2008; (7) Gros et al., 2010; (8) Chang et al., 2007; (9) Nakada et al., 2006; (10) Wick et al., 2009; (11) Zorita et al., 2009; (12) Spongberg and Witter, 2008; (13) Benotti and Brownawell, 2007; (14) Prasse et al., 2011; (15) Postigo et al., 2010; (16) Boleda et al., 2009; (17) Van De Steene et al., 2007; (18) Alder et al., 2010; (19) BLAC, 2003 ; (20) Maurer et al., 2007; (21) Vieno et al., 2007; (22) Li and Zhang, 2011; (23) Wahlberg et al., 2010; (24) Caldwell et al., 2010; (25) Hummel et al., 2006; (26) Miao and Metcalfe et al., 2003; (27) Metcalfe et al., 2010; (28) Ghosh et al., 2010; (29) Castiglioni et al., 2006a; (30) Prasse et al., 2010; (31) Castiglioni et al., 2006b; (32) Zuccatto et al., 2010; (33) Rosal et al., 2010; (34) Svanfelt et al., 2010; (35) Yosjima et al., 2006; (36) Lee et al., 2007; (37) Li et al., 2009; (38) Straub, 2008; (39) Leknes et al., 2012; (40) Buerge et al., 2006; (41) Gracia-Lor et al., 2012; (42) Huerta-Fontela et al., 2008; (43) Postigo et al., 2008; (44) Chang et al., 2011; (45) Kodama et al., 1988; (46) Mahnik et al., 2007; (48) Bisceglia et al., 2010; (49) Lubliner et al., 2010; (50) Fernandez et al., 2007; (51) Straub, 2013.

Appendix J: Removal of PhACs in Primary WWTPs

Typically, only limited actual performance data is available for the removal of PhACs in primary WWTPs (R_1). Therefore, the SimpleTreat model (RIVM, 2003) was used to estimate the removal of the evaluation set in primary WWTPs.

In a primary WWTP, a contaminant is expected to be removed through its volatilization and/or its adsorption onto primary sludge. Therefore, the important inputs to the model were established using the following methods/models:

- **Vapour pressure:** The modified grain method as embedded in USEPA's EPI suite program (2011) was used.
- **Sludge sorption coefficients (K_d):** Preference was given to actual measured data for K_d . In cases, where only experimentally measured K_{oc} (i.e., organic carbon-water partition coefficient) values were available instead, the respective K_d values were estimated using the following equation:

$$K_d = f_{oc} \cdot K_{oc} \quad (J.1)$$

where: f_{oc} is fraction of sludge that is organic carbon, for which the typical value for primary sludge of 0.30 was used (Struijs et al., 1991).

In cases, where experimental measured data for the PhACs' K_{oc} and K_d were not available, the following methods/models were used to estimate the respective K_{oc} values:

- **Neutrals** - For neutral PhACs the MCI (Molecular Connectivity Index) methodology (Meylan et al., 1992) was used.
- **Single Acids** - For single acids, the QSPR (quantitative structure–property relationships) of Franco and co-workers (Franco et al., 2009; Franco and Trapp, 2008) was used.
- **Single Bases** - For single bases, the QSPR of ECETOC (2014) used to estimate the respective K_{oc} values.

- **All other acid-base characteristics-** Since only QSPRs derived from limited data (i.e., $n = 3$) are currently available for PhACs with such acid-base characteristics as double acidic, double basic and zwitterionic (e.g. Cunningham et al., 2008) no attempt was made to estimate the sorption of PhACs with such acid base characteristics. Hence, for such PhACs it was conservatively assumed that they are not removed in WWTPs via sorption.

For sake of consistency with values reported in Appendix I for R_{1+2} , a condition was imposed on the estimated values of R_1 . Specifically, the estimated value for a given PhAC's R_1 (Table J.1) was not allowed to be greater than its estimated R_{1+2} value in Appendix I. In other words, the level with which a PhAC is removed in a primary treatment plant cannot be higher than the level with which it is removed in secondary treatment plants.

Table J.1 Removal of evaluation set in Primary WWTP

PhAC	Rationale	R ₁ (%)
5-Aminosalicylic acid	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0005 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Acarbose	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 6.97×10^{-30} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was neglected. Nevertheless, the log D of the PhAC is such that minimal absorption of the PhAC onto sludge is expected.	0
Acebutolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.2×10^{-9} Pa (US EPA, 2011) and an estimated Log K _{oc} using the QSPR of ECETOC (2014).	5
Acetaminophen	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.00026 Pa (US EPA, 2011) and a measured K _d of 6.5 L/kg (Radjenovic et al., 2009).	0.2
Acetylcysteine	Since, the sorption of the PhAC could not be reliably modeled it was neglected. The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.46×10^{-3} Pa (US EPA, 2011).	0
Acetylsalicylic acid	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.00875 Pa (US EPA, 2011) and an estimated Log K _{oc} of 1.3 using the QSPR of Franco et al. (2009)	0.2
Acyclovir	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.2×10^{-13} Pa (US EPA, 2011) and a measured Log K _{oc} of 2.6 (GSK, 2011f).	3.4
Alendronate	Alendronate is expected to bind to divalent ions upon release. Nevertheless, it was assumed that the PhAC is not removed in WWTPs.	0
Allopurinol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.6×10^{-6} Pa (US EPA, 2011) and a measured Log K _{oc} of 1.25 (GSK, 2013).	0.2
Alprazolam	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.2×10^{-6} Pa (US EPA, 2011) and a measured Log K _{oc} of 3.27 (Horsing et al., 2011).	13
Amantadine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.531 Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.6 using the QSPR of ECETOC (2014).	3.4
Amiloride	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.7×10^{-8} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.1 using the QSPR of ECETOC (2014).	8.8
Amiodarone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.5×10^{-11} Pa (US EPA, 2011) and an estimated Log K _{oc} of 4.9 using the QSPR of ECETOC (2014).	61
Amitriptyline	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.8×10^{-5} Pa (US EPA, 2011) and a measured Log K _{oc} of 3.85 (Horsing et al., 2011). The predicted removal rate was 33%. However, since highly variable removal rates of this PhAC has been reported in secondary treatment plants (Appendix I), it was conservatively assumed that this PhAC is not removed in primary WWTPs.	0
Amlodipine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.6×10^{-7} Pa (US EPA, 2011) and a measured Log K _d of 2.8 (FASS.se- Swedish database).	15
Amoxicillin	Absorption of this PhAC onto sludge is expected to be of minor importance. The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 6.3×10^{-15} Pa (US EPA, 2011).	0

PhAC	Rationale	R ₁ (%)
Amphetamine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.31 Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	6.4
Amphotericin B	Since the sorption for this PhAC could not be modeled it was ignored. The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.21×10^{-39} Pa (US EPA, 2011).	0
Ampicillin	Since the sorption for this PhAC could not be modeled it was ignored. The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.8×10^{-11} Pa (US EPA, 2011).	0
Anastrozole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.58×10^{-6} Pa (US EPA, 2011) and Log K _{oc} (mean AstraZeneca ERAD (2011a)) of 2.68.	4
Androstenedione	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.00024 Pa (US EPA, 2011) and the measured K _d reported of Steves-Garmon et al. (2011).	5
Atenolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1×10^{-7} Pa (US EPA, 2011) and a measured Log K _{oc} of 1.53 (Barron et al., 2009).	0.3
Atorvastatin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 9.3×10^{-23} Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	6
Atropine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 6×10^{-6} Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.5 using the QSPR of ECETOC (2014).	2.7
Azathioprine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.2×10^{-10} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.1 using the MCI methodology (US EPA, 2011).	10
Azithromycin	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Baclofen	Since, the sorption of the PhAC could not be reliably modeled it was ignored. The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.7×10^{-6} Pa (US EPA, 2011).	0
Beclometasone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.5×10^{-12} Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.5 using the MCI methodology (US EPA, 2011).	2.5
Benserazide	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.8×10^{-11} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Benzatropine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 6.9×10^{-7} mmHg (US EPA, 2011) and an estimated Log K _{oc} of 3.44 using the QSPR of ECETOC (2014).	18
Benzydamine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.8×10^{-6} mmHg (US EPA, 2011) and an estimated Log K _{oc} of 3.35 using the QSPR of ECETOC (2014).	16
Betamethasone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.8×10^{-12} Pa (US EPA, 2011) and the measured K _d reported by Cunningham et al. (2009).	1.1
Betaxolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 9.8×10^{-6} mmHg (US EPA, 2011) and an estimated Log K _{oc} of 2.96 using the QSPR of ECETOC (2014).	7.3

PhAC	Rationale	R ₁ (%)
Bezafibrate	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 8.2×10^{-9} Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	3.4
Bicalutamide	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.5×10^{-15} mmHg (US EPA, 2011) and the measured K _d of 140 L/kg AstraZeneca ERAD (2011b).	4.0
Bisoprolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure 3.9×10^{-6} Pa (US EPA, 2011) and a measured Log K _{oc} of 2.44 (Horsing et al., 2011).	2.4
Bleomycin	Assumed to be not removed in WWTPs.	0
Bromazepam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.53×10^{-7} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Bromocriptine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 8.7×10^{-24} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was neglected.	0
Budesonide	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.2×10^{-12} Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	11
Buprenorphine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.3×10^{-11} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was neglected.	0
Bupropion	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.044 Pa (US EPA, 2011) and the measured K _d of Horsing et al. (2011).	2.5
Buserelin	Assumed to be not removed in WWTPs.	0
Butalbital	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.4×10^{-8} Pa (US EPA, 2011) and an estimated Log K _{oc} using the QSPR of Franco et al. (2009).	0.7
Candesartan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.39×10^{-18} Pa (US EPA, 2011) and K _d of 17 L/kg (measured (AstraZeneca ERAD, 2011d)).	0.5
Capecitabine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.63×10^{-10} Pa (US EPA, 2011), and a K _d (measured (Roche, 2010d)) of 272 L/kg.	7.3
Captopril	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.67×10^{-4} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Carbamazepine	Since generation of the PhAC is often reported in secondary treatment plants it was assumed that the PhAC is not removed in WWTPs.	0
Carbidopa	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.65×10^{-7} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Carboplatin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.77×10^{-9} Pa (US EPA, 2011) and K _d (measured) of 331 to 2691 L/kg (Lenz et al., 2007).	9 to 37
Carmustine	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.91×10^{-2} Pa (US EPA, 2011) and a Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.85.	0.6
Carvedilol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.9×10^{-9} Pa (US EPA, 2011) and a measured Log K _{oc} of 4.5 (GSK, 2011f).	54

PhAC	Rationale	R ₁ (%)
Cefaclor	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.2×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Cefadroxil	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.42×10^{-15} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Cefazolin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.00×10^{-16} Pa (US EPA, 2011), and a $K_d \approx 0$ L/kg (Cunningham et al., 2009).	0
Cefixime	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.34×10^{-16} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Cefprozil	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.60×10^{-16} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ceftazidime	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.09×10^{-19} Pa (US EPA, 2011) and $K_d \approx 0$ L/kg (Cunningham et al., 2009).	0
Ceftriaxone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.61×10^{-22} Pa (US EPA, 2011). Since, sorption of the PhAC could not be reliably modeled it was ignored.	0
Cefuroxime	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.29×10^{-13} Pa (US EPA, 2011) and K_d of 7.9 L/kg (Cunningham et al., 2009).	0.2
Celecoxib	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.59×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.5.	2.7
Cephalexin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.3×10^{-13} Pa (US EPA, 2011). Since, sorption of the PhAC could not be reliably modeled it was ignored.	0
Cetirizine	Since generation of the PhAC has been reported in secondary treatment plants it was assumed that the PhAC is not removed by primary WWTPs.	0
Chloral hydrate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2000 Pa (US EPA, 2011), Log K_{oc} (estimated using the MCI methodology (US EPA, 2011)) of 0.	0.1
Chloramphenicol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.3×10^{-10} Pa (US EPA, 2011), Log K_{oc} (VSDB, 2011) of 2.	0.9
Chlorhexidine	Assumed to be not removed in primary WWTP, since removal was not observed in secondary WWTPs.	0
Chloroquine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.66×10^{-7} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Chlorpromazine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0007 Pa (US EPA, 2011) and an estimated Log K_{oc} of 3.8 using the QSPR of ECETOC (2014).	30

PhAC	Rationale	R ₁ (%)
Cimetidine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.3×10^{-7} Pa (US EPA, 2011) and the measured K_d data of Cunningham et al. (2009).	12
Ciprofloxacin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.8×10^{-11} Pa (US EPA, 2011) and the measured K_d data of Okuda et al. (2009).	13
Cisplatin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.42×10^{-18} Pa (US EPA, 2011), K_d (measured) of 1122 to 21379 L/kg (Lenz et al., 2007).	22-60
Citalopram	Since generation of the PhAC has been reported in secondary treatment plants it was assumed that the PhAC is not removed by primary WWTPs.	0
Clarithromycin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.1×10^{-23} Pa (US EPA, 2011) and the measured K_d data of Okuda et al. (2009).	4
Clavulanic acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.27×10^{-7} Pa (US EPA, 2011), K_d (measured) of ≈ 0 L/kg (Cunningham et al., 2009).	0
Clindamycin	Since net generation of this PhAC is reported in secondary treatment plants it was assumed that the PhAC is not removed by primary WWTPs.	0
Clodronic acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.66×10^{-10} Pa (US EPA, 2011), K_d of 0 L/kg (Roche, 2004b).	0
Clofibrate	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.38×10^{-1} Pa (US EPA, 2011) Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.51.	2.8
Clofibric acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.01 Pa and a measured Log K_{oc} of 1.23 (Barron et al., 2009).	0.2
Clonazepam	SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 9.76×10^{-9} Pa (US EPA, 2011), K_d for sludge as reported by Hörsing et al. (2011).	14
Clonidine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.49×10^{-3} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.32.	15
Clopidogrel	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.86×10^{-5} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.62.	24
Clorazepate	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.49×10^{-11} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.77.	0.5
Clotrimazole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure 2.8×10^{-7} Pa (US EPA, 2011) and the measured K_d reported by Horsing et al. (2011). However, the predicted level was higher than the removal levels observed in secondary treatment plants (see Appendix I). Therefore, conservatively the removal in primary WWTP was set equal to levels seen in secondary WWTPs.	30
Clozapine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.49×10^{-6} Pa (US EPA, 2011) and the measured K_d of Steves-Garmon et al. (2011).	29
Cocaine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.002 Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	5
Codeine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.6×10^{-8} Pa (US EPA, 2011) and the measured K_d of Wick et al. (2009).	0.4
Cortisone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6×10^{-11} Pa (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.05.	1.0

PhAC	Rationale	R ₁ (%)
Cromolyn	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.8×10^{-17} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Cyclophosphamide	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.6×10^{-8} Pa (US EPA, 2011) and the measured K _d of Ternes et al. (2004).	2
Cyproterone	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.5×10^{-8} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.35.	16
Cytarabine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.17×10^{-9} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 1.0.	0.1
Dactinomycin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Daunorubicin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.27×10^{-18} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Desloratadine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure 4.6×10^{-6} Pa (US EPA, 2011) and the measured K _d reported by Horsing et al. (2011). However, the predicted level was higher than levels observed in secondary treatment plants (see Appendix I). Therefore, the removal in primary WWTP was set equal to levels seen in secondary WWTPs.	15
Desogestrel	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure 8.3×10^{-6} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 5.05.	63
Dexamethasone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.8×10^{-12} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.46.	2.5
Dextropropoxyphene	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Diphenoxylate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.84×10^{-10} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 4.14.	43
Dihydrotestosterone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.17×10^{-9} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.34.	15
Diatrizoate	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Diazepam	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Diclofenac	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 8.2×10^{-6} Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	1
Didanosine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.08×10^{-8} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Digoxin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.30×10^{-27} Pa	2

PhAC	Rationale	R ₁ (%)
	(US EPA, 2011), K _d (measured (Cunningham et al., 2009)) of 60 L/kg.	
Diltiazem	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.0x10 ⁻⁹ Pa (US EPA, 2011) and the measured K _d data of Okuda et al. (2009).	6
Dipyridamole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.6x10 ⁻²⁸ Pa (US EPA, 2011) and the measured K _d data of Okuda et al. (2009).	11
Disulfiram	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 8.8x10 ⁻⁴ Pa (US EPA, 2011) Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.91.	35
Docusate	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.63x10 ⁻¹² Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Domperidone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.1x10 ⁻¹² Pa (US EPA, 2011) and an estimated Log K _{oc} using the QSPR of ECETOC (2014).	32
Doxepin	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Doxorubicin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.4x10 ⁻²¹ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Doxycycline	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Drospirenone	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3x10 ⁻⁷ Pa (US EPA, 2011) Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 4.89.	61
Enalapril	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.4x10 ⁻¹⁰ Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	<0.9
Enalaprilat	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.4x10 ⁻¹⁰ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Epirubicin	Expected to demonstrate high removal via absorption onto sludge. However, since specific data for its removal has not been reported it was assumed to be not removed in primary WWTPs.	0
Eprosartan	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.55x10 ⁻¹³ Pa (US EPA, 2011) and the measured K _d of Horsing et al. (2011).	2.1
Erythromycin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.0x10 ⁻²⁵ Pa (US EPA, 2011) and a measured Log K _{oc} of 2.79 (Barron et al., 2009).	5.1
Escitalopram	Removal assumed to be similar to that of citalopram.	0
Esomeprazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.55x10 ⁻⁹ Pa (US EPA, 2011), K _d =48 L/kg (AstraZeneca ERAD, 2011e).	1.4
Estradiol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.6x10 ⁻⁷ Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	13
Estriol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.3x10 ⁻⁹ Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	1.7
Estrone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.68 Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	15
Ethacrynic acid	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 8.2x10 ⁻⁵ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.85.	0.6
Ethambutol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000236 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0

PhAC	Rationale	R ₁ (%)
Ethinylestradiol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.6×10^{-7} Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	21
Ethinodiol	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 3.2×10^{-7} Pa (US EPA, 2011) Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.43.	18
Etidronic acid	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.7×10^{-8} Pa (US EPA, 2011) and the measured K _d reported in HERA (2004).	36
Etodolac	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 2.7×10^{-6} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Etonogestrel	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.68×10^{-7} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 4.12.	43
Etoposide	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.2×10^{-19} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.26.	0.2
Exemestane	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.000147 Pa (US EPA, 2011), K _{oc} of 2285 L/kg (Ericsson, 2010).	18
Famciclovir	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.5×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.78.	5
Famotidine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.9×10^{-8} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Felodipine	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Fenofibrate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.27×10^{-5} Pa (US EPA, 2011), K _{oc} (using the MCI methodology for neutral chemicals (USEPA, 2011)) of 3,862.	23
Fenofibric Acid	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.2×10^{-19} Pa (US EPA, 2011) and Log K _{oc} estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)).	0.3
Fenoprofen	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.00024 Pa (US EPA, 2011) and Log K _{oc} estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)).	0.4
Fenoterol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.26×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Fentanyl	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Finasteride	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs (Appendix I).	0
Fluconazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4×10^{-7} Pa and a log K _{oc} of 3.59 (Estimated using MCI methodology for neutral chemicals (USEPA, 2011), since at pH of wastewater it has neutral charge).	23
Fluocinonide	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.44×10^{-12} Pa	2.1

PhAC	Rationale	R ₁ (%)
	(US EPA, 2011), K _{oc} (using the MCI methodology for neutral chemicals (USEPA, 2011)) of 244.	
Fluorouracil	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of Pa and the measured K _d reported by Straub (2010).	7.3
Fluoxetine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 9.5x10 ⁻⁶ Pa (US EPA, 2011) and a measured Log K _{oc} of 4.18 (Horsing et al., 2011). However, the predicted level was higher than levels observed in secondary treatment plants (see Appendix I). Therefore, the removal in primary WWTP was set equal to levels seen in secondary WWTPs.	13
Fluphenazine	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.5x10 ⁻⁸ (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Flurazepam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.05x10 ⁻⁶ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Flutamide	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.00015 Pa (US EPA, 2011), K _d for sludge as reported by Hörsing et al. (2011).	27
Fluticasone	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.93x10 ⁻¹¹ Pa (US EPA, 2011), K _d (measured-Cunningham et al., 2009) of 1995.3 L/kg.	31
Fluvoxamine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.55x10 ⁻³ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.18.	11
Formoterol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.61x10 ⁻¹² Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Fosfomycin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00221 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Fosphenytoin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.07x10 ⁻⁹ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Fulvestrant	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.7x10 ⁻¹⁵ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Furosemide	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 4.1x10 ⁻⁹ Pa (US EPA, 2011) and the K _d data reported by Okuda et al. (2009).	3.6
Gabapentin	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.9x10 ⁻¹⁰ Pa (US EPA, 2011). Sorption of the PhAC on sludge is expected to be of minor importance (US FDA, 2009).	0
Gemfibrozil	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.05x10 ⁻⁵ Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	1.3
Gentamicin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.33x10 ⁻¹¹ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0

PhAC	Rationale	R ₁ (%)
Gliclazide	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.65×10^{-7} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Glyburide	Since net generation of this PhAC is reported in secondary treatment plants, it was assumed that the PhAC is not removed by primary WWTPs (see Appendix I).	0
Goserelin	Assumed to be not removed in primary WWTP.	0
Haloperidol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2×10^{-8} Pa (US EPA, 2011) and a measured Log K _{oc} of 3.86 (Horsing et al., 2011). However, the predicted level was higher than the removal levels observed in secondary treatment plants (see Appendix I). Therefore, conservatively the removal in primary WWTP was set equal to levels seen in secondary WWTPs.	28
Heroin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.6×10^{-10} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.05 using the QSPR of ECETOC (2014).	9
Hydrochlorothiazide	Since highly variable removal rates of this PhAC has been reported in secondary treatment plants (Appendix I), it was conservatively assumed that this PhAC is not removed in primary WWTPs.	0
Hydrocodone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.6×10^{-5} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.0 using the QSPR of ECETOC (2014).	8
Hydrocortisone	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.6×10^{-11} Pa (US EPA, 2011) Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.05.	1
Hydromorphone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.56×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.82.	5.5
Hydroxychloroquine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.32×10^{-7} Pa (US EPA, 2011).	0
Hydroxyzine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.6×10^{-9} (US EPA, 2011) and a measured Log K _{oc} of 3.26 (Horsing et al., 2011).	13
Ibuprofen	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.025 Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	< 0.9
Idarubicin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.04×10^{-19} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ifosfamide	Assumed to be not removed in primary WWTP, since no removal was observed in secondary WWTPs.	0
Imipramine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.5×10^{-5} Pa (US EPA, 2011), Log K _{oc} 3.99 (VKM, 2010).	38
Indomethacin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 6.8×10^{-8} Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	5.7
Ipratropium	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.23×10^{-14} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Irbesartan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.6×10^{-14} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Isoniazid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in	0.1

PhAC	Rationale	R ₁ (%)
	WWTPs with the following input data: predicted vapour pressure of 0.00162 Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (which isoniazid is at circa neutral pH values(US EPA, 2011)) of 1.	
Isosorbide-5-mononitrate	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.2×10^{-19} Pa (US EPA, 2011) and Log K _{oc} estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)).	0.1
Isosorbide-dinitrate	Readily biodegradable (Kummerer, 2008). The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.02×10^{-12} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals) of 1.3.	0.2
Ketamine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.2×10^{-5} Pa (US EPA, 2011) and an estimated Log K _{oc} using the QSPR of ECETOC (2014).	18
Ketoconazole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 8.6×10^{-12} (US EPA, 2011) and a measured Log K _{oc} of 4.33 (Steven-Garmon et al., 2011).	50
Ketoprofen	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.5×10^{-6} Pa (US EPA, 2011) and the measured log K _{oc} of 2.45 (VKM, 2010)	2.4
Labetalol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4×10^{-11} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored	0
Lamotrigine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.25×10^{-6} Pa (US EPA, 2011), K _d (measured (Cunningham et al., 2009)) of 14.1 L/kg.	0.4
Lansoprazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.23×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored	0
Letrozole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.08×10^{-7} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.4 using the QSPR of ECETOC (2014).	16
Leuprolide	Peptide, expected to degrade easily. However, assumed to not be removed in primary WWTP, since in such WWTPs removal of contaminants tends to be through absorption onto sludge and/or volatilization.	0
Levobunolol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.93×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.78.	5
Levodopa	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.41×10^{-8} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Levofloxacin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.3×10^{-10} Pa (US EPA, 2011) and the measured K _d of Okuda et al. (2009).	0.1
Levothyroxine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.7×10^{-20} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored	0
Lidocaine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.0009 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Liothyronine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in	0

PhAC	Rationale	R ₁ (%)
	WWTPs with the following input data: predicted vapour pressure of 6.75×10^{-13} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	
Lisinopril	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.27×10^{-13} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Lorazepam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.11×10^{-10} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Loratadine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.2×10^{-6} Pa (US EPA, 2011) and a measured K _d of 2336 L/kg (Radjenovic et al., 2009).	34
Losartan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.11×10^{-10} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Loxapine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.8×10^{-17} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
MDMA	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0002 Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.5 using the QSPR of ECETOC (2014).	2.7
Mefenamic acid	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.8×10^{-6} Pa (US EPA, 2011) and the measured K _d data of Okuda et al. (2009).	30
Melphalan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.05×10^{-8} Pa (US EPA, 2011), K _d (measured (Cunningham et al. (2009)) of 0.2 L/kg.	0
Meprobamate	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0008 Pa (US EPA, 2011) and the measured K _d of Steves-Garmon et al. (2011).	1.2
Metformin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.01 Pa (US EPA, 2011) and the measured log K _{oc} of 2.03 (VKM, 2010)	1
Methadone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.00015 (US EPA, 2011) and a measured Log K _{oc} of 1.78 (Barron et al., 2009).	0.5
Methamphetamine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.598 Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.6 using the QSPR of ECETOC (2014).	3.5
Methotrexate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.78×10^{-17} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Methotrimeprazine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.23×10^{-5} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.76.	29
Methyldopa	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.07×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Methylphenidate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00786 Pa (US EPA, 2011) Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single	6.3

PhAC	Rationale	R ₁ (%)
	bases) of 2.89.	
Methylprednisolone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.9×10^{-12} Pa (US EPA, 2011) and an estimated Log K _{oc} of 3.36 using the MCI methodology (US EPA, 2011).	1.6
Metoprolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.8×10^{-5} Pa (US EPA, 2011) and a measured Log K _{oc} of 1.78 (Barron et al., 2009).	0.5
Metronidazole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.8×10^{-5} (US EPA, 2011) and a measured Log K _{oc} of 1.65 (Tolls, 2001).	0.4
Miconazole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.4×10^{-8} Pa (US EPA, 2011) and an estimated Log K _{oc} of 4.6 using the QSPR of ECETOC (2014).	56
Midazolam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.83×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.99.	38
Minocycline	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5×10^{-21} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Misoprostol	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 6.05×10^{-10} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.2.	1.4
Mitomycin C	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.93×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Mitotane	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00225 Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 5.08.	63
Mometasone Furoate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.66×10^{-13} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 4.30.	49
Mometasone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.46×10^{-11} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.464.	2.5
Morphine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.5×10^{-8} Pa and sorption data of Wick et al. (2009)	0.4
Mupirocin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 2.07×10^{-16} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.95	0.8
Nabumetone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00269 Pa (US EPA, 2011), K _d (measured (Cunningham et al., 2009)) of 42 L/kg.	1.2
Nadolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.3×10^{-8} Pa (US EPA, 2011) and an estimated Log K _{oc} of 2.5 using the QSPR of ECETOC (2014).	2.9
Naloxone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.67×10^{-9} Pa	0

PhAC	Rationale	R ₁ (%)
	(US EPA, 2011) and the lack of sorption reported by Hörsing et al. (2011).	
Naltrexone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.26×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Naproxen	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 0.0002 Pa (US EPA, 2011) and the measured log K _{oc} of 2.54 (VKM, 2010)	3.0
Neomycin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.14×10^{-26} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Nifedipine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.5×10^{-6} Pa (US EPA, 2011), K _d of 27 L/kg (Barron et al., 2009).	0.8
Nilutamide	SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.84×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.11.	1.1
Nimodipine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.8×10^{-8} Pa (US EPA, 2011) and an estimated Log K _{oc} of 4.0 using the QSPR of ECETOC (2014).	37
Nitrazepam	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 4.1×10^{-8} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals- which Nitrazepam is at circa neutral pH values(US EPA, 2011)) of 3.85.	7.9
Nizatidine	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.28×10^{-6} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Nitrofurantoin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.05×10^{-9} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.5.	0.3
Norfloxacin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of Pa (US EPA, 2011) and the measured K _d data of Okuda et al. (2009).	3.6
Norgestimate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.49×10^{-9} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 6.08.	66
Norethindrone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.1×10^{-7} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.62.	24
Nortriptyline	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0003 (US EPA, 2011) and a measured Log K _{oc} of 3.29 (Barron et al., 2009).	14
Nystatin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000116 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ofloxacin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.3×10^{-10} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Omeprazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.55×10^{-9} Pa	3.7

PhAC	Rationale	R ₁ (%)
	(US EPA, 2011), $K_d = 130 \text{ L/kg}$ (Stevens-Garmon et al., 2011).	
Ondansetron	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $9.92 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), $K_d = 12303 \text{ L/kg}$ (measured (Cunningham et al., 2009)).	56
Orlistat	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.3 \times 10^{-11} \text{ Pa}$ (US EPA, 2011), $K_d = 3.2 \times 10^4 \text{ L/kg}$ (measured (Roche, 2011b)).	62
Orphenadrine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $6.8 \times 10^{-8} \text{ Pa}$ (US EPA, 2011) and the lack of sorption reported by Hörsing et al. (2011)	0
Oseltamivir	Leknes et al. (39) reported minimal degradation of the compound in a secondary wastewater treatment; hence, it was assumed that PhAC is not removed in primary treatment plants.	0
Oseltamivir-Carboxylate	Leknes et al. (39) reported minimal degradation of the compound in a secondary wastewater treatment; hence, it was assumed that PhAC is not removed in primary treatment plants.	0
Oxaprozin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $6.77 \times 10^{-7} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.92.	0.7
Oxazepam	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Oxprenolol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $4.16 \times 10^{-5} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.84.	5.7
Oxycodone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $3 \times 10^{-8} \text{ Pa}$ and sorption data of Wick et al. (2009)	0.5
Pamidronate	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $2.74 \times 10^{-9} \text{ Pa}$ (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Pantoprazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.67 \times 10^{-10} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals- which Pantoprazole is at circa neutral pH values (US EPA, 2011)) of 3.675.	26
Paroxetine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of $6.4 \times 10^{-6} \text{ Pa}$ (US EPA, 2011) and a measured Log K_{oc} of 4.32 (Horsing et al., 2011).	49
Penicillin G	Predicted to be not readily biodegradable (Boethling et al., 2004). The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $1.2 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.75.	0.5
Penicillin V	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of $1.4 \times 10^{-10} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) 1.6.	0.4
Pentoxifylline	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $1.65 \times 10^{-8} \text{ Pa}$ (US EPA, 2011), Log K_{oc} (predicted using MCI method for neutral chemicals) of 1.0.	0
Perindopril	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of $7.5 \times 10^{-10} \text{ Pa}$ (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Perphenazine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in	0

PhAC	Rationale	R ₁ (%)
	WWTPs with the following input data: predicted vapour pressure of 1×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	
Phenobarbital	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.8×10^{-9} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) 1.9.	0.7
Phenyltoloxamine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.0158 (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.49.	20
Phenytoin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.8×10^{-9} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.9.	0.8
Piperacillin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.3×10^{-20} Pa (US EPA, 2011). Absorption is not expected to be of significance for this PhAC.	0
Piroxicam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.34×10^{-12} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Pravastatin	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 8.1×10^{-14} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.7.	0.8
Prednisolone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.1×10^{-12} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.05.	1.0
Prednisone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.09×10^{-11} Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 2.05.	1.0
Primidone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.4×10^{-8} Pa and sorption data of Wick et al. (2009)	0.3
Procainamide	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.28×10^{-5} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Prochlorperazine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.58×10^{-7} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Promethazine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0013 Pa (US EPA, 2011) and the measured K _d of Horsing et al. (2011).	37
Propafenone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.7×10^{-7} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.24.	12.7
Propofol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.3 Pa (AstraZeneca ERAD, 2011h), Log K _{oc} of 2.49 (AstraZeneca ERAD, 2011h) and a solubility of 172 mg/L (AstraZeneca ERAD, 2011h).	3.3
Propranolol	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of	7

PhAC	Rationale	R ₁ (%)
	(US EPA, 2011) and a measured Log K _{oc} of 3.03 (Barron et al., 2009). However, the predicted level was higher than the removal levels observed in secondary treatment plants (see Appendix I). Therefore, conservatively the removal in primary WWTPs was set equal to levels seen in secondary WWTPs.	
Propylthiouracil	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.22×10^{-6} Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009) - note that pK _{a2} of the PhAC is predicted to be 12.89) of 1.84.	0.6
Quetiapine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.66×10^{-6} Pa (USEPA, 2011), K _d of 355 L/kg (measured (AstraZeneca-fass, 2011c)).	9.2
Quinapril	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.44×10^{-12} Pa (US EPA, 2011). Since, sorption of the PhAC could not be reliably modeled it was ignored.	0
Quinidine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.27×10^{-8} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Quinine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.27×10^{-8} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Rabeprazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.23×10^{-11} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ramipril	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.7×10^{-9} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ranitidine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 0.0002 Pa (US EPA, 2011) and the measured K _{oc} data of Barron et al. (2009).	10
Rifampin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.09×10^{-32} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Risperidone	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Rizatriptan	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.41×10^{-6} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Rosuvastatin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7×10^{-17} Pa (US EPA, 2011) and the log K _{oc} reported by AstraZeneca (2008).	1
Roxithromycin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.4×10^{-27} Pa (US EPA, 2011) and the measured K _d data of Okuda et al. (2009).	18
Salbutamol	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 1.2×10^{-6} Pa (US EPA, 2011) and the measured log K _{oc} of 1.51 (VKM, 2010)	0.3
Salmeterol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.57×10^{-13} Pa (US EPA, 2011), K _d of 7943 L/kg (measured (Cunningham et al., 2009)).	52

PhAC	Rationale	R ₁ (%)
Selegiline	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.35 Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.54.	21
Sertraline	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.2x10 ⁻⁶ Pa (US EPA, 2011) and a measured Log K _{oc} of 4.63 (Horsing et al., 2011).	57
Sildenafil	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.47x10 ⁻¹⁵ Pa (USEPA), K _d of 165 L/kg (measured (Pfizer-fass, 2011)).	4.6
Simvastatin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.7x10 ⁻¹⁰ Pa (US EPA, 2011) and the measured K _{oc} data of Barron et al. (2009).	25
Sincalide	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Sotalol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.7x10 ⁻¹² Pa and sorption data of Wick et al. (2009).	0.5
Spiramycin	Since generation of this PhAC has been reported in secondary WWTPs (see Appendix C) it was assumed that it is not removed in primary WWTPs.	0
Spironolactone	The SimpleTreat model (RIVM, 2003) was run with the following input data: predicted vapour pressure of 7.32x10 ⁻⁹ Pa (US EPA, 2011), Log K _{oc} (predicted using MCI method for neutral chemicals (US EPA, 2011)) of 3.70.	27
Sulfacetamide	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.42x10 ⁻⁶ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Sulfamethoxazole	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.7x10 ⁻⁵ Pa (US EPA, 2011) and the measured K _d data of Hörsing et al. (2011).	8.4
Sulfasalazine	Since generation of this PhAC has been reported in secondary WWTPs (see Appendix I) it was assumed that it is not removed in primary WWTPs.	0
Sulfapyridine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.5x10 ⁻⁶ Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	1.9
Sulfisoxazole	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.77x10 ⁻⁶ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Sulindac	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 4.07x10 ⁻⁸ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.94.	0.8
Sumatriptan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 9.39x10 ⁻⁷ Pa (US EPA, 2011), K _d of 2 L/kg (measured (Cunningham et al., 2009)).	0.1
Tamoxifen	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 4.6x10 ⁻⁶ Pa (US EPA, 2011) and a measured Log K _{oc} of 3.92 (Barron et al., 2009). However, the predicted level was higher than the removal levels observed in secondary treatment plants (see Appendix I). Therefore, conservatively the removal in primary WWTPs was set equal to levels seen in secondary WWTPs.	26
Tamsulosin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 5.28x10 ⁻⁹ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Tazobactam	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.72x10 ⁻⁸ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco	0.4

PhAC	Rationale	R ₁ (%)
	and Trapp, 2008; Franco et al., 2009)) of 1.61.	
Telithromycin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 7.6×10^{-29} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Temazepam	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Terbutaline	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Testosterone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure 2.3×10^{-6} Pa (US EPA, 2011) and the measured K_d of Steves-Garmon et al. (2011).	4.9
Tetracycline	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.8×10^{-19} Pa (US EPA, 2011) and the measured K_d data of Okuda et al. (2009).	22
THC	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.2×10^{-6} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 4.31.	49
Theophylline	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 7.4×10^{-8} Pa (US EPA, 2011) and the measured K_d data of Okuda et al. (2009).	1.2
Tiaprofenic Acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.000135 Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.83.	0.6
Ticarcillin	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 8.74×10^{-13} Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Ticlopidine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.7×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.77.	30
Timolol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.7×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 2.63.	3.6
Tolbutamide	SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.46×10^{-5} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 1.80.	0.6
Tramadol	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 6.1×10^{-5} Pa (US EPA, 2011) and the lack of sorption reported by Hörsing et al. (2011).	0
Trazodone	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.07×10^{-7} Pa (US EPA, 2011), Log K_{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.62.	24
Triamterene	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.45×10^{-5} Pa (US EPA, 2011), K_d of 371 L/kg (measured (Cunningham et al., 2009)).	9.5
Trifluoperazine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.06×10^{-6} Pa (US EPA, 2011), K_d of 1445 L/kg (measured (GSK, 2005)).	26
Trihexyphenidyl	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 1.3×10^{-12} Pa (US EPA, 2011) and a measured K_d data of Horsing et al. (2011).	16
Trimethoprim	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of	8.3

PhAC	Rationale	R ₁ (%)
	1.0x10 ⁻⁶ Pa (US EPA, 2011) and a measured Log K _{oc} of 3.02 (Horsing et al., 2011).	
Trimipramine	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.00153 Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Valacyclovir	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 2.28x10 ⁻¹¹ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Valproic Acid	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 0.09 Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco for single acids (Franco and Trapp, 2008; Franco et al., 2009)) of 2.6.	3.2
Valsartan	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 1.1x10 ⁻¹³ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0
Vancomycin	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants	0
Venlafaxine	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 3.3x10 ⁻⁵ Pa (US EPA, 2011) and a measured Log K _{oc} of 2.40 (Horsing et al., 2011).	2.2
Verapamil	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 5.6x10 ⁻⁷ Pa (US EPA, 2011) and a measured Log K _{oc} of 3.00 (Horsing et al., 2011).	7.9
Warfarin	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure of 2.3x10 ⁻⁸ Pa (US EPA, 2011) and the measured sorption data of Barron et al. (2009).	0.8
Xylometazoline	The SimpleTreat model (RIVM, 2003) was run to predict the removal of the PhAC in WWTPs with the following input data: predicted vapour pressure of 3.75x10 ⁻⁵ Pa (US EPA, 2011), Log K _{oc} (estimated with the model of Franco and Gouin (2011) for single bases) of 3.63.	24
Zidovudine	Since generation of the PhAC has been reported in secondary treatment plants (see Appendix I), it was assumed that it is not removed in primary treatment plants.	0
Zopiclone	The SimpleTreat model (RIVM, 2003) was run with a predicted vapour pressure 1.3 x10 ⁻⁸ Pa (US EPA, 2011). Since, the sorption of the PhAC could not be reliably modeled it was ignored.	0

Appendix K: Sources for each PhAC of the evaluation set

Table K.1 summarizes the relative importance of each source term ($M_{cu}/M_{HU}/M_{OCD}/M_{OHD}/M_{endo}/M_{IDU}/M_{OID}$) to net environmental load of each PhAC (M_T).

Table K.1 Importance of each source term to the environmental loading of each PhAC

PhAC	Importance of Each Source [($M_{cu}/M_{HU}/M_{OCD}/M_{OHD}/M_{endo}/M_{IDU}/M_{OID}$)/ $M_T \times 100$] (%)							M_T
	M_{cu}	M_{HU}	M_{OCD}	M_{OHD}	M_{endo}	M_{IDU}	M_{OID}	kg/yr
Acarbose	98	2						410
Acebutolol	99	1						4,340
Acetaminophen	97	≈ 3						1,824,000
Acetylcysteine	0.1	0.1			99.8			105,000
Acetylsalicylic Acid	96.5	≈ 3.5						8,130
Acyclovir	29	2	68	1				8,610
Alendronate	98	2						1,210
Allopurinol	98	2						5,320
Alprazolam	99	1						9.1
Amantadine	95	5						396
Amiloride	99	1						98
Aminosalicylic Acid	93.4	1.3	5.2	≈ 0				24,010
Amiodarone	90	10						2,550
Amitriptyline	98	2						1,440
Amlodipine	98	2						125
Amoxicillin	98	2						60,420
Amphetamine	12.8	0.1	30.5	≈ 0			56.4	229
Amphotericin B	9	91						8.8
Ampicillin	20	80						2,260
Anastrozole	84	16						1.9
Androstenedione					100			257
Atenolol	98	2						10,060
Atorvastatin	99	1						9,460
Atropine	71	29						3.7
Azathioprine	96	4						231
Azithromycin	94	6						1,670
Baclofen	85	15						427
Beclomethasone	95	5						6.1
Benserazide	92	8						83
Benztropine	87	13						22
Benzydamine	97	3						114
Betamethasone	95	5						103
Betaxolol	96	4						3.6
Bezafibrate	99.6	0.4						1,320
Bicalutamide	90	10						112
Bisoprolol	98	2						250
Bleomycin	4	96						0.2
Bromazepam	99	1						9.7
Bromocriptine	93	7						10
Budesonide	96	4						20
Bupropion	99	1						1,230
Buserelin	79	21						0.09

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCd} /M _{OHd} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							
	M _{cu}	M _{HU}	M _{OCd}	M _{OHd}	M _{endo}	M _{IDU}	M _{OID}	kg/yr
Butalbital	99.8	0.2						58
Candesartan	99	1						897
Capecitabine	57	43						73
Captopril	94	6						250
Carbamazepine	95	5						5,60
Carbidopa	89	11						1,410
Carboplatin		100						19
Carmustine	39	61						0.01
Carvedilol	97	3						204
Cefaclor	98	2						614
Cefadroxil	97	3						788
Cefazolin	3	97						4,000
Cefixime	90	10						312
Cefprozil	99	1						4,350
Ceftazidime	1	99						3,080
Ceftriaxone	3	97						528
Cefuroxime	1	99						279
Celecoxib	98	2						861
Cephalexin	93	7						23,820
Cetirizine	49.4	0.9	46.5	3.1				364
Chloral Hydrate	81	19						0.44
Chloramphenicol	26	74						8.1
Chlorhexidine	10	90						2,220
Chloroquine	99	1						279
Chlorpromazine	88	12						25
Cimetidine	99	1						4,730
Ciprofloxacin	89	11						10,870
Cisplatin		100						3.7
Citalopram	97	3						1,910
Clarithromycin	98	2						7,210
Clavulanic Acid	91	9						930
Clindamycin	86	14						1,070
Clodronic Acid	59	41						680
Clofibric Acid			100	≈ 0				0.1
Clonazepam	97	3						2.7
Clonidine	94	6						3.3
Clopidogrel	95	5						3,530
Clorazepate	98	2						5.2
Clotrimazole	99	1						2,000
Clozapine	49	51						182
Cocaine	≈ 0	0.3				100		3,230
Codeine	97	3			≈ 0			9,180
Cortisone	≈ 0	≈ 0	0.2	≈ 0	99.8			1,550
Cromolyn	99	1						50
Cyclophosphamide	30	70						29
Cyproterone	81	20						98
Cytarabine		100						146
Dactinomycin	0.1	99.9						0.0028
Daunorubicin		100						0.098
Desloratadine	64	0.4	33	3				3.4
Desogestrel	98	2						0.2

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCD} /M _{OHD} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							kg/yr
	M _{cu}	M _{HU}	M _{OCD}	M _{OHD}	M _{endo}	M _{IDU}	M _{OID}	
Dexamethasone	54	46						35
Dextroamphetamine	37.4	0.3	9.5	≈ 0			52.7	219
Dextropropoxyphene	96	4						59
Diatrizoate	1	99						270
Diazepam	95	5						34
Diclofenac	99	2						2,640
Didanosine	50	50						134
Digoxin	94	6						7.4
Dihydrotestosterone			0.3	≈ 0	99.7			239
Diltiazem	97	3						4,050
Diphenoxylate	98	2						7.4
Dipyridamole	95	5						2,840
Disulfiram	93	7						0.2
Docusate	73	27						21,260
Domperidone	93	7						104
Doxepin	97	3						5.3
Doxorubicin	≈ 0	100						1.5
Doxycycline	95	5						909
Drospirenone	96	4						70
Enalapril	98	2						243
Enalaprilat		≈ 0	98.0	2.0				657
Epirubicin	0.1	99.9						1.6
Eprosartan	99.8	0.2						3,100
Erythromycin	96	4						1,260
Escitalopram	4.4	0.0	92.5	3.2				1,030
Esomeprazole	93.9	1.3	4.6	0.1				34
Estradiol	39	≈ 0	2	≈ 0	59			140
Estriol	≈ 0	≈ 0	1	≈ 0	99			1,100
Estrone	≈ 0	≈ 0	9	≈ 0	91			194
Ethacrynic acid	27	73						28
Ethambutol	38	62						319
Ethinyl estradiol	98	2						5.9
Etidronic Acid	99	1						28,200
Etodolac	99.8	0.2						105
Etonogestrel	24	1	74	1				11
Etoposide	12	88						16
Exemestane	75	26						15
Famotidine	98	2						229
Felodipine	98	2						20
Fenofibrate	99	1						1,600
Fenofibric Acid			99	1				3,780
Fenoterol	87	13						0.6
Fentanyl	85	15						33
Finasteride	98	2						0.06
Fluconazole	76	24						390
Fluocinonide	98	2						5.5
Fluorouracil	13.1	85.5	0.8	0.6				179
Fluoxetine	96	4						417
Fluphenazine	81	19						11
Flurazepam	98	2						33
Flutamide	42	58						18

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCD} /M _{OHD} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							
	M _{cu}	M _{HU}	M _{OCD}	M _{OHD}	M _{endo}	M _{IDU}	M _{OID}	
Fluticasone	96	4						5.4
Fluvoxamine	97	3						45
Formoterol	98	2						0.4
Fosfomycin	99	1						12
Fosphenytoin	4	97						0.009
Fulvestrant	76	24						0.03
Furosemide	91	9						6,110
Gabapentin	94	6						44,200
Gemfibrozil	98	2						1,720
Gentamicin	15	85						109
Gliclazide	97	3						57
Glyburide	98	2						93
Goserelin	81	19						0.1
Haloperidol	72	28						17
Heroin						100		0.2
Hydrochlorothiazide	99	1						13,800
Hydrocodone	13.2	≈ 0	84.0	2.7				165
Hydrocortisone	42.8	4.8			52			2,680
Hydromorphone	75.6	12.6	10.8	0.9				263
Hydroxychloroquine	99	1						3,460
Hydroxyzine	94	6						5.6
Ibuprofen	99	≈ 1	0	0				157,320
Idarubicin		100						0.01
Ifosfamide		100						6.2
Imipramine	98	2						39
Indomethacin	95	5						340
Ipratropium	84	16						19
Irbesartan	99	1						10,000
Isoniazid	28	73						332
Isosorbide Dinitrate	94	6						6
Isosorbide-5-Mononitrate	81	5	13	1				317
Ketamine	18	82						1.6
Ketoconazole	88	13						359
Ketoprofen	95	5						320
Labetalol	93	7						2,000
Lamotrigine	96	4						2,190
Lansoprazole	94	6						25
Letrozole	80	20						1
Leuprolide	65	35						1.4
Levobunolol	97	4						5.6
Levodopa	54	7			39			1,140
Levofloxacin	77.8	16.1	6.0	0.1				1,890
Thyroxine	6.2	≈ 0			94			256
Lidocaine	9	91						396
Triiodothyronine	≈ 0	≈ 0			100			142
Lisinopril	98	2						1,510
Loratadine	92	9						2.3
Lorazepam	94	6						237
Losartan	99	1						3,730
Loxapine	76	24						0.7
MDMA						100		411

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCd} /M _{OHd} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							kg/yr
	M _{cu}	M _{HU}	M _{OCd}	M _{OHd}	M _{endo}	M _{IDU}	M _{OID}	
Mefenamic Acid	98	2						64.1
Melphalan	36	64						0.4
Meprobamate	100		0	0				0.005
Metformin	98	2						382,250
Methadone	94	6						57
Methamphetamine			0.2	0.0		99.7		647
Methotrexate	85	15						49
Methotrimeprazine	88	12						18
Methyldopa	97	3						2,210
Methylphenidate	99.5	0.5	0	0				132
Methylprednisolone	15	85						84
Metoprolol	96	4						3,340
Metronidazole	86	15						3,470
Miconazole	92	8						93
Midazolam	3	97						2.9
Minocycline	99	1						1,170
Misoprostol	99	1						0.2
Mitomycin	9	91						0.05
Mitotane	89	11						27
Mometasone	99	1						39
Morphine	55.9	5.2	24.4	0.8	≈ 0		13.5	3,260
Mupirocin	83	17						233
Nabumetone	99	1						160
Nadolol	98	2						854
Naloxone	2	99						0.1
Naltrexone	89	12						2.8
Naproxen	97	3						39,580
Neomycin	79	21						25
Nifedipine	98	2						4.6
Nilutamide	76	24						1.3
Nimodipine	18	82						0.09
Nitrazepam	99	2						17
Nitrofurantoin	95	5						561
Nizatidine	99.6	0.4						748
Norfloxacin	96	4						1,080
Norgestimate	97	3						8.5
Nortriptyline			98	2				82
Norethindrone	88	1	11	1				26
Nystatin	82	19						1,280
Ofloxacin	98	2						238
Omeprazole	98	2						3.3
Ondansetron	46	54						6.8
Orlistat	99.7	0.3						1,640
Orphenadrine	98	2						119
Oseltamivir	75	25						8.3
Oseltamivir carboxylate			75	25				25
Oxaprozin	99	1						65
Oxazepam	78.9	5.0	15.6	0.5				1,430
Oxprenolol	99	2						14
Oxycodone	98	2						393
Pamidronate	8	92						63

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCD} /M _{OHD} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							
	M _{cu}	M _{HU}	M _{OCD}	M _{OHD}	M _{endo}	M _{IDU}	M _{OID}	kg/yr
Pantoprazole	87	13						0.06
Paroxetine	98	2						76
Penicillin G	0.2	99.8						8,450
Penicillin V	96	4						7,940
Pentoxifylline	95	5						185
Perphenazine	92	8						28
Perindopril	99	1						43
Phenobarbital	65	4	29	2				256
Phenytoin	92	8	≈ 0	≈ 0				2,970
Phenyltoloxamine	99	1						14
Piperacillin	1	99						3,800
Piroxicam	99	1						2.99
Pravastatin	98	2						687
Prednisolone	47.8	1.2	44.3	6.7				198
Prednisone	81.8	12.3	5.8	0.1				42
Primidone	95	5						675
Procainamide	73	27						77
Prochlorperazine	79	21						76
Promethazine	89	11						0.3
Propafenone	96	4						249
Propofol	0.2	99.8						284
Propranolol	98	2						404
Propylthiouracil	96	5						224
Quinapril	99	1						531
Quetiapine	89	11						295
Quinidine	95	5						41
Quinine	96	4						1,590
Ramipril	98	2						1,290
Ranitidine	99	1						389
Rifampin	40	60						246
Risperidone	90	10						31
Rizatriptan	100	1						5.4
Rosuvastatin	99	1						1,480
Salbutamol	81	19	0	0				227
Salmeterol	95	6						0.4
Selegiline	94	6						1.1
Sertraline	97	3						666
Simvastatin	99	1						77
Sincalide		100						0.000006
Sotalol	98	2						2,490
Spiramycin	99.9	0.1						1.8
Spironolactone	96	4						38
Sulfacetamide	99	1						83
Sulfamethoxazole	92	8						5,040
Sulfasalazine	99	2						6,050
Sulfapyridine			99	2				1,930
Sulfisoxazole	96	4						166
Sulindac	99	1						88
Sumatriptan	99	1						37
Tamoxifen	74	27						24
Tamsulosin	96	4						2.8

PhAC	Importance of Each Source							M _T
	[(M _{cu} / M _{HU} /M _{OCD} /M _{OHD} /M _{endo} /M _{IDU} /M _{OID})/M _T ×100] (%)							
	M _{cu}	M _{HU}	M _{OCD}	M _{OHD}	M _{endo}	M _{IDU}	M _{OID}	
Tazobactam	1	99						406
Telithromycin	99	1						242
Temazepam	92.0	2.3	5.4	0.3				988
Terbutaline	98	2						24
Testosterone	41.3	0.2			59			598
Tetracycline	99	1						6,970
Theophylline	0.8	0.1	99.1	≈ 0				67,830
Tetrahydrocannabinol						100		853
Tiaprofenic Acid	99.6	0.4						1,150
Ticarcillin	1	99						947
Ticlopidine	95	5						97
Timolol	97	3						57
Tolbutamide	89	11						137
Tramadol	99	1						210
Trazodone	95	5						816
Triamterene	99	1						1,390
Trifluoperazine	92	8						30
Trihexyphenidyl	91	10						12
Trimethoprim	92	8						2,880
Trimipramine	98	2						38
Valacyclovir	99	1						48
Valproic Acid	17	3	75	5				8,580
Valsartan	99	1						10,850
Vancomycin	29	71						288
Venlafaxine	98	2						1,360
Verapamil	98	2						1,350
Warfarin	95	5						43.5
Xylometazoline	48	52						2
Zidovudine	76	24						1,250
Zopiclone	95	5	0	0				82

Appendix L: PEC estimates

Tabulation of PEC estimates

Summarized in Table L.1 are the three PEC estimates for each PhAC of the evaluation set. PEC_1 estimates assumed no loss through metabolism and no removal in sewage treatment plants. PEC_2 estimates considered metabolic losses (see Appendix D), however still assumed no removal in sewage treatment plants. PEC_3 considered both metabolic losses and removal in sewage treatment plants. All PEC estimates were furnished through the use of Eq. 2 (main body).

Table L.1 PEC estimates for each PhAC of the evaluation set

PhAC	PEC_1	PEC_2	PEC_3
	ng/L		
Acetaminophen	33,000	30,000	10,000
Metformin	7,700	6,400	3,500
Ibuprofen	7,700	2,600	1,000
Acetylcysteine	1,800	1,700	710
Theophylline	39,000	1,100	460
Amoxicillin	1,100	1,000	420
Naproxen	880	660	330
Gabapentin	770	730	270
Docusate	350	350	260
Hydrochlorothiazide	230	230	230
Etidronic Acid	470	470	220
Cephalexin	400	400	180
Aminosalicylic Acid	990	400	170
Penicillin G	210	140	140
Irbesartan	410	170	130
Atenolol	190	170	120
Sulfasalazine	210	100	100
Clarithromycin	300	120	98
Codeine	240	150	96
Penicillin V	230	130	96
Ciprofloxacin	260	180	91
Carbamazepine	360	89	89
Valsartan	220	180	85
Atorvastatin	160	160	81
Furosemide	130	100	76
Cefazolin	67	67	67
Piperacillin	71	63	63
Hydroxychloroquine	120	58	58
Sulfamethoxazole	280	84	54
Cefprozil	76	72	52
Tetracycline	120	120	52
Acetylsalicylic Acid	7,100	140	51
Acyclovir	160	140	51
Ceftazidime	57	51	51
Diltiazem	290	67	50

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Cimetidine	130	79	49
Metoprolol	340	56	46
Valproic Acid	570	140	46
Acebutolol	190	72	45
Clopidogrel	105	59	43
Losartan	95	62	41
Metronidazole	140	58	41
Chlorhexidine	37	37	37
Methyldopa	42	37	37
Lamotrigine	39	36	36
Eprosartan	53	52	35
Phenytoin	150	49	35
Allopurinol	300	89	34
Fenofibric Acid	150	63	33
Sotalol	41	41	33
Citalopram	65	32	32
Labetalol	42	33	32
Diclofenac	150	44	31
Trimethoprim	61	48	29
Azithromycin	51	28	28
Oxazepam	57	28	28
Quinine	94	26	26
Clotrimazole	33	33	25
Lisinopril	25	25	25
Amitriptyline	68	24	24
Carbidopa	33	23	23
Levofloxacin	36	31	22
Morphine	280	54	22
Triamterene	47	23	21
Zidovudine	23	21	21
Alendronate	20	20	20
Fenofibrate	170	27	20
Ramipril	52	21	20
Tiaprofenic Acid	20	19	19
Venlafaxine	340	23	19
Ampicillin	46	38	18
Clindamycin	103	18	18
Cocaine	660	54	18
Bupropion	200	21	17
Escitalopram	69	17	17
Verapamil	110	23	17
Erythromycin	75	21	16
Temazepam	23	16	16
Ticarcillin	17	16	16
Amiodarone	56	42	15
Candesartan	19	15	15
Dipyridamole	47	47	15
Doxycycline	16	15	15
Gemfibrozil	73	29	15
Hydrocortisone	50	45	15
Celecoxib	310	14	14
Clavulanic Acid	29	15	14

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Rosuvastatin	30	25	14
Cefadroxil	14	13	13
Sulfapyridine	130	32	13
Nizatidine	18	12	12
Bezafibrate	29	22	11
Clodronic Acid	11	11	11
Enalaprilat	16	11	11
Levodopa	150	19	10
Norfloxacin	31	18	10
Trazodone	88	14	10
Nadolol	14	14	9.8
Nitrofurantoin	23	9.3	9.3
Primidone	24	11	9.2
Ceftriaxone	14	8.8	8.8
Orlistat	33	27	8.8
Sertraline	79	11	8.8
Nystatin	21	21	8.7
Cortisone	53	26	8.4
Quinapril	22	8.8	8.1
Methamphetamine	25	11	7.8
Baclofen	7.9	7.1	7.1
Pravastatin	27	11	7.1
Tazobactam	8.7	6.8	6.7
Lidocaine	24	6.6	6.6
Propranolol	38	6.7	6.3
Estriol	20	18	6.2
Fluoxetine	20	6.9	6.2
Minocycline	41	19	6.2
Cetirizine	16	6.1	6.1
Oxycodone	54	6.5	5.8
Isoniazid	14	5.5	5.5
Ethambutol	5.4	5.3	5.3
Amantadine	7.6	6.6	5.2
Cefixime	5.2	5.2	5.2
Acarbose	13	6.9	5.0
Fluconazole	6.7	6.5	4.8
Vancomycin	5.1	4.8	4.8
Chloroquine	8.3	4.6	4.6
Diatrizoate	4.5	4.5	4.5
Isosorbide-5-Mononitrate	23	5.3	4.5
Propofol	11	4.7	4.4
Quetiapine	170	4.9	4.4
Testosterone	19	10	4.3
Captopril	5.8	4.2	4.2
Hydromorphone	58	4.4	4.1
MDMA	34	6.8	4.1
Rifampin	9.1	4.1	4.1
Telithromycin	8.8	4.0	4.0
Lorazepam	4.8	3.9	3.9
Mupirocin	3.9	3.9	3.8
Propylthiouracil	5.2	3.7	3.7
Ranitidine	7.4	6.5	3.7

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Propafenone	41	4.1	3.6
Cefaclor	14	10	3.5
Tetrahydrocannabinol	1,400	14	3.5
Tramadol	8.3	3.5	3.5
Azathioprine	17	3.8	3.4
Cefuroxime	4.6	4.6	3.3
Dihydrotestosterone	17	4.0	3.3
Bisoprolol	6.7	4.2	3.1
Pentoxifylline	62	3.1	3.1
Salbutamol	4.0	3.8	3.1
Ketoprofen	6.4	5.3	3.0
Indomethacin	20	5.7	2.9
Sulfisoxazole	5.4	2.8	2.8
Nabumetone	29	2.7	2.6
Famotidine	4.7	3.8	2.5
Triiodothyronine	2.4	2.4	2.4
Thyroxine	4.9	4.3	2.3
Tolbutamide	21	2.3	2.3
Ketoconazole	8.1	6.0	2.2
Clozapine	30	3.0	2.1
Fluorouracil	17	3.0	2.1
Ofloxacin	4.8	4.0	2.1
Methylphenidate	24	2.2	2.0
Bicalutamide	3.9	1.9	1.8
Carvedilol	5.1	3.4	1.8
Cytarabine	12	2.4	1.8
Etodolac	5.1	1.8	1.8
Gentamicin	1.8	1.8	1.8
Betamethasone	2.0	1.7	1.7
Estrone	5.4	3.2	1.7
Benzylamine	1.9	1.9	1.6
Enalapril	17	4.1	1.6
Glyburide	26	1.5	1.5
Prednisolone	15	3.3	1.5
Sulindac	7	1.5	1.5
Amlodipine	28	2.1	1.4
Amphetamine	27	3.8	1.4
Androstenedione	4.3	4.3	1.4
Orphenadrine	4.8	2.0	1.4
Phenobarbital	37	4.3	1.4
Sulfacetamide	1.4	1.4	1.4
Zopiclone	14	1.4	1.4
Cyproterone	2.6	1.6	1.3
Dextroamphetamine	27	3.6	1.3
Domperidone	24	1.7	1.3
Procainamide	2.3	1.3	1.3
Prochlorperazine	1.3	1.3	1.3
Amiloride	1.8	1.6	1.2
Nortriptyline	65	1.4	1.2
Capecitabine	22	1.2	1.1
Oxaprozin	3.5	1.1	1.1
Pamidronate	1.1	1.1	1.1

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Ticlopidine	18	1.6	1.1
Benserazide	1.4	1.4	1.0
Butalbital	14	1.0	1.0
Dextropropoxyphene	4.2	1.0	1.0
Gliclazide	68	1.0	1.0
Hydrocodone	240	2.8	1.0
Didanosine	2.7	2.2	0.9
Estradiol	3.8	2.3	0.9
Timolol	1.2	0.9	0.9
Methotrexate	1.2	0.8	0.8
Miconazole	1.5	1.5	0.8
Cromolyn	0.9	0.8	0.7
Fluvoxamine	19	0.8	0.7
Mefenamic Acid	18	1.1	0.7
Methadone	2.5	0.9	0.7
Paroxetine	42	1.3	0.7
Quinidine	3.1	0.7	0.7
Diazepam	4.7	0.6	0.6
Esomeprazole	110	0.6	0.6
Fentanyl	0.9	0.6	0.6
Flurazepam	5.0	0.6	0.6
Mometasone	0.8	0.6	0.6
Simvastatin	64	1.3	0.6
Trimipramine	6.2	0.6	0.6
Valacyclovir	160	0.8	0.6
Ethacrynic acid	0.5	0.5	0.5
Oseltamivir carboxylate	0.6	0.5	0.5
Perphenazine	0.5	0.5	0.5
Risperidone	1.6	0.5	0.5
Drospirenone	1.2	1.2	0.4
Imipramine	7.8	0.7	0.4
Lansoprazole	42	0.4	0.4
Methylprednisolone	3.3	1.4	0.4
Spironolactone	31	0.6	0.4
Sumatriptan	5.1	0.6	0.4
Terbutaline	0.6	0.4	0.4
Trifluoperazine	0.5	0.5	0.4
Ipratropium	0.42	0.31	0.31
Benztropine	0.4	0.4	0.3
Budesonide	1.0	0.3	0.3
Chlorpromazine	6.0	0.4	0.3
Cyclophosphamide	2.2	0.5	0.3
Felodipine	3.3	0.3	0.3
Perindopril	5.4	0.7	0.3
Tamoxifen	4.4	0.4	0.3
Carboplatin	0.35	0.31	0.24
Oxprenolol	0.35	0.24	0.22
Bromazepam	1.9	0.2	0.2
Dexamethasone	0.8	0.6	0.2
Flutamide	5.8	0.3	0.2
Fosfomycin	0.3	0.2	0.2
Haloperidol	0.8	0.3	0.2

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Methotrimeprazine	4.3	0.3	0.2
Nitrazepam	1.3	0.3	0.2
Prednisone	15	0.7	0.2
Warfarin	10	0.7	0.2
Phenyltoloxamine	0.24	0.24	0.19
Neomycin	0.42	0.42	0.17
Amphotericin B	0.23	0.15	0.15
Etoposide	0.27	0.27	0.14
Alprazolam	0.5	0.2	0.1
Bromocriptine	0.2	0.2	0.1
Doxepin	8.8	0.1	0.1
Etonogestrel	0.18	0.18	0.10
Exemestane	0.6	0.3	0.1
Fluocinonide	0.1	0.1	0.1
Fluphenazine	0.2	0.2	0.1
Fluticasone	1.8	0.1	0.1
Hydroxyzine	12	0.1	0.1
Ifosfamide	0.2	0.1	0.1
Levobunolol	0.1	0.1	0.1
Mitotane	0.8	0.5	0.1
Nifedipine	76	0.1	0.1
Norethindrone	1	0.4	0.1
Omeprazole	55	0.1	0.1
Oseltamivir	0.6	0.1	0.1
Rizatriptan	0.3	0.1	0.1
Trihexyphenidyl	0.2	0.2	0.1
Clorazepate	0.43	0.09	0.09
Digoxin	0.15	0.12	0.09
Beclomethasone	0.11	0.10	0.08
Atropine	0.07	0.06	0.06
Diphenoxylate	0.30	0.12	0.06
Chloramphenicol	0.14	0.13	0.05
Clonidine	0.06	0.05	0.05
Desloratadine	1.0	0.06	0.05
Naltrexone	0.29	0.05	0.05
Piroxicam	0.5	0.05	0.05
Tamsulosin	0.44	0.05	0.05
Clonazepam	2.3	0.05	0.04
Ethinyl estradiol	0.22	0.10	0.04
Ondansetron	0.32	0.11	0.04
Isosorbide Dinitrate	7.1	0.1	0.04
Norgestimate	0.4	0.1	0.04
Anastrozole	0.12	0.03	0.03
Cisplatin	0.08	0.06	0.03
Epirubicin	0.06	0.03	0.03
Spiramycin	0.68	0.03	0.03
Betaxolol	0.06	0.06	0.02
Doxorubicin	0.08	0.02	0.02
Loratadine	0.6	0.04	0.02
Midazolam	0.48	0.05	0.02
Nilutamide	0.32	0.02	0.02
Xylometazoline	0.03	0.03	0.02

PhAC	PEC ₁	PEC ₂	PEC ₃
	ng/L		
Ketamine	0.38	0.03	0.01
Letrozole	0.17	0.02	0.01
Leuprolide	0.02	0.02	0.01
Loxapine	2.38	0.01	0.01
Selegiline	0.12	0.02	0.01
Fenoterol	0.021	0.009	0.009
Chloral Hydrate	15	0.007	0.007
Formoterol	0.014	0.007	0.007
Melphalan	0.012	0.006	0.004
Bleomycin	0.005	0.003	0.003
Misoprostol	0.27	0.003	0.003
Promethazine	0.93	0.006	0.003
Salmeterol	0.13	0.01	0.003
Disulfiram	0.017	0.003	0.002
Heroin	13	0.003	0.002
Daunorubicin	0.0033	0.0016	0.0016
Buserelin	0.002	0.002	0.001
Clofibric Acid	0.002	0.002	0.001
Desogestrel	0.130	0.003	0.001
Finasteride	1.8	0.001	0.001
Goserelin	0.009	0.002	0.001
Nimodipine	0.14	0.001	0.001
Naloxone	0.0023	0.0009	0.0009
Mitomycin	0.0039	0.0008	0.0008
Pantoprazole	110	0.0010	0.0007
Carmustine	0.0240	0.0002	0.0002
Fosphenytoin	0.004	0.0002	0.0002
Fulvestrant	0.0025	0.0005	0.0002
Idarubicin	0.0004	0.0002	0.0002
Meprobamate	0.00029	0.00009	0.00008
Dactinomycin	0.00008	0.00005	0.00005
Sincalide	0.0000001	0.0000001	0.0000001
Clofibrate	0.002	≈ 0	≈ 0
Ethinodiol	0.24	≈ 0	≈ 0
Famciclovir	27	≈ 0	≈ 0
Rabeprazole	35	≈ 0	≈ 0
Sildenafil	7.9	≈ 0	≈ 0
Buprenorphine	Was not approved for sale in Canada in 2006.		
Fenoprofen	Has been discontinued from clinical use in Canada since 2002.		
Roxithromycin	Yet to be approved for use in Canada.		

Impact of metabolic loss and removal in sewage treatment plants on PEC estimates

Accounting for metabolic loss (PEC_2 estimates relative to PEC_1 estimates) resulted in a median reduction of 56%, accounting for removal in sewage treatment plants on top of that (PEC_3 estimates relative to PEC_2 estimates) resulted in an added median reduction of 22% (See Figure L.1).

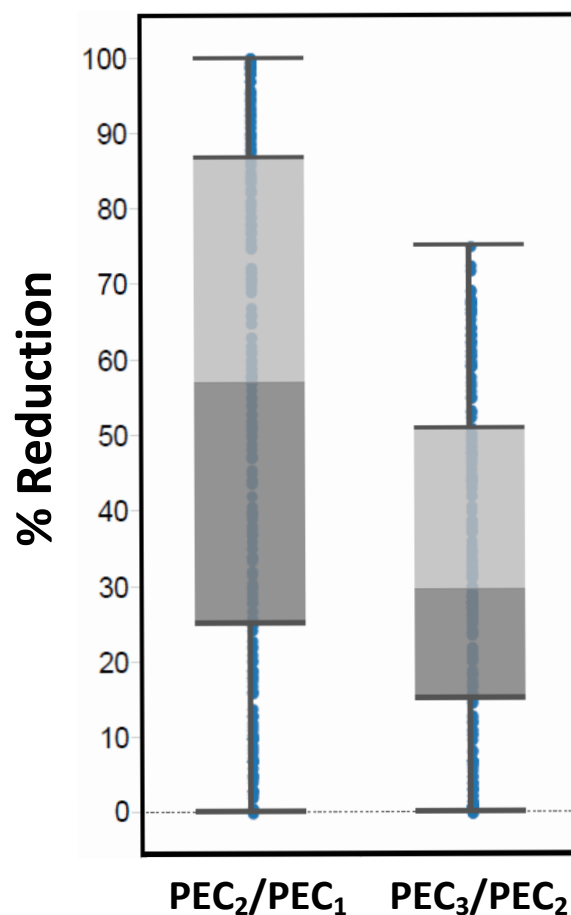


Figure L.1 Impact of metabolic loss and removal in sewage treatment plants on *PEC* estimates

Appendix M: Analysis of carbamazepine MECs

Two hundred and twenty one (221) MECs for carbamazepine in finished Canadian drinking waters were compiled from the following sources: Chen et al. (2006), Garcia-Ac et al. (2009a), Kleywegt et al. (2011), MDDEP (2011), Metcalfe et al. (2010) and Tabe et al.(2010). The compiled data was sorted and plotted as a frequency plot (see Figure M.1) All non-detects were plotted at the respective detection limits.

Figure M.1 suggests that MEC_{95} for carbamazepine in finished Canadian drinking waters was 9.8 ng/L. The figure also suggests that the PEC_3 estimate for carbamazepine of 82 ng/L is greater than 98% of the MECs measured for the PhAC.

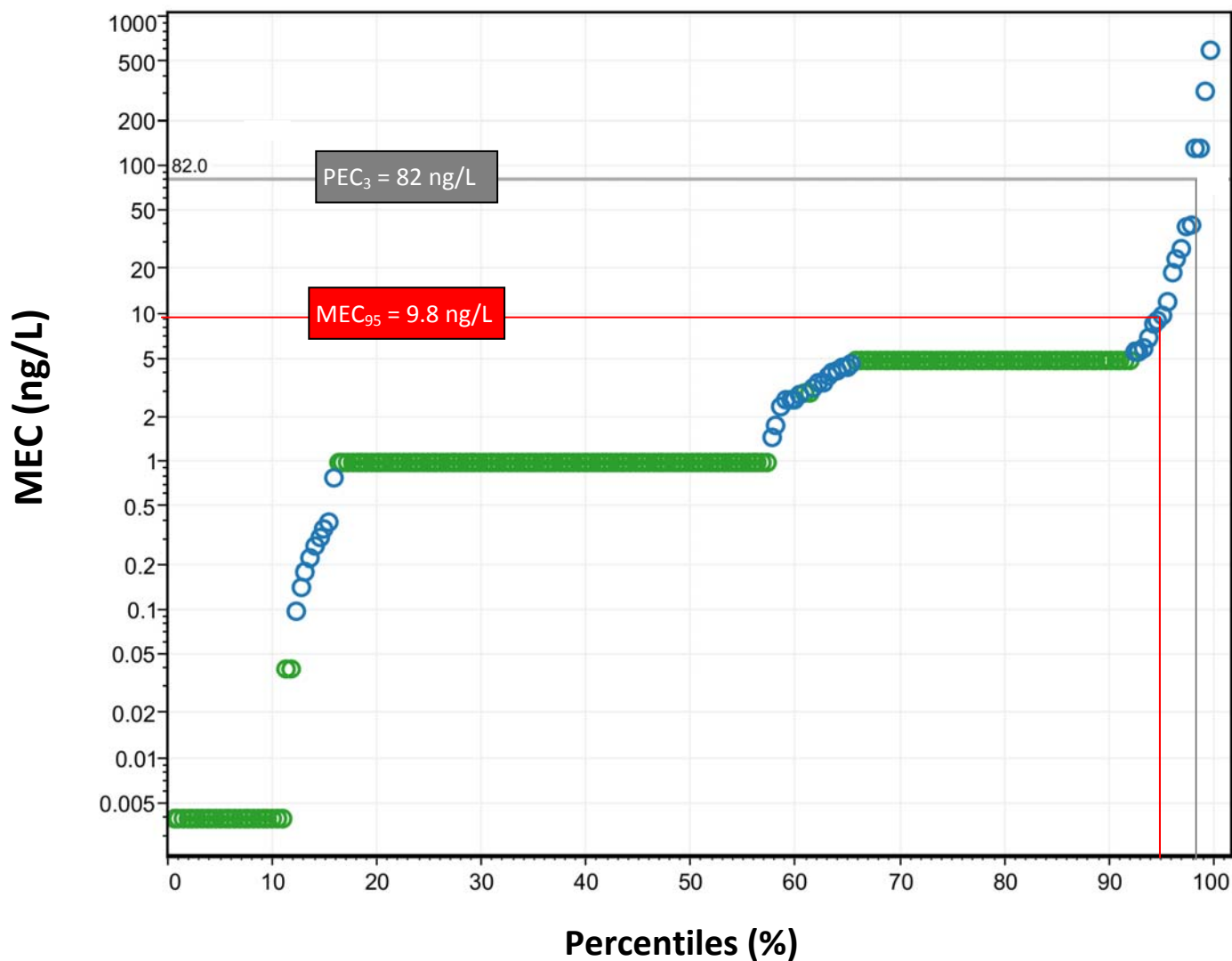


Figure M.1 Compiled MECs for carbamazepine in finished Canadian drinking water samples. All positive detections have been shown as blue hollow circles and all non-detects, which have been plotted at the respective detection limits, have been shown as green hollow circles.

Appendix N: Analysis of adult and pediatric LOTDs

For 224 PhACs of the evaluation set, adult as well as pediatric dosing schedules were available. Such data was used to estimate an adult and a pediatric LOTD for each of the 224 PhACs. In turn, pediatric to adult LOTD ratios ($\text{LOTD}_{\text{pediatric}}/\text{LOTD}_{\text{adult}}$) for each of the 224 PhACs were estimated. These ratios have been plotted in Figure N.1 as a probability plot. Figure N.1 suggests that for 88% of the evaluated cases, or 199 PhACs, LOTDs for adults were lower, hence more conservative, than their pediatric counterparts.

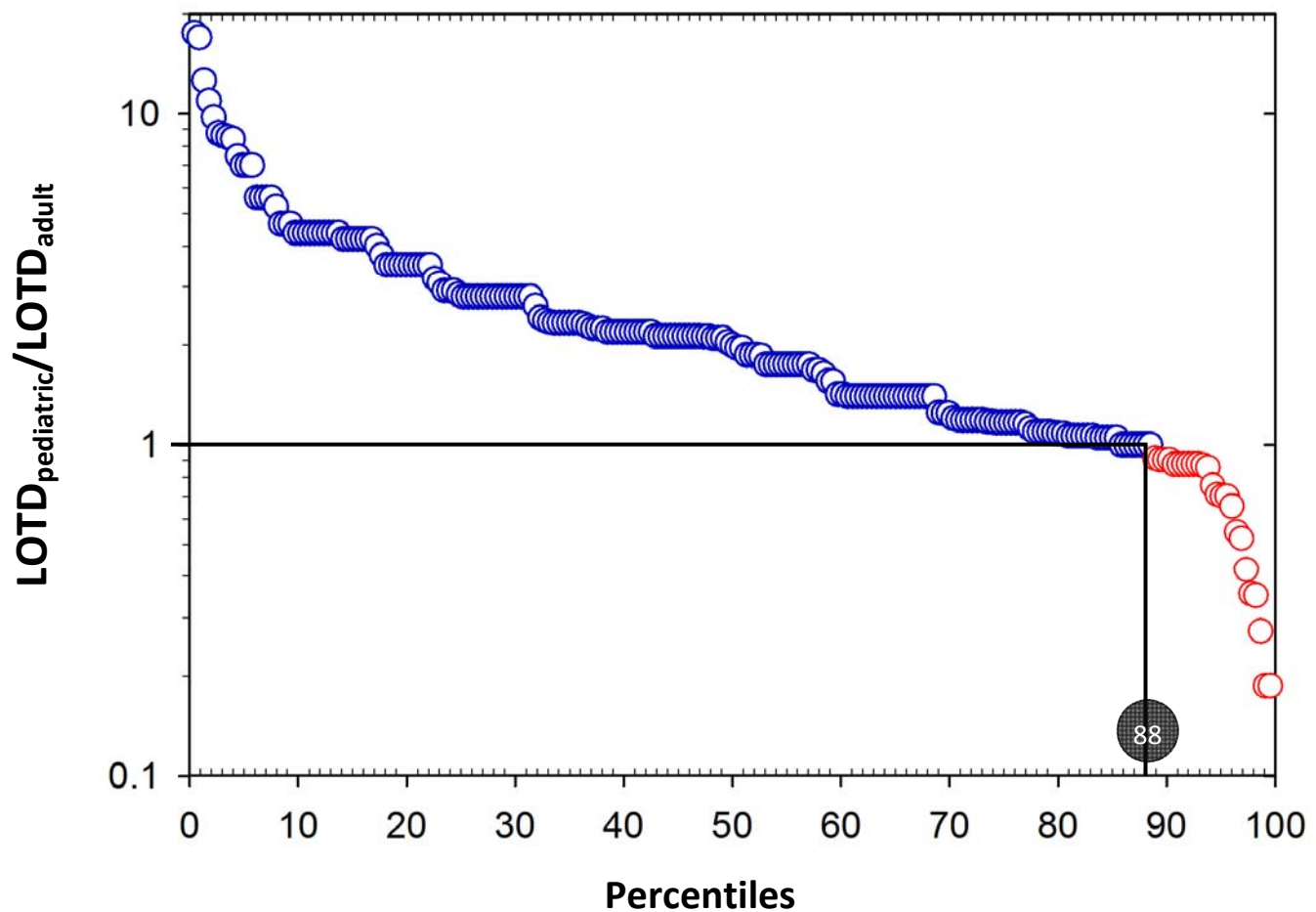


Figure N.1 $\text{LOTD}_{\text{pediatric}}/\text{LOTD}_{\text{adult}}$ for 224 PhAC of the evaluation set.

Appendix O: Estimation of the acceptable daily intake for PhACs

The Acceptable Daily Intake (ADI) values for each of the PhACs in the evaluation set were estimated using the approach presented in the main body and summarized in Figure 1. Based on this approach, the following information are summarized in Table O.1 for each PhAC:

- the types of inputs that were available and used as a basis for ADI evaluations;
- the particular method and the input value ultimately selected to estimate the ADI (as per Figure 1);
- the estimated ADI value.

Table O.1 ADI evaluation for each PhAC of the evaluation set

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Acarbose			✓	✓		LOTD (25 mg/d) with a default SF of 1,000 was used.	0.36
Acebutolol			✓			LOTD (200 mg/d) with a default SF of 1,000 was used.	2.9
Acetaminophen	✓		✓	✓		The established ADI of 0.05 mg/kg·d (EMEA, 1999) was adopted.	50
Acetylcysteine			✓	✓		OEL of 5 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	7.1
Acetylsalicylic Acid	✓		✓	✓		The established ADI of 0.0083 mg/kg·d (EMEA, 1999) was adopted.	8.3
Acyclovir			✓	✓		OEL of 5 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	7.1
Alendronate			✓	✓		OEL of 0.03 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.043
Allopurinol			✓	✓		LOTD (100 mg/d) with a default SF of 1,000 was used.	1.4
Alprazolam			✓	✓		LOTD (0.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.00071
Amantadine			✓	✓		LOTD (100 mg/d) with a default SF of 1,000 was used.	1.4
Amiloride			✓	✓		LOTD (5 mg/d) with a default SF of 1,000 was used	0.07
Aminosalicic Acid			✓	✓		OEL of 0.2 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.29
Amiodarone			✓	✓		OEL of 0.07mg/m ³ (Hospira MSDS) with a default SF of 100 was used	0.10
Amitriptyline			✓	✓		OEL of 0.1 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.10 ^(a)
Amlodipine			✓	✓		LOTD (2.5 mg/d) with a default SF of 1,000 was used.	0.036
Amoxicillin	✓		✓	✓		The established ADI of 0.00043 mg/kg·d (NWQMS, 2008) was adopted.	0.43
Amphetamine			✓	✓		OEL of 0.035 mg/m ³ (Covidien MSDS) with a default SF of 100 was used.	0.05
Amphotericin B			✓	✓		OEL of 0.08 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.11
Ampicillin	✓		✓	✓		The established ADI of 0.00043 mg/kg·d (NWQMS, 2008) was adopted.	0.43
Anastrozole			✓	✓		OEL of 0.0001 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.00014
Androstenedione			✓			Androstenedione is not used clinically. As a preliminary estimate, the lowest dose administered to postmenopausal women of 50 mg (Leder et al., 2002) was used as the	0.071

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
						POD with a highly conservative SF of 10,000.	
Atenolol			✓	✓		LOTD (25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.036
Atorvastatin			✓	✓		LOTD (10 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.014
Atropine			✓	✓		OEL of 0.0025 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0036
Azathioprine			✓	✓	✓	OEL of 0.003 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0043
Azithromycin			✓	✓		OEL of 0.5 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.71
Baclofen			✓	✓		OEL of 0.1 mg/m ³ (Novartis MSDS) with a default SF of 100 was used.	0.14
Beclomethasone		✓		✓		The established ADI of 0.00004 mg/kg·d (EMA, 2004a) was adopted.	0.040
Benserazide			✓	✓		OEL of 0.25 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.36
Benztropine			✓	✓		LOTD (0.5 mg/d) with a default SF of 1,000 was used.	0.0071
Benzydamine			✓			LOTD (22.5 mg/d) with a default SF of 1,000 was used.	0.32
Betamethasone		✓	✓	✓		The established ADI of 0.000015 mg/kg·d (EMA, 1999c) was adopted.	0.015
Betaxolol			✓			LOTD (5 mg/d) with a default SF of 1000 was used.	0.071
Bezafibrate			✓	✓		OEL of 1 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	1.4
Bicalutamide			✓	✓		OEL of 0.01 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.014
Bisoprolol			✓	✓		LOTD (1.25 mg/d) with a default SF of 1,000 was used.	0.018
Bleomycin			✓	✓		OEL of 0.00005 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.00007
Bromazepam			✓	✓		LOTD (3 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0043
Bromocriptine			✓			LOTD (0.8 mg/d) with a default SF of 1000 was used.	0.011
Budesonide			✓	✓		OEL of 0.01 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.014
Buprenorphine			✓	✓		OEL of 0.0003 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.00043
Bupropion			✓	✓		OEL of 1 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	1.4

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Buserelin			✓	✓		LOTD (1 mg/d) with a default SF of 1,000 was used.	0.014
Butalbital			✓			LOTD (50 mg/d) with a default SF of 1,000 was used.	0.71
Candesartan			✓	✓		OEL of 0.001 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.0014
Capecitabine			✓	✓		OEL of 0.01 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.014
Captopril			✓			LOTD (6.25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0089
Carbamazepine			✓			LOTD (200 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.29
Carbidopa			✓	✓		OEL of 0.1 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	0.14
Carboplatin			✓	✓		OEL of 0.002 mg/m ³ for platinum (ACGIH, 2010) with a default SF of 100 was used.	0.0029
Carmustine			✓	✓		OEL of 0.0001 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.00014
Carvedilol			✓	✓		OEL of 0.03 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.043
Cefaclor			✓	✓		OEL of <0.15 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.21
Cefadroxil			✓	✓		OEL of 1 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	1.4
Cefazolin	✓		✓	✓		The established ADI of 0.01 mg/kg.d (EMEA, 1996b) was adopted.	10
Cefixime			✓			LOTD (400 mg/d) with a default SF of 1,000 was used.	5.7
Cefprozil			✓	✓		OEL of 1 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	1.4
Ceftazidime			✓	✓		OEL of < 0.15 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.21
Ceftriaxone			✓	✓		OEL of 0.02 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.029
Cefuroxime			✓	✓		OEL of 0.1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.14
Celecoxib			✓	✓		OEL of 1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	1.4
Cephalexin	✓		✓	✓		The established ADI of 0.01 mg/kg.d (Department of Health and Ageing-Australia, 2011) was adopted.	10
Cetirizine			✓	✓		LOTD (5 mg/d) with a default SF of 1,000 was used.	0.071
Chloral Hydrate	✓		✓			The established TDI of 0.0045 mg/kg.d (Health Canada, 2009) was adopted.	4.5

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Chloramphenicol			✓	✓		Due to genotoxic carcinogenicity, LOTD of 875 mg/d was divided by 10^5	0.125
Chlorhexidine	✓		✓	✓		The established ADI of 0.2 mg/kg.d (Australia ADI, 2011) was adopted.	200
Chloroquine			✓			LOTD (71 mg/d) with a default SF of 1,000 was used.	1.0
Chlorpromazine			✓	✓		OEL of 0.04 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.057
Cimetidine			✓	✓		OEL of 0.5 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.71
Ciprofloxacin	✓		✓	✓		The suggested ADI of 0.00015 mg/kg.d (Jeong et al., 2009) was adopted.	0.15
Cisplatin			✓	✓		Due to genotoxic carcinogenicity LOTD of 3.1 mg/d was divided by 10^5	0.00044
Citalopram			✓	✓		OEL of 0.01 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.014
Clarithromycin			✓	✓		OEL of 1 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	1.4
Clavulanic Acid	✓		✓	✓		The established ADI of 0.05 mg/kg.d (EMA, 2001) was adopted.	50
Clindamycin			✓	✓		OEL of 0.1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.14
Clodronic Acid			✓	✓		OEL of 0.2 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.29
Clofibrate			✓	✓		OEL of 0.8 mg/m ³ (Sargent et al., 2002) with a default SF of 100 was used.	1.1
Clofibric Acid						Established ADI of Clofibrate (see above) was used	1.1
Clonazepam			✓	✓		LOTD (0.25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.00036
Clonidine			✓	✓		OEL of 0.00019 mg/m ³ (Boehringer Ingelheim MSDS) with a default SF of 100 was used.	0.00027
Clopidogrel			✓	✓		OEL of 0.02 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.029
Clorazepate			✓			LOTD (15 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.021
Clotrimazole			✓	✓		OEL of 0.05 mg/m ³ (Schering Plough MSDS) with a default SF of 100 was used.	0.071
Clozapine			✓	✓		OEL of 0.1 mg/m ³ (Novartis MSDS) with a default SF of 100 was used.	0.14
Cocaine			✓			Oral dose of 4.3 mg/d (Jenkins et al., 1996) with a SF of 10,000 was used.	0.0069
Codeine			✓	✓		OEL of 0.07 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.10

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Cortisone			✓	✓		LOTD (25 mg/d) with a SF of 1,000 was used.	0.36
Cromolyn			✓			LOTD (800 mg/d) with a SF of 1,000 was used.	11
Cyclophosphamide			✓	✓	✓	OEL of 0.001 mg/m ³ (BMS MSDS) with a default SF of 100 was used	0.0014
Cyproterone			✓	✓		OEL of 0.02 mg/m ³ (Bayer MSDS) with a default SF of 100 was used.	0.029
Cytarabine			✓	✓		OEL of 0.002 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0029
Dactinomycin			✓	✓	✓	CAL EPA's NSRL of 0.08 ng/day was used.	0.0000011
Daunorubicin			✓	✓		OEL of 0.0001 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00014
Desloratadine			✓	✓		LOTD (5 mg/d) with a default SF of 1,000 was used.	0.063 ^(a)
Desogestrel			✓	✓		N.V. Organon In-house target limit of 0.1 µg/day is used with a SF of 100.	0.000014
Dexamethasone	✓		✓	✓		The established ADI of 0.000015 mg/kg·d (EMA, 2003) was adopted.	0.015
Dextroamphetamine			✓	✓		OEL of 0.008 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.011
Dextropropoxyphene			✓	✓		OEL of 0.3 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.43
Diatrizoate			✓			LOTD (22,500 mg/d) with a default SF of 1,000 was used.	320
Diazepam			✓	✓		LOTD (4 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0057
Diclofenac	✓		✓	✓		The suggested ADI of 0.0005 mg/kg·d (EMA, 2004) was adopted.	0.50
Didanosine			✓	✓		OEL of 0.2 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.29
Digoxin			✓	✓		LOTD (0.05 mg/d) with a default SF of 1,000 was used.	0.0007
Dihydrotestosterone			✓			Dihydrotestosterone is not used clinically. As a preliminary estimate, the lowest dose administered to postmenopausal women of 10 mg (Schanzer et al., 1996) was used as the POD with a highly conservative SF of 10,000.	0.014
Diltiazem			✓	✓		OEL of 1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	1.4
Diphenoxylate			✓	✓		OEL of 0.0025 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0036
Dipyridamole			✓	✓		OEL of 1 mg/m ³ (Boehringer Ingelheim MSDS) with a default SF of 100 was used.	1.4

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Disulfiram			✓	✓		LOTD (125 mg/d) with a default SF of a 1,000 was used.	1.8
Docusate			✓	✓		OEL of 0.1 mg/m ³ (Boehringer Ingelheim MSDS) with a default SF of 100 was used.	0.14
Domperidone			✓	✓		LOTD (30 mg/d) with a default SF of 1000 was used.	0.43
Doxepin			✓	✓		LOTD (3 mg/d) with a default SF of 1,000 was used.	0.043
Doxorubicin			✓	✓		OEL of 0.0005 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00071
Doxycycline	✓		✓	✓		The suggested ADI of 0.003 mg/kg.d (EMA, 1997) was adopted.	3.0
Drospirenone			✓			LOTD (0.25 mg/d) with a default SF of 10,000 was used.	0.00036
Enalapril			✓	✓		LOTD (2.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0036
Enalaprilat			✓	✓		LOTD of Enalapril (2.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0036
Epirubicin			✓	✓		OEL of 0.0006 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00086
Eprosartan			✓	✓		OEL of 0.1 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	0.14
Erythromycin	✓		✓	✓		The suggested ADI of 0.005 mg/kg.d (EMA, 2002) was adopted.	5.0
Escitalopram			✓			LOTD (10 mg/d) with a default SF of 1,000 was used.	0.14
Esomeprazole			✓	✓		OEL of 0.1 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.14
Estradiol	✓		✓	✓	✓	The suggested ADI of 0.00005 mg/kg.d (FAO/WHO, 2000) was adopted.	0.050
Estriol			✓	✓		OEL of 0.0001 mg/m ³ (Caldwell et al., 2010) with a default SF of 100 was used.	0.00014
Estrone			✓	✓		OEL of 0.0001 mg/m ³ (Caldwell et al., 2010) with a default SF of 100 was used.	0.00014
Ethacrynic acid			✓			LOTD (50 mg/d) with a default SF of 1,000 was used.	0.71
Ethambutol			✓			LOTD (1050 mg/d) with a default SF of 1,000 was used.	15
Ethinylestradiol			✓	✓		LOTD (0.01 mg/d) with a default SF of 10,000 was used.	0.000014
Ethinodiol			✓	✓		OEL of 0.25 µg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00036
Etidronic Acid			✓			LOTD (350 mg/d) with a default SF of 1000 was used.	5.0

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Etodolac			✓			LOTD (200 mg/d) with a default SF of 1,000 was used.	2.9
Etonogestrel				✓		N.V. Organon In-house target limit of 0.25 µg/day is used with a SF of 100.	0.000036
Etoposide			✓	✓		OEL of 0.00014 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.00020
Exemestane			✓	✓		OEL of 0.008 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.011
Famciclovir			✓	✓		OEL of 1.25 mg/m ³ (Novartis MSDS) with a default SF of 100 was used.	1.8
Famotidine			✓	✓		OEL of 0.1 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.14
Felodipine			✓	✓		LOTD (2.5 mg/d) with a default SF of 1,000 was used.	0.036
Fenofibrate			✓	✓		LOTD (40 mg/d) with a default SF of 1,000 was used.	0.57
Fenofibric Acid						LOTD of Fenofibrate (40 mg/d) with a default SF of 1,000 was used.	0.57
Fenoprofen			✓			LOTD (800 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	1.14
Fenoterol			✓			LOTD (7.5 mg/d) with a default SF of 1,000 was used.	0.11
Fentanyl			✓	✓		OEL of 0.0001 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.00014
Finasteride			✓	✓		OEL of 0.0005 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.00071
Fluconazole			✓	✓		OEL of 0.2 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.29
Fluocinonide				✓		OEL of 0.00009 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.00013
Fluorouracil			✓	✓		Genotoxic carcinogen, hence LTD ₁₀ of 0.28 mg/kg-d was linearly extrapolated by dividing by 10 ⁵ .	0.0028
Fluoxetine			✓	✓		OEL of 0.05 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.071
Fluphenazine			✓	✓		OEL of 0.002 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.0029
Flurazepam			✓			LOTD (15 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.021
Flutamide			✓	✓		OEL of 0.001 mg/m ³ (Schering Plough MSDS) with a default SF of 100 was used.	0.0014
Fluticasone				✓		OEL of 0.003 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.0043
Fluvoxamine			✓	✓		LOTD (50 mg/d) with a SF of 1,000 was used	0.71

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Formoterol			✓	✓		OEL of 0.00008 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.00011
Fosfomycin			✓			LOTD (3000 mg/d) with a SF of 1,000 was used.	43
Fosphenytoin				✓		OEL of 0.6 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.86
Fulvestrant			✓	✓		OEL of 0.001 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.0014
Furosemide			✓	✓		OEL of 0.1 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.14
Gabapentin			✓	✓		OEL of 1.2 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	1.7
Gemfibrozil			✓	✓		OEL of 1.0 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	1.4
Gentamicin	✓		✓	✓		The established ADI of 0.004 mg/kg.d (EMA, 2000) was adopted.	4.0
Gliclazide			✓			LOTD(80 mg/d) with a SF of 1,000 was used.	1.1
Glyburide			✓	✓		OEL of 0.001 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0014
Goserelin			✓	✓		OEL of 0.0025 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.0036
Haloperidol			✓	✓		OEL of 0.001 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0014
Heroin			✓			LOTD (5 mg/d) with a SF of 10,000 was used.	0.0071
Hydrochlorothiazide	✓		✓	✓		The suggested ADI of 0.025 mg/kg.d (EMA, 1999d) was adopted.	25
Hydrocodone			✓	✓		LOTD (10 mg/d) with a SF of 1,000 was used.	0.10 ^(a)
Hydrocortisone			✓	✓		OEL of 0.1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.14
Hydromorphone			✓	✓		OEL of 0.002 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.0029
Hydroxychloroquine			✓			LOTD (58 mg/d) with a SF of 1,000 was used.	0.83
Hydroxyzine			✓	✓		OEL of 0.3 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.43
Ibuprofen			✓	✓		LOTD (200 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug	0.29
Idarubicin			✓	✓		OEL of 0.0001 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00014
Ifosfamide			✓	✓		OEL of 0.0001 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.00014
Imipramine			✓			LOTD (75 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.11

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Indomethacin			✓	✓		OEL of 0.1 mg/m ³ (Sargent et al., 2002) with a default SF of 100 was used.	0.14
Ipratropium				✓		OEL of 0.015 mg/m ³ (Boehringer Ingelheim MSDS) with a default SF of 100 was used.	0.021
Irbesartan			✓	✓		OEL of 0.03 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.043
Isoniazid			✓			LOTD (300 mg/d) with a SF of 1,000 was used.	4.3
Isosorbide Dinitrate			✓	✓		OEL of 0.01 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.014
Isosorbide-5-Mononitrate			✓	✓		OEL of 0.05 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.071
Ketamine			✓	✓		OEL of 0.025 mg/m ³ (Fort Dodge Animal Health MSDS) with a default SF of 100 was used.	0.036
Ketoconazole			✓	✓		OEL of 0.2 mg/m ³ (McNeil Consumer Health MSDS) with a default SF of 100 was used.	0.29
Ketoprofen	✓		✓	✓		The established ADI of 0.001 mg/kg.d (EMA, 2000) was adopted.	1.0
Labetalol			✓	✓		OEL of 0.2 mg/m ³ (FARO MSDS) with a default SF of 100 was used.	0.29
Lamotrigine			✓	✓		OEL of 0.2 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.15 ^(a)
Lansoprazole			✓	✓		OEL of 0.06 mg/m ³ (Wyeth MSDS) with a default SF of 100 was used.	0.086
Letrozole			✓	✓		OEL of 0.0001 mg/m ³ (Novartis MSDS) with a default SF of 100 was used.	0.00014
Leuprolide				✓		OEL of 0.00005 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	0.00007
Levobunolol						Lowest daily ophthalmic dose of 0.6 mg/d with a SF of 1,000 was used.	0.0086
Levodopa			✓	✓		OEL of 0.01 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.014
Levofloxacin			✓	✓		OEL of 0.1 mg/m ³ (Greenstone MSDS) with a default SF of 100 was used.	0.14
Thyroxine			✓	✓		LOTD (0.1 mg/d) with a SF of 10,000 was used.	0.00014
Lidocaine			✓	✓		OEL of 0.5 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.71
Triiodothyronine			✓			LOTD (0.005 mg/d) with a SF of 10,000 was used	0.0000071
Lisinopril			✓	✓		LOTD (2.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0036
Loratadine			✓	✓		LOTD (10 mg/d) with a SF of 1,000 was used.	0.14

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Lorazepam			✓	✓		LOTD (0.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.00071
Losartan			✓	✓		LOTD (25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.036
Loxapine			✓			LOTD (20 mg/d) with a SF of 1,000 was used.	0.29
MDMA			✓			NOAEL 0.4 mg/kg.d (Van Aerts, 1998) is used as the POD with a SF of 1,000.	0.40
Mefenamic Acid			✓	✓		OEL of 3 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	4.3
Melphalan			✓	✓	✓	CAL EPA's NSRL (2013) of 5 ng/day was used.	0.000071
Meprobamate			✓			LOTD (1200 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.60 ^(a)
Metformin			✓	✓		OEL of 0.8 mg/m ³ (BMS MSDS) with a default SF of 100 was used.	1.1
Methadone			✓	✓		OEL of 0.02 mg/m ³ (Mallinckrodt MSDS) with a default SF of 100 was used.	0.029
Methamphetamine			✓			LOTD (5 mg/d) with a SF of 10,000 was used.	0.0071
Methotrexate			✓	✓		OEL of 0.002 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.0029
Methotrimeprazine			✓			LOTD (6 mg/d) with a SF of 1,000 was used.	0.086
Methyldopa			✓	✓		OEL of 5 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	7.1
Methylphenidate			✓	✓		LOTD (2.5 mg/d) with a SF of 1,000 was used.	0.036
Methylprednisolone	✓		✓	✓		The suggested ADI of 0.00016 mg/kg.d (EMA, 2004) was adopted.	0.16
Metoprolol			✓	✓		LOTD (25 mg/d) with a default SF of 1,000 was used.	0.36
Metronidazole			✓	✓		Due to genotoxic carcinogenicity concerns LTD ₁₀ of 53.4 mg/kg.d (Gold, 2008) was linearly extrapolated by dividing by 10 ⁵ .	0.53
Miconazole			✓	✓		OEL of 0.2 mg/m ³ (Wyeth MSDS) with a default SF of 100 was used.	0.29
Midazolam			✓	✓		OEL of 0.002 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.0029
Minocycline			✓	✓		LOTD (65 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.093
Misoprostol			✓	✓		LOTD (0.4 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.00057
Mitomycin			✓		✓	CAL EPA's NSRL (2013) of 0.09 ng/day was used.	0.0000013

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Mitotane			✓	✓		OEL of 0.001 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.0014
Mometasone				✓		OEL of 0.001 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.0014
Morphine			✓	✓		OEL of 0.005 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.0071
Mupirocin			✓	✓		OEL of 5 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	7.1
Nabumetone			✓	✓		OEL of 1 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	1.4
Nadolol			✓			LOTD (40 mg/d) with a SF of 1,000 was used.	0.50 ^(a)
Naloxone			✓	✓		LOTD (1 mg/d) with a SF of 1,000 was used.	0.014
Naltrexone			✓	✓		OEL of 0.08 mg/m ³ (Bristol Myers Squibb MSDS) with a default SF of 100 was used.	0.11
Naproxen			✓	✓		OEL of 1 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	1.43
Neomycin	✓		✓	✓		The suggested ADI of 0.06 mg/kg.d (EMEA, 2002) was adopted.	60
Nifedipine			✓	✓		LOTD (30 mg/d) with a SF of 1,000 was used.	0.25 ^(a)
Nilutamide			✓			LOTD (150 mg/d) with a SF of 10,000 was used since it is defined as a hazardous drug by NIOSH (2011).	0.21
Nimodipine			✓			LOTD (300 mg/d) with a SF of 1,000 was used.	4.3
Nitrazepam			✓			LOTD (5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0071
Nitrofurantoin			✓	✓		LOTD (50 mg/d) with a SF of 1,000 was used.	0.71
Nizatidine			✓	✓		OEL of < 0.15 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.21
Norfloxacin			✓	✓		OEL of 2 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	2.9
Norgestimate			✓	✓		LOTD (0.18 mg/d) with a SF of 10,000 was used.	0.00026
Nortriptyline				✓		OEL of 0.015 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.021
Norethindrone			✓	✓		LOTD (0.35 mg/d) with a SF of 10,000 was used.	0.0005
Nystatin			✓	✓		LOTD (320 mg/d) with a SF of 1,000 was used.	4.6
Ofloxacin			✓			LOTD (400 mg/d) with a SF of 1,000 was used.	5.7

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Omeprazole			✓	✓		LOTD (10mg/d) with a SF of 1,000 was used.	0.14
Ondansetron			✓	✓		LOTD (0.5 mg/d) with a SF of 1,000 was used.	0.0071
Orlistat			✓	✓		LOTD (180 mg/d) with a SF of 1,000 was used.	2.6
Orphenadrine			✓			LOTD (200 mg/d) with a SF of 1,000 was used.	2.9
Oseltamivir			✓	✓		OEL of 0.2 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.29
Oseltamivir carboxylate						The established ADI of Oseltamivir was multiplied by 0.75 to estimate an ADI for Oseltamivir-Carboxylate, where 0.75 represents the fraction of administered Oseltamivir that reaches systemic circulation as Oseltamivir Carboxylate.	0.21
Oxaprozin			✓	✓		OEL of 0.1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.14
Oxazepam			✓			LOTD (20 mg/d) with a SF of 1,000 was used.	0.28
Oxprenolol			✓			LOTD (40 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.06
Oxycodone			✓	✓		OEL of 0.04 mg/m ³ (PurduePharma MSDS) with a default SF of 100 was used.	0.057
Pamidronate			✓	✓		LOTD (30 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.043
Pantoprazole			✓	✓		LOTD (20 mg/d) with a SF of 1,000 was used.	0.29
Paroxetine			✓	✓		OEL of 0.04 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.057
Penicillin G		✓	✓	✓		The suggested ADI of 0.00043 mg/kg.d (EMA, 2004c) was adopted.	0.43
Penicillin V		✓	✓	✓		The suggested ADI of 0.00043 mg/kg.d (EMA, 2004c) was adopted.	0.43
Pentoxifylline			✓			LOTD (800 mg/d) with a SF of 1,000 was used.	11
Perphenazine			✓			LOTD (12 mg/d) with a SF of 1,000 was used.	0.17
Perindopril			✓			LOTD (2 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0029
Phenobarbital			✓	✓		OEL of 0.03 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	0.043
Phenytoin			✓	✓		OEL of 0.2 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.29
Phenyltoloxamine			✓			LOTD (20 mg/d) with a SF of 1,000 was used.	0.29

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Piperacillin				✓		OEL of 3 mg/m ³ (Wyeth MSDS) with a default SF of 100 was used.	4.3
Piroxicam			✓	✓		OEL of 0.1 mg/m ³ (Wyeth MSDS) with a default SF of 100 was used.	0.14
Pravastatin			✓	✓		LOTD (10 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.014
Prednisolone	✓		✓			The suggested ADI of 0.0002 mg/kg.d (EMA, 2001a) was adopted.	0.20
Prednisone			✓			LOTD (0.5 mg/d) with a SF of 1,000 was used.	0.0071
Primidone			✓	✓		LOTD (12.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug	0.018
Procainamide			✓	✓		OEL of 1 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	1.4
Prochlorperazine			✓	✓		OEL of 0.03 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.043
Promethazine			✓	✓		OEL of 0.01 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.014
Propafenone			✓	✓		OEL of 0.75 mg/m ³ (Abbott MSDS) with a default SF of 100 was used.	1.1
Propofol			✓	✓		OEL of 2 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	2.9
Propranolol			✓	✓		LOTD (30 mg/d) with a SF of 1,000 was used.	0.43
Propylthiouracil			✓			LOTD (100 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.14
Quinapril			✓	✓		LOTD (5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0071
Quetiapine			✓	✓		OEL of 0.1 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.14
Quinidine			✓	✓		OEL of 0.45 mg/m ³ (Eli Lilly MSDS) with a default SF of 100 was used.	0.64
Quinine			✓			LOTD (1810 mg/d) with a SF of 1,000 was used.	26
Ramipril			✓	✓		LOTD (1.25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug	0.0018
Ranitidine			✓	✓		OEL of 0.5 mg/m ³ (Boehringer Ingelheim MSDS) with a default SF of 100 was used.	0.71
Rabeprazole			✓			LOTD (10 mg/d) with a SF of 1,000 was used.	0.14
Rifampin			✓	✓		OEL of 0.2 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.29
Risperidone			✓	✓		LOTD (0.25 mg/d) with a SF of 10,000 was used since the drug is defined as a hazardous drug by NIOSH (2011).	0.00036

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Rizatriptan			✓	✓		OEL of 0.04 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.057
Rosuvastatin			✓	✓		OEL of 0.005 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.0071
Roxithromycin			✓			LOTD (150 mg/d) with a SF of 1,000 was used.	2.1
Salbutamol			✓	✓		OEL of 0.01 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.014
Salmeterol				✓		OEL of 0.001 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.0014
Selegiline			✓	✓		LOTD (1.25 mg/d) with a SF of 1,000 was used.	0.018
Sertraline			✓	✓		LOTD (25 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.036
Sildenafil			✓	✓		LOTD (25 mg/d) with a SF of 1,000 was used.	0.36
Simvastatin			✓	✓		LOTD (5 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.0071
Sincalide						Lowest intravenous dose of 0.0014 mg/d was used as the POD with a SF of 1,000.	0.000020
Sotalol			✓			LOTD (160 mg/d) with a SF of 1,000.	2.3
Spiramycin		✓	✓			The suggested ADI of 0.05 mg/kg·d (EMEA, 1997) was adopted.	50
Spironolactone			✓	✓		OEL of 0.05 mg/m ³ (Roche MSDS) with a default SF of 100 was used.	0.071
Sulfacetamide		✓				The suggested ADI for sulfonamide antibiotics of 0.01 mg/kg·d (NWQMS, 2008) was adopted.	10
Sulfamethoxazole		✓	✓	✓		The suggested ADI for sulfonamide antibiotics of 0.01 mg/kg·d (NWQMS, 2008) was adopted.	10
Sulfasalazine			✓	✓		OEL of 0.6 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.86
Sulfapyridine						OEL of Sulfasalazine was adjusted for Sulfapyridine content with a default SF of 100 was used.	0.054
Sulfisoxazole		✓	✓	✓		The suggested ADI for sulfonamide antibiotics of 0.01 mg/kg·d (NWQMS, 2008) was adopted.	10
Sulindac			✓	✓		OEL of 1 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	1.4
Sumatriptan			✓	✓		OEL of 0.05 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.071
Tamoxifen			✓	✓		OEL of 0.0005 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used.	0.00071

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Tamsulosin			✓	✓		OEL of 0.003 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	0.0043
Tazobactam			✓	✓		OEL of 1 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used/	1.4
Telithromycin			✓			LOTD (800 mg/d) with a SF of 1,000 was used.	11
Temazepam			✓	✓		LOTD (7.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class X drug.	0.011
Terbutaline			✓	✓		OEL of 0.01 mg/m ³ (AstraZeneca MSDS) with a default SF of 100 was used.	0.014
Testosterone	✓		✓	✓		The suggested ADI of 0.002 mg/kg-d (WHO/FAO, 2000) was adopted.	2.0
Tetracycline	✓		✓	✓		The suggested ADI of 0.003 mg/kg-d (EMA, 1996) was adopted	3.0
Theophylline			✓	✓		OEL of 1.8 mg/m ³ (Pfizer MSDS) with a default SF of 100 was used	2.6
Tetrahydrocannabinol			✓			LOTD (5 mg/d) with a SF of 1,000 was used.	0.071
Tiaprofenic Acid			✓			LOTD (300 mg/d) with a SF of 1,000 was used.	4.3
Ticarcillin			✓	✓		OEL of 1.0 mg/m ³ (GSK MSDS) with a default SF of 100 was used	1.4
Ticlopidine			✓	✓		OEL of 0.4 mg/m ³ (Roche MSDS) with a default SF of 100 was used	0.57
Timolol			✓	✓		OEL of 0.02 mg/m ³ (Merck MSDS) with a default SF of 100 was used.	0.029
Tolbutamide			✓			LOTD (1,000 mg/d) with a SF of 1,000 was used.	14
Tramadol			✓			LOTD (100 mg/d) with a SF of 1,000 was used.	1.4
Trazodone			✓	✓		OEL of 0.02 mg/m ³ (BMS MSDS) with a default SF of 100 was used.	0.029
Triamterene			✓			LOTD (50 mg/d) with a SF of 1,000.	0.71
Trifluoperazine			✓	✓		OEL of 0.003 mg/m ³ (BMS MSDS) with a default SF of 100 was used.	0.0043
Trihexyphenidyl			✓	✓		LOTD (1 mg/d) with a SF of 1,000 was used.	0.014
Trimethoprim	✓		✓	✓		The suggested ADI of 0.004 mg/kg-d (EMA, 1994) was adopted.	4.0
Trimipramine			✓			LOTD (75 mg/d) with a SF of 1,000 was used.	1.1
Valacyclovir			✓	✓		OEL of 5 mg/m ³ (GSK MSDS) with a default SF of 100 was used.	7.1

PhAC	Types of Data Available					Method and the Input Selected to Evaluate ADI (as per Fig. 1 (main body))	ADI µg/kg.d
	TDI	ADI	LOTD	OEL	NSRL		
Valproic Acid			✓	✓		LOTD (250 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.36
Valsartan			✓	✓		LOTD (40 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.057
Vancomycin			✓	✓		OEL of 1 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	1.4
Venlafaxine			✓	✓		LOTD (18.75 mg/d) with a SF of 1,000 was used.	0.27
Verapamil			✓	✓		OEL of 0.05 mg/m ³ (Hospira MSDS) with a default SF of 100 was used.	0.071
Warfarin			✓	✓		LOTD (0.5 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.00071
Xylometazoline			✓			LOTD (0.24 mg/d) with a SF of 1,000 was used.	0.0034
Zidovudine			✓	✓		Due to genotoxic carcinogenicity concerns, an LTD ₁₀ of 29.4 mg/kg·d (Gold, 2008) was linearly extrapolated by dividing by 10 ⁵ to derive an estimated ADI.	0.29
Zopiclone			✓			LOTD (1.75 mg/d) with a SF of 10,000 was used since it is a pregnancy class D drug.	0.0025

Notes: (a) Based on pediatric LOTD since it was found to be lower than its adult counterpart.

Appendix P: Margin of Exposure estimates

Summarized in Table P.1 are the three margins of exposure (*MOE*) estimates for each PhAC of the evaluation set. MOE_{p1} , MOE_{p2} and MOE_{p3} evaluations were performed using Eq. 5 (main body) with PEC_1 , PEC_2 and PEC_3 estimates (see Appendix K) serving as respective inputs.

Table O.1 MOE estimates for each PhAC of the evaluation set

PhAC	MOE_{p1}	MOE_{p2}	MOE_{p3}
Acarbose	750	1400	2000
Acebutolol	420	1100	1800
Acetaminophen	42	45	140
Acetylcysteine	110	110	270
Acetylsalicylic Acid	32	1700	4500
Acyclovir	1200	1400	3800
Alendronate	58	58	58
Allopurinol	130	440	1100
Alprazolam	37	130	180
Amantadine	5200	5900	7500
Amiloride	1100	1200	1600
Aminosalicic Acid	7.9	20	46
Amiodarone	48	65	180
Amitriptyline	40	110	110
Amlodipine	34	470	700
Amoxicillin	11	12	28
Amphetamine	50	360	1000
Amphotericin B	13400	21200	21200
Ampicillin	260	310	640
Anastrozole	32	130	130
Androstenedione	460	460	1400
Atenolol	5.1	5.8	8.0
Atorvastatin	2.5	2.5	4.8
Atropine	1500	1600	1600
Azathioprine	6.7	30	34
Azithromycin	380	700	700
Baclofen	490	540	540
Beclomethasone	9700	11000	13000
Benserazide	7100	7100	9900
Benzatropine	530	530	690
Benzydamine	4600	4600	5600
Betamethasone	210	240	240
Betaxolol	32600	32600	86600
Bezafibrate	1300	1800	3600
Bicalutamide	100	210	220
Bisoprolol	73	120	160
Bleomycin	430	620	620

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Bromazepam	60	730	730
Bromocriptine	1500	1800	3300
Budesonide	400	1200	1300
Buprenorphine	Not approved for use in Canada until 2007		
Bupropion	190	1900	2200
Buserelin	168000	254000	622000
Butalbital	1400	20000	20000
Candesartan	2.1	2.6	2.6
Capecitabine	18	320	350
Captopril	42	58	58
Carbamazepine	22	88	88
Carbidopa	120	170	170
Carboplatin	220	250	330
Carmustine	165	18400	18500
Carvedilol	230	340	650
Cefaclor	430	570	1700
Cefadroxil	2800	3000	3000
Cefazolin	4100	4100	4100
Cefixime	30100	30100	30100
Cefprozil	510	540	750
Ceftazidime	100	110	110
Ceftriaxone	54	89	89
Cefuroxime	840	840	1200
Celecoxib	130	2700	2800
Cephalexin	690	690	1500
Cetirizine	120	320	320
Chloral Hydrate	8440	16900000	17400000
Chloramphenicol	25000	25000	69000
Chlorhexidine	147000	148000	148000
Chloroquine	3300	6000	6000
Chlorpromazine	260	3700	5200
Cimetidine	150	250	400
Ciprofloxacin	16	23	45
Cisplatin	160	200	350
Citalopram	6	12	12
Clarithromycin	130	330	400
Clavulanic Acid	46700	88200	101000
Clindamycin	38	220	220
Clodronic Acid	690	690	690
Clofibrate	17000000	∞	∞
Clofibric Acid	19290000	19290000	29250000
Clonazepam	4.3	210	250
Clonidine	110	140	160
Clopidogrel	7.5	13	18
Clorazepate	1400	6800	6800
Clotrimazole	59	59	78
Clozapine	130	1300	1900

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Cocaine	0.28	3.5	10
Codeine	11	18	29
Cortisone	190	380	1200
Cromolyn	335000	374000	470000
Cyclophosphamide	17	78	110
Cyproterone	300	480	580
Cytarabine	6.4	32	44
Dactinomycin	410	680	680
Daunorubicin	1200	2400	2400
Desloratadine	1630	29400	33600
Desogestrel	3.0	150	400
Dexamethasone	490	700	2200
Dextroamphetamine	11	86	240
Dextropropoxyphene	2800	12000	12000
Diatrizoate	1950000	1950000	1950000
Diazepam	33	270	270
Diclofenac	91	310	440
Didanosine	2900	3500	8500
Digoxin	130	160	220
Dihydrotestosterone	23	98	120
Diltiazem	130	580	780
Diphenoxylate	330	790	1500
Dipyridamole	830	830	2700
Disulfiram	2932000	14660000	23740000
Docusate	11	11	15
Domperidone	500	6700	9200
Doxepin	133	13300	13300
Doxorubicin	230	790	1100
Doxycycline	5000	5400	5400
Drospirenone	8.4	8.4	25
Enalapril	5.8	24	59
Enalaprilat	6.2	8.9	8.9
Epirubicin	420	890	890
Eprosartan	73	76	110
Erythromycin	1800	6500	8400
Escitalopram	56	230	230
Esomeprazole	36	6800	6900
Estradiol	360	600	1500
Estriol	0.19	0.21	0.63
Estrone	0.72	1.2	2.3
Ethacrynic acid	41900	41900	42200
Ethambutol	75800	77300	77300
Ethinylestradiol	1.8	4	10
Ethinodiol	41	∞	∞
Etidronic Acid	290	290	630
Etodolac	15200	44500	44500
Etonogestrel	5.4	5.4	10

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Etoposide	21	21	38
Exemestane	520	1200	3700
Famciclovir	1800	∞	∞
Famotidine	830	1000	1600
Felodipine	300	2900	2900
Fenofibrate	92	590	790
Fenofibric Acid	100	250	470
Fenoprofen	Discounted in 2002		
Fenoterol	137000	318000	318000
Fentanyl	4.3	7.1	7.1
Finasteride	11	18000	18000
Fluconazole	1200	1200	1600
Fluocinonide	38	38	39
Fluorouracil	4.6	26	36
Fluoxetine	96	280	320
Fluphenazine	430	430	990
Flurazepam	120	1100	1100
Flutamide	6.7	130	180
Fluticasone	66	1300	2000
Fluvoxamine	1040	26000	29500
Formoterol	220	420	420
Fosfomycin	3910000	5750000	5750000
Fosphenytoin	6146200	153660000	153660000
Fulvestrant	15600	82300	161000
Furosemide	30	38	52
Gabapentin	61	64	170
Gemfibrozil	530	1400	2600
Gentamicin	60300	60300	60300
Gliclazide	459	32800	32800
Glyburide	1.5	25	25
Goserelin	10700	53300	131000
Haloperidol	47	140	180
Heroin	15	58600	118000
Hydrochlorothiazide	3000	3000	3000
Hydrocodone	11	990	2600
Hydrocortisone	79	87	260
Hydromorphone	1.4	18	19
Hydroxychloroquine	200	390	390
Hydroxyzine	1010	126000	197000
Ibuprofen	1	3	7.6
Idarubicin	9380	20400	20400
Ifosfamide	21	38	38
Imipramine	378	4490	7770
Indomethacin	196	689	1340
Ipratropium	1400	1900	1900
Irbesartan	2.9	7	9.3
Isoniazid	8490	21200	21200

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Isosorbide Dinitrate	55	3900	9600
Isosorbide-5-Mononitrate	84	370	440
Ketamine	2580	36900	101000
Ketoconazole	960	1300	3500
Ketoprofen	4300	5100	9100
Labetalol	190	230	250
Lamotrigine	100	110	110
Lansoprazole	56	5600	5600
Letrozole	23	230	280
Leuprolide	84	84	210
Levobunolol	2500	2500	2700
Levodopa	2.6	21	38
Levofloxacin	110	120	170
Thyroxine	0.8	0.92	1.7
Lidocaine	830	3000	3000
Triiodothyronine	0.083	0.083	0.083
Lisinopril	3.9	3.9	3.9
Loratadine	6520	102000	166000
Lorazepam	4.1	4.9	4.9
Losartan	10	16	24
Loxapine	3280	671000	671000
MDMA	320	1600	2700
Mefenamic Acid	6590	110000	160000
Melphalan	160	320	480
Meprobamate	57282000	190940000	205290000
Metformin	4.1	4.9	8.8
Methadone	310	830	1100
Methamphetamine	7.8	18	25
Methotrexate	63	96	96
Methotrimeprazine	550	7850	11600
Methyldopa	4600	5300	5300
Methylphenidate	40	450	480
Methylprednisolone	1300	3100	9900
Metoprolol	29	180	210
Metronidazole	110	250	350
Miconazole	5000	5000	9600
Midazolam	160	1600	3400
Minocycline	61	130	410
Misoprostol	59	5900	6000
Mitomycin	9	45	45
Mitotane	51	85	280
Mometasone	51	60	62
Morphine	0.7	3.6	9
Mupirocin	50000	50000	51000
Nabumetone	1400	15000	15000
Nadolol	960	960	1400
Naloxone	172000	443000	443000

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Naltrexone	11000	67000	67000
Naproxen	44	59	120
Neomycin	3890000	3890000	9540000
Nifedipine	90	90000	91000
Nilutamide	18000	260000	270000
Nimodipine	808900	80890000	139400000
Nitrazepam	150	690	1000
Nitrofurantoin	840	2100	2100
Nizatidine	330	470	470
Norfloxacin	2500	4300	7800
Norgestimate	18	49	180
Nortriptyline	9	430	510
Norethindrone	14	33	120
Nystatin	5850	5850	14300
Ofloxacin	32300	39400	74200
Omeprazole	71	71000	74000
Ondansetron	610	1700	4500
Orlistat	2100	2600	8000
Orphenadrine	16200	39400	56200
Oseltamivir	12500	56900	56900
Oseltamivir carboxylate	10300	12700	12700
Oxaprozin	1100	3600	3700
Oxazepam	130	270	270
Oxprenolol	4500	6600	7000
Oxycodone	29	240	270
Pamidronate	1100	1100	1100
Pantoprazole	69.7	7500000	10500000
Paroxetine	37	1200	2200
Penicillin G	55	84	84
Penicillin V	52	89	120
Pentoxifylline	5070	101000	101000
Perphenazine	9910	10200	10200
Perindopril	14	110	280
Phenobarbital	32	280	850
Phenytoin	52	160	230
Phenyltoloxamine	32600	32600	41500
Piperacillin	1600	1900	1900
Piroxicam	7850	78500	78500
Pravastatin	14	34	55
Prednisolone	370	1700	3500
Prednisone	13	280	860
Primidone	20	43	53
Procainamide	17000	30000	30000
Prochlorperazine	930	930	930
Promethazine	422	70300	118000
Propafenone	710	7100	8100
Propofol	7300	17000	18000

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Propranolol	300	1700	1900
Propylthiouracil	750	1000	1100
Quinapril	8.8	22	24
Quetiapine	23	780	860
Quinidine	5600	26000	26000
Quinine	7500	27000	27000
Ramipril	0.93	2.3	2.4
Ranitidine	2600	3000	5300
Rabeprazole	110	∞	∞
Rifampin	860	1900	1900
Risperidone	5.9	19	19
Rizatriptan	5100	17500	17500
Rosuvastatin	6.5	7.9	14
Roxithromycin	Has never been approved for sale in Canada		
Salbutamol	98	100	130
Salmeterol	290	5800	13000
Selegiline	4070	27300	35900
Sertraline	12	88	110
Sildenafil	1200	∞	∞
Simvastatin	3	150	340
Sinacalide	5662000	5662000	5662000
Sotalol	1500	1500	1900
Spiramycin	2007000	45620000	45620000
Spironolactone	62	3100	4400
Sulfacetamide	193600	198500	198500
Sulfamethoxazole	980	3300	5000
Sulfasalazine	110	230	230
Sulfapyridine	11	46	110
Sulfisoxazole	50400	98800	98800
Sulindac	5590	26600	26800
Sumatriptan	380	3200	4400
Tamoxifen	4.4	49	63
Tamsulosin	269	2510	2510
Tazobactam	4500	5770	5820
Telithromycin	35700	77600	77600
Temazepam	13	18	18
Terbutaline	700	980	980
Testosterone	2900	5500	13000
Tetracycline	710	710	1600
Theophylline	1.8	62	150
Tetrahydrocannabinol	1.4	140	550
Tiaprofenic Acid	5800	6100	6200
Ticarcillin	2400	2500	2500
Ticlopidine	870	9700	14000
Timolol	640	830	860
Tolbutamide	18900	172000	173000
Tramadol	4680	11100	11100

PhAC	MOE _{p1}	MOE _{p2}	MOE _{p3}
Trazodone	8.9	57	78
Triamterene	410	840	940
Trifluoperazine	230	230	320
Trihexyphenidyl	2000	2000	2800
Trimethoprim	1800	2300	3700
Trimipramine	4700	47000	47000
Valacyclovir	1210	242000	338700
Valproic Acid	17	68	210
Valsartan	7	8.6	18
Vancomycin	7590	8150	8150
Venlafaxine	21	320	380
Verapamil	17	87	120
Warfarin	1.9	27	83
Xylometazoline	2810	2810	3850
Zidovudine	350	390	390
Zopiclone	5	50	50

Appendix P: MECs of atenolol and atorvastatin in Canadian surface waters

Atenolol

As summarized in Table P.1, atenolol has been analysed in 19 Canadian surface water samples with an overall detection frequency of 47% and a maximum of 53 ng/L.

Table P.1 Monitoring of atenolol in Canadian surface waters

Sample #	Atenolol MECs in Canadian surface waters	Reference
1	< LOD	Li et al., 2010
2	< LOD	Li et al., 2010
3	< LOD	Li et al., 2010
4	< LOD	Li et al., 2010
5	<0.3	MacLeod et al., 2007
6	<0.3	MacLeod et al., 2007
7	<0.4	MacLeod et al., 2007
8	<0.4	MacLeod et al., 2007
9	<0.7	MacLeod et al., 2007
10	0.7	MacLeod et al., 2007
11	0.7	MacLeod et al., 2007
12	0.8	MacLeod et al., 2007
13	<2	MacLeod et al., 2007
14	12.4	Li et al., 2010
15	12.8	Li et al., 2010
16	28.2	Li et al., 2010
17	39	MacLeod et al., 2007
18	43	MacLeod et al., 2007
19	53	MacLeod et al., 2007

Atorvastatin

As summarized in Table P.2, atorvastatin has been analysed in 27 Canadian surface water samples with an overall detection frequency of 33% and a maximum of 59 ng/L.

Table P.2 Monitoring of atorvastatin in Canadian surface waters

Sample #	Atorvastatin MECs in Canadian surface waters	Reference
1	<LOD	Miao and Metcalfe, 2003
2	<LOD	Metcalfe et al., 2003
3	<LOD	Metcalfe et al., 2003
4	< 1	Rahman et al., 2010
5	< 1	Rahman et al., 2010
6	< 1	Rahman et al., 2010
7	< 1	Rahman et al., 2010
8	< 1	Lee et al., 2009
9	< 1	Lee et al., 2009
10	< 1	Lee et al., 2009
11	< 1	Lee et al., 2009
12	< 1	Lee et al., 2009
13	< 1	Lee et al., 2009
14	< 1	Lee et al., 2009
15	< 1	Lee et al., 2009
16	< 1	Lee et al., 2009
17	< 1	Lee et al., 2009
18	< 1	Lee et al., 2009
19	1.0	Miao and Metcalfe, 2003
20	1.1	Rahman et al., 2010
21	1.2	Lee et al., 2009
22	8.7	Lee et al., 2009
23	10	Metcalfe et al., 2003
24	11.9	Lee et al., 2009
25	15	Metcalfe et al., 2003
26	46.6	Lee et al., 2009
27	59.1	Lee et al., 2009

Appendix Q: References for mobility and degradation data presented in Table V (main body)

Summarized in Table Q.1 are the references for the mobility and degradation data presented in Table V.

Table Q.1 References for mobility and degradation data for PhACs listed in Table V

PhAC	Potential to transport to drinking water intakes			
	Sorption	Reference	Degradation	Reference
Triiodothyronine	Sorption could not be modelled. Log D (@ pH 7.4) = 2.50	Log D estimated using ACD Labs (2011)	$t_{1/2}$ = 60 d est.	Estimated using the method of Aronson et al. (2006)
Estriol	Log $K_{oc-sediment}$ = 2.99	Chen et al., 2012	$t_{1/2}$ = 0.12 d	Caldwell et al., 2010
Thyroxine	Sorption could not be modelled. Log D (@ pH 7.4) = 2.89	Estimated using ACD Labs (2011)	$t_{1/2}$ = 180 d est.	Estimated using the method of Aronson et al. (2006)
Estrone	Log $K_{oc-sediment}$ = 3.44	Chen et al., 2012	$t_{1/2}$ = 2.3 d	Caldwell et al., 2010
Ramipril	Sorption could not be modelled. Log D (@ pH 7) = -0.16	Log D estimated using ACD Labs (2011)	$t_{1/2}$ = 38 d est. 20-50% degradation of the compound seen after 28 days in an OECD 301 test.	Estimated using the method of Aronson et al. (2006) Sanofi, 2012
Candesartan	$K_d-sediment$ = 2-4 L/kg	AstraZeneca ERAD , 2011d	$t_{1/2}$ = 95-222 d	AstraZeneca ERAD , 2011d
Lisinopril	Sorption could not be modelled. Log D (@ pH 7.4) = -1.81	Log D estimated using ACD Labs (2011)	$t_{1/2}$ = 15 d est. 0% degradation of the compound seen after 28 days in an OECD 301 test.	Estimated using the method of Aronson et al. (2006) AstraZeneca ERAD, 2013
Atorvastatin	Log $K_{oc-sediment}$ = 3.20	Ottmar et al., 2010	$t_{1/2}$ = 6.6 d (Half-life observed in a microcosm)	Lam et al. 2004
Lorazepam	Sorption could not be modelled. Log D (@ pH 7.4) = -1.81	Log D estimated using ACD Labs (2011)	$t_{1/2}$ = < 1 d (Photolysis half-lives)	Calisto et al., 2011
Fentanyl	Log K_{oc} = 3.20 (est.)	Estimated using the QSPR of ECETOC (2014) for single bases.	$t_{1/2}$ = 15 d est. Unstable in raw sewage.	Estimated using the method of Aronson et al. (2006) Baker and Kasprzyk-Hordern, 2011
Ibuprofen	Log $K_{oc-sediment}$ = 2.08	Yamamoto et al., 2005	$t_{1/2}$ = 2.5 -5 d	Kunkel and Radke, 2008
Atenolol	Log $K_{oc-sediment}$ = 1.9 - 2.1	Ramil et al., 2010	$t_{1/2}$ = 2.3 -30d	Ramil et al., 2010; Yamamoto et al., 2009
Metformin	Log K_{oc} = 1.5	EMA, 2013	$t_{1/2}$ = 6-53d	EMA, 2011
Enalaprilat	Sorption could not be modelled. Log D (@ pH 7) = 2.50	Log D estimated using ACD Labs (2011)	$t_{1/2}$ = < 1d (Photolysis half-lives)	Perez et al., 2007
Morphine	Log $K_{oc-sediment}$ = 2.6 - 2.7	Stein et al., 2008	$t_{1/2}$ = 0.3 d	Lin et al., 2014
Irbesartan	Log K_{oc} = 2-3	Sanofi, 2009	$t_{1/2}$ = 0.3 -24 d (Photolysis half-lives)	Sanofi, 2009

Appendix R: Availability of monitoring data for the 50 most potent PhACs of the evaluation set

The number of samples with which the 50 most potent (lowest $PNEC_{dw}$ values) PhACs of the evaluation set have been monitored in Canadian surface and drinking waters is listed in Table R.1.

Table R.1: Fifty top ranked PhACs according to estimates of $PNEC_{dw}$ and the reported number of Canadian drinking water and surface water samples that have been analysed for their presence.

PhAC	ATC Class	$PNEC_{dw}$	Number of samples that have been analyzed for their presence	
			Surface Water ^(a)	Treated Drinking Water ^(b)
Alprazolam	N	20	- ^(c)	-
Anastrozole	L	4	-	-
Bleomycin	L	2	-	-
Buprenorphine	N	12	-	-
Candesartan	C	39	-	-
Carmustine	L	4	-	-
Cisplatin	L	12	-	-
Clonazepam	N	10	-	-
Clonidine	C	7	-	-
Cyclophosphamide	L	38	33	-
Dactinomycin	L	0.03	-	-
Daunorubicin	L	4	-	-
Desogestrel	G	0.4	-	-
Digoxin	C	19	-	-
Doxorubicin	L	20	-	-
Drospirenone	G	10	-	-
Epirubicin	L	23	-	-
Estriol	G	4	262	236
Estrone	G	4	275	237
Ethinylestradiol	G	0.4	279	236
Ethinodiol	G	10	-	-
Etonogestrel	G	1	-	-
Etoposide	L	5	-	-
Fentanyl	N	4	-	-
Finasteride	G	20	-	-
Fluocinonide	D	4	-	-
Flutamide	L	39	-	-
Formoterol	R	3	-	-
Fulvestrant	L	39	-	-
Glyburide	A	39	-	-
Haloperidol	N	39	-	-
Idarubicin	L	4	-	-
Ifosfamide	L	4	-	-
Letrozole	L	4	-	-
Leuprolide	L	2	-	-
Lorazepam	N	20	-	-
Melphalan	L	2	-	-
Misoprostol	A	16	-	-
Mitomycin	L	0.04	-	-
Mitotane	L	39	-	-
Mometasone	D	39	-	-
Norethindrone	G	14	26	32
Norgestimate	G	7	-	-
Risperidone	A	10	-	-
Salmeterol	R	39	-	-
Sinacalide	V	0.5	-	-

Tamoxifen	L	20	-	-
Thyroxine	H	4	-	-
Triiodothyronine	H	0.2	-	-
Warfarin	B	20	151	155

Notes: **(a)** Surface water counts based on data compiled from all 34 references listed in Appendix A; **(b)** Based on data compiled from all studies reporting on the presence of PhACs in finished Canadian drinking waters (Boyd et al., 2003; Chen et al., 2006; Garcia-Ac et al., 2009; Kleywegt et al., 2011; MDDEP, 2011; Metcalfe et al., 2010; Tabe et al., 2010); **(c)** not measured.

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Appendices for Chapter 5

Contraceptive Options and their Associated Estrogenic Environmental Loads: Relationships and Trade-offs

Usman Khan and Jim A. Nicell

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S1 Estimated Anthropogenic Steroidal Estrogen Loads in the USA circa 2002

Table S1 Estimated Net Load of Steroidal Estrogens Via Domestic Wastewater Treatment Plants circa 2002.

Population cohorts/ Pregnancy outcomes	Number	Daily per capita excretion			Excretion per pregnancy outcome			Net contribution				Pre- treatment Load	Post- treatment Load	40d Post Release Load ^(s)
		E ₁	E ₂	E ₃	E ₁	E ₂	E ₃	E ₁ ^(d)	E ₂ ^(d)	E ₃ ^(d)	EE ₂	E _{2–Eq} ^(e)	E _{2–Eq} ^{(e),(t)}	E _{2–Eq} ^{(e),(u)}
		µg/cap·d			mg/outcome			kg/yr				kg/yr		
Endogenous														
Females														
Prepubescent girls	24,433,426 ^{(a),(b)}	0.08	0.06	0.2 ^(c)				0.7	0.6	1.9		0.9	0.1	0.0
Menstruating women not on OC	64,701,425 ^(m)	8.7	4.4	9.4 ^(r)				205	104	223		182	25	0.0
Menstruating women on OC	11,635,029 ^(g)	3.1	1.2	2.5 ^(r)				13	5	11		10	1	0.0
Menopausal women	42,205,554 ^{(h),(b)}	1.7	0.8	1.9 ^(r)				26	12	30		22	3	0.0
Pregnancy – Births	4,022,000 ⁽ⁱ⁾				259	134	1525 ^(j)	1040 ⁽ⁿ⁾	539 ⁽ⁿ⁾	6132 ⁽ⁿ⁾		1131	135	0.0
Pregnancy – Induced abortions	1,269,000 ⁽ⁱ⁾				12	4	22 ^(k)	15 ⁽ⁿ⁾	5 ⁽ⁿ⁾	28 ⁽ⁿ⁾		11	2	0.0
Pregnancy – Spontaneous abortions	1,016,206 ^(l)				18	6	45 ^(k)	19 ⁽ⁿ⁾	6 ⁽ⁿ⁾	46 ⁽ⁿ⁾		14	2	0.0
Pregnancy – Ectopic	40,621 ^(l)				15	5	29 ^(k)	1 ⁽ⁿ⁾	0.2 ⁽ⁿ⁾	1 ⁽ⁿ⁾		0.4	0.1	0.0
Males														
Prepubescent boys	24,924,262 ^{(p),(b)}	0.08	0.06	0.2 ^(c)				0.7	0.5	1.8		0.9	0.1	0.0
Males	116,306,297 ^{(q),(b)}	3.6	2.13	2.4 ^(r)				153	90	102		145	20	0.0
Exogenous														
Women on HRT ^(o)							232	67	38		146	24	0.0	
Women on OC ^(f)											30.7	307	49	3.0
											E _{2–Eq} (Total)	1,970	261	3.0

OC = Oral Contraceptive, HRT = Hormone Replacement Therapy

Footnotes

- (a) Women less than the age of menarche of 12.5 years¹.
- (b) Estimated using the data reported by US Census data² for the year 2002.
- (c) Shi et al.³.
- (d) Unless otherwise indicated, estimated as follows: daily per capita excretion ($\mu\text{g}/\text{cap-d}$) $\times$ cohort population $\times$ 365 (d/yr) $\times$ $1/10^9$ (kg/ μg).
- (e) $E_{2-Eq} = [E_1]/3 + [E_2] + [E_3]/25 + 10[EE_2]$; where: $[E_{2-Eq}]$, $[E_1]$, $[E_2]$, $[E_3]$ and $[EE_2]$ are the mass loads of Estradiol equivalents, estrone, estradiol, estriol and ethinylestradiol, respectively. See Section S2 for justification for the potencies (i.e., 1/3, 1, 1/25 and 10) used within this equation.
- (f) Estimated by multiplying the annual consumption of EE_2 in the USA of 82.4 kg⁴ by fraction of the drug that is excreted as unchanged EE_2 and its conjugates (estimated in Section S3).
- (g) Mosher and Jones⁵.
- (h) Women aged more than the mean menopausal age of 51 years⁶.
- (i) Ventura et al.⁷
- (j) The urinary contribution was estimated by firstly multiplying data reported by Berg and Kuss⁸, which reported the mean excretions curves of natural estrogens for women of various gestational ages in the units of grams of estrogen per gram of creatinine by the average daily excretion of creatinine (g of creatinine/24hr) by pregnant women⁹. The resultant excretion curves were integrated over the duration of a pregnancy that results in the outcome of birth⁴¹ to arrive at cumulative levels of the various natural estrogens that are eliminated via the urinary release of pregnant women who end up giving birth. Thus far, only a handful of analyses^{11,12} have been performed for the fecal release of natural estrogens by pregnant women. Therefore, as the best approximation, the limited fecal data^{11,12} that was available was used to estimate fecal-to-urinary excretion ratios for each natural estrogen. Subsequently, the estimated ratios for each natural estrogen were multiplied by their respective the urinary levels to arrive at best possible estimates for each estrogen's fecal release over the course of a pregnancy that results in the outcome of birth. As a last step, the estimated urinary and fecal levels were summed to arrive at the cumulative levels of natural estrogens excreted by pregnant women who end up giving birth.
- (k) Estimated in similar manner with the same data sources as in footnote (j), with the only difference being the gestational age over which the developed excretions curves for the various natural estrogens were integrated. Specifically, the time to an induced abortion, spontaneous abortion and ectopic pregnancy were modeled based on the data of Pazol et al.¹³, Jones and Kost¹⁴ and Goldhaber and Fireman⁴¹, respectively.
- (l) Estimating using data reported by Ventura et al.⁷ and Hoover et al.⁴⁰.
- (m) Estimated from demographic data as follows: [Women between the average age of menarche (i.e., 12.5 years¹) and the average age of menopause (i.e., 51 years⁶)] - [Number of menstruating women on OC⁵] - [Number of pregnancies⁷ $\times$ (time to birth⁴¹/5)] - [Number of induced abortions⁷ $\times$ (time to induced abortion¹³/52)] - [Number of spontaneous abortions⁷ $\times$ (time to spontaneous abortion¹⁴/52)] - [Number of ectopic pregnancies^(item l) $\times$ (time to ectopic pregnancy⁴¹/52)]
- (n) Excretion per pregnancy outcome (mg/events) $\times$ Pregnancy events per year (events/yr) $\times$ $1/10^6$ (kg/mg).

(o) Estimated as follows:

HRT formulations	Mass Sold Nationally (2007-2008) ^{4,17}	Fraction converted to each steroidal estrogen	E ₁	E ₂	E ₃
	Kg/yr			Kg/yr	
Estradiol	508.6	30% (E ₁), 10% (E ₂), 6% (E ₃) ¹⁵	153	51	31
Conjugated Estrogen	536.7	≈11% (E ₁), ≈2% (E ₂) ³¹	59	11	
Esterified Estrogen	93.8	≈15%(E ₁), ≈3% (E ₂) (Estimated from Johnson et al. ³¹)	14	3	
Estropipate	36.4	≈16%(E ₁), ≈3% (E ₂) (Estimated from Johnson et al. ³¹)	5	1	
Estriol	7.2	Assumed to be 100% (E ₃), since it is minimally metabolized in the body ³³			7
Estrone	1.1	17.8% (E ₁), 4.3% (E ₂), < 1% (E ₃)-(Disposition of I.V. Estrone) ³²	0.2	0.05	≈ 0
		Sum	232	67	38

(p) Boys less than the age of 12.2 years¹⁶.

(q) Men greater than the age of 12.2 years.

(r) Estimated by Anderson et al.⁴ by extending the model of Johnson and Williams²⁸.

(s) 40 day post-release load, where 40 days is the typical residence time of wastewater in rivers³⁷.

(t) Estimated as follows $E_{2-EQ} = [E_1]/3 \cdot (1 - (f_s \cdot R_{s-E1} + f_{ad} \cdot R_{ad-E1})) + [E_2] \cdot (1 - (f_s \cdot R_{s-E2} + f_{ad} \cdot R_{ad-E2})) + [E_3]/25 \cdot (1 - (f_s \cdot R_{s-E3} + f_{ad} \cdot R_{ad-E3})) + 10[EE_2] \cdot (1 - (f_s \cdot R_{s-EE2} + f_{ad} \cdot R_{ad-EE2}))$. Where: $[E_{2-EQ}]$, $[E_1]$, $[E_2]$, $[E_3]$ and $[EE_2]$ are the mass loads of estradiol equivalents, estrone, estradiol, estriol and ethinylestradiol, respectively; f_s and f_a are the fractions of wastewater volume that currently undergo secondary and advanced treatment in USA³⁶, respectively; R_{s-E1} , R_{s-E2} , R_{s-E3} and R_{s-EE2} are the removals of E_1 , E_2 , E_3 and EE_2 in secondary treatment plants¹⁷, respectively; R_{a-E1} , R_{a-E2} , R_{a-E3} and R_{a-EE2} are the removals of E_1 , E_2 , E_3 and EE_2 in advanced treatment plants¹⁷, respectively.

(u) Estimated as follows $E_{2-EQ} = [E_1]/3 \cdot (1 - (f_s \cdot R_{s-E1} + f_{ad} \cdot R_{ad-E1})) \cdot (e^{-k-E1 \cdot tr}) + [E_2] \cdot (1 - (f_s \cdot R_{s-E2} + f_{ad} \cdot R_{ad-E2})) \cdot (e^{-k-E2 \cdot tr}) + [E_3]/25 \cdot (1 - (f_s \cdot R_{s-E3} + f_{ad} \cdot R_{ad-E3})) \cdot (e^{-k-E3 \cdot tr}) + 10[EE_2] \cdot (1 - (f_s \cdot R_{s-EE2} + f_{ad} \cdot R_{ad-EE2})) \cdot (e^{-k-EE2 \cdot tr})$. Where: $k-E1$, $k-E2$, $k-E3$, $k-EE2$ are first order degradation constants for E_1 , E_2 , E_3 and EE_2 ¹⁷, respectively; tr is the typical residence time of wastewater in rivers³⁷ and all other variables are as previously defined in item (t).

S2 Eco-toxicological Potency of Steroidal Estrogens

Based on a critical review of available eco-toxicological data, the European Union has proposed Environmental Quality Standard (EQS) for E_2 and EE_2 of 400 and 35 pg/L, respectively.^{42,43} In developing these standards, the committee considered the relative *in vivo* potency of EE_2 to E_2 in fish and was of the opinion that the current data suggested that EE_2 was about 10 times more potent than E_2 .⁴³ The Commission's proposed benchmarks, as well as the relative potency of E_2 to that of EE_2 , are at odds with the values proposed by an effort led by the pharmaceutical industry.⁴⁴ Specifically, Caldwell et al.⁴⁴ proposed benchmarks of 2,000 and 100 pg/L, respectively, for E_2 and EE_2 , which puts the relative potency of E_2 at one-twentieth of that of EE_2 . As detailed in the SCHER opinions^{42,43}, the EU regulators do not agree with these industry-derived benchmarks. Hence, for our evaluation, EE_2 was assumed to be 10 times more potent than E_2 . E_1 is assumed to be one-third as potent as E_2 .⁴⁶ Limited data has been reported for the *in vivo* eco-toxicological potency of E_3 , however, aquaculture literature suggests that E_3 is 25 times less potent than E_2 in inducing sex reversal in fish.^{57,58} Therefore, E_3 was assumed to be 25 times less potent than E_2 .

S3 Modeling the Steroidal Estrogen Load Released Directly Via the Use of a Particular Contraceptive Option ($J_{d,n}$)

The definitions of all variables used below along with their estimated values are provided in Section S9.

The steroidal estrogen load released directly via the use of a contraceptive option ($J_{d,n}$) is modeled as follows:

$$J_{d,n} = \sum_{i=1}^I L_n \cdot (U_{i,n} + F_{i,n}) \cdot \frac{Mw_i}{Mw_n} \cdot P_i \cdot 365 \quad (S1)$$

where: i refers to one of the following estrogens: E_1 , E_2 , E_3 and EE_2 ; L_n is the per user consumption of a given contraceptive option n ; $U_{i,n} + F_{i,n}$ is the net fraction of an administered dose of contraceptive option n that is excreted as unchanged and conjugated i ; P_i is the potency of estrogen i relative to that of E_2 ; and Mw_i and Mw_n are the molecular weights of i and n , respectively.

Of the various contraceptive options considered here, the contribution $J_{d,n}$ is non-zero for EE_2 -based preparations and the recently authorized E_2 -based oral contraceptives only. Parameterization for L_{EE_2-OC} and L_{E_2-OC} , and $U_{EE_2,EE_2} + F_{EE_2,EE_2}$ (i.e., the fractions of an administered dose of EE_2 excreted in its unchanged form and its conjugated forms) are discussed and estimated below.

S3.1 Daily Consumption of EE_2 by Users of EE_2 -based Oral Contraceptives (L_{EE_2-OC})

Two lines of evidence were used to estimate the mean daily per user consumption of EE_2 (L_{EE_2-OC}). The first approach used to estimate L_{EE_2} was based on the mass of EE_2 used as reported in IMS Health sales data (for the period from March 2007 to February 2008) divided by the estimated number of oral contraceptive users in the USA around the time of the available sales data⁵, as follows:

$$L_{EE_2-OC} = \frac{82.4 \text{ kg/yr (Caldwell et al.}^{17})}{10,702,000 \text{ (Mosher and Jones}^5)} \times \frac{10^9 \mu\text{g}}{1 \text{ kg}} \times \frac{1 \text{ yr}}{365 \text{ d}} = 21.1 \frac{\mu\text{g}}{\text{user} \cdot \text{d}}$$

The second approach was based on the NSFG survey data reported on the types and proportions with which each EE_2 -based oral contraceptive brand is used within the USA. As described in Table S2 below, this data³⁸ was analyzed to arrive at a second independent estimate for L_{EE_2-OC} of 22.3 μg of EE_2 /user·d.

As can be seen, the two independent estimates of L_{EE_2-OC} yielded remarkably similar values and, hence, the mean of the two estimates, 21.7 μg of EE_2 /user·d, was used for the analyses presented in this study.

Table S2 Estimate of L_{EE2} Using NSFG Survey Data from Hall and Trussell³⁸.

Brand ^(a)	EE ₂ dose in each active pill ^(b)	Correction for inert pills or days of non-use ^(b)	% of all OC users ^(a)	Daily contribution from the users of each brand ^(c)
	µg/active pill			µg/user-d
Ortho Tri-Cyclen Lo®	25	0.75	12.3	2.30
Yasmin®	30	0.75	10.8	2.43
Yaz®	20	0.86	5.6	0.97
Ortho Tri-Cyclen®	35	0.75	5.2	1.37
Tri-Sprintec®	35	0.75	4.6	1.20
Loestrin FE 1/20®	20	0.75	4.7	0.71
Trinessa®	35	0.75	3.8	1.01
Ortho-Cyclen®	35	0.75	3.3	0.87
Microgestin 1.5/30®	30	0.75	3.1	0.70
Aviane®	20	0.75	2.9	0.44
Lutera™	20	0.75	2.5	0.38
Seasonale®	30	0.92	2.5	0.69
Apri®	30	0.75	2.4	0.54
Sprintec®	35	0.75	2.3	0.61
Lo/Ovral®	30	0.75	1.9	0.44
Kariva®	20	0.82	1.7	0.28
Estrostep FE®	28.3	0.75	1.7	0.36
Necon 1/35®	35	0.75	1.6	0.43
Levora®	30	0.75	1.5	0.34
Trivora®	32.3	0.75	1.5	0.36
Ortho-Novum 7/7/7®	35	0.75	1.3	0.35
Ortho-Novum 1/35®	35	0.75	1.2	0.32
Alesse®	20	0.75	1.1	0.17
Desogen®	30	0.75	1.1	0.25
Ortho-Cept®	30	0.75	1.1	0.25
Mononessa®	35	0.75	1.1	0.28
Seasonique®	30	0.92	0.9	0.26
Zovia 1/50®	50	0.75	0.8	0.32
Junel FE 20™	20	0.75	0.8	0.12
Loestrin 21 1.5/30®	30	0.75	0.8	0.18
Mircette®	18.1	0.93	0.7	0.11
Cryselle®	30	0.75	0.6	0.14
Ovcon 35®	35	0.75	0.6	0.17
Levlen®	30	0.75	0.6	0.13
Nortrel 28®	35	0.75	0.6	0.15
Oegstrel®	50	0.75	0.6	0.22
Triphasil®	32.4	0.75	0.5	0.13
Tri-Levlen®	32.4	0.75	0.5	0.13
Necon 7/7/7®	35	0.75	0.5	0.12
Low-Ogestel®	30	0.75	0.5	0.11
Cyclessa®	25	0.75	0.5	0.09
Enpresse®	32.4	0.75	0.5	0.12
Portia®	30	0.75	0.5	0.11
Nortrel 7/7/7®	35	0.75	0.4	0.10
Femcon FE™	35	0.75	0.4	0.10
Ortho-Novum 1/50® ^(d)	50	0.75	0.3	0.12
Zovia 1/35E®	35	0.75	0.3	0.08
Nordette®	30	0.75	0.3	0.06
Norethin 1/35E	35	0.75	0.3	0.07
Loestrin 24FE®	20	0.86	0.3	0.05
Jenest®	35	0.75	0.3	0.07
Ocella™	30	0.75	0.2	0.05
Levlite™	20	0.75	0.2	0.03
Nortrel 0.5/0.035®	35	0.75	0.2	0.06
Ovcon 50®	50	0.75	0.2	0.08

Reclipsen™	30	0.75	0.2	0.05
Necon 1/50® (d)	50	0.75	0.2	0.08
Demulen 1/35®	35	0.75	0.2	0.04
Modicon®	35	0.75	0.2	0.04
Ortho-Novumd®	35	0.75	0.2	0.04
Ortho-Novum 10/11®	35	0.75	0.2	0.04
Kelnor™	35	0.75	0.2	0.04
Velivet™	25	0.75	0.2	0.03
Jolessa™	30	0.92	0.1	0.03
Demulen 1/50®	50	0.75	0.1	0.04
Junel 30™	30	0.75	0.1	0.02
Tri-Previfem™	35	0.75	0.1	0.03
Junel FE 30™	30	0.75	0.1	0.02
Norinyl 1+35®	35	0.75	0.1	0.03
Ovral®	50	0.75	0.1	0.04
Nortrel®	35	0.75	0.1	0.03
Lessina®	20	0.75	0.1	0.02
Zenchant®	35	0.75	0.1	0.03
Zovia®d	35-50	0.75	0.1	0.01-0.02
Microgestin FE 1/20®	20	0.75	0.1	0.01
Previfem™	35	0.75	0.1	0.01
Necon 10/11®	35	0.75	0.1	0.01
Norinyl 1/50® (d)	50	0.75	0.1	0.02
Junel 20™	20	0.75	0.1	0.01
Balziva™	35	0.75	0.1	0.01
Azurette™	20	0.75	0.1	0.01
Mercilon®	20	0.82	0.1	0.01
Miranovae	20	0.75	0.1	0.01
Nueva Perla	30	0.75	0.1	0.02
Microgynone	30	0.75	0.1	0.01
Valette	30	0.75	0.1	0.01
Nocicline	30	0.75	0.1	0.01
Gynera	30	0.75	0.1	0.01
			L_{EE2-OC}	22.3

Footnotes: (a) From Hall and Trusell³⁸; (b) From Hall and Trusell³⁸ and/or respective drug monographs⁴⁸; (c) Estimated for each brand as follows: EE₂ dose in each active pill × correction for inert pills × % of all OC users/100; (d) Not included in the summation since these are Mestranol based brands

S3.2 Daily Consumption of E₂ by Users of E₂-based Oral Contraceptives (L_{E2})

Over the 28-day dosing regimen of the recently authorized E₂-based oral contraceptive, Natazia, its users end up administering 52 mg of estradiol valerate³⁹. Hence, on an average daily basis, the users of Natazia administer 1.86 mg of estradiol valerate, which is equivalent to 1.42 mg of free estradiol.

S3.3 Fraction of Administered EE₂ Excreted Unchanged and as Conjugates via Urinary and Fecal Excretions (U_{EE2,EE2} + F_{EE2,EE2})

Overall, the analysis presented below of the excretion profile of EE₂ was done to assess the suitability of the assumption that 50% of EE₂ dose is released in unchanged form and as it glucuronide and sulphate conjugates^{4,17}.

The urinary excretion profile of EE₂ is summarized in Table S3 below. Urinary elimination of EE₂ is largely complete 5 days post-administration.^{19,20} The pooled data of the number of subjects from all studies in which the elimination of EE₂ was monitored for the minimum of five days^{18-20,22,23} suggests that 34%

(n=38) of an administered dose EE₂ is eliminated via the urinary route. As initially noted by Johnson and Williams²⁸, considerable uncertainty exists as to the fraction of the net urinary levels that is in the form of unchanged EE₂ and its conjugates. Over time, the fraction of the urinary excretions that is composed of EE₂ and its conjugates decreases.^{19,20} Recognizing this, only the data of Reed²⁰ and Abdel-Aziz and Williams¹⁹ was pooled and weighted by the number of subjects to estimate that approximately 40% of the total urinary levels are present as free EE₂ and its glucuronide conjugates. The sulfate conjugates of EE₂ at best amounts to an additional 2% of the net urinary release.^{21,27} Therefore, 42% of the net urinary levels is estimated to be present as free EE₂ and its conjugates. Multiplying this by the net level of EE₂ expected to be eliminated via the urinary route of 34% (estimated above) allows one to estimate that 14.3% administered dose of EE₂ is eliminated via the urinary route as free EE₂ and its conjugates.

Table S3 Urinary Excretion Profile of Ethinylestradiol.

Ref.	n	Duration	Dose	Total				EE ₂			
				Total	Free	Glucuronide	Sulphate	Total	Free	Glucuronide	Sulphate
		hr	µg	% Dose	% Urine radioactivity			% Dose	% Urine radioactivity		
(18)	5	120	50	28 ± 3.4	16.7	74	10				
(19)	9	120	64	40.5 ± 8.5							
	2	120	64		< 1	67				12.4,19.4	
	2	21.5	64		< 1					31,45	
(20)	13	120	50	30.4 ± 1.5	18.8	65.4	10.9		20	23	
(21)	4-9	48-72	25		3.8	70.4	11.6				<1.8
(22)	3	120	25	31 ± 4.3	<3						
(23)	8	240	50	38 ± 8							
(24)	6	72	50	27 ± 11	3	68	16				
(25)	6	72	50	17 ± 8	1-10	66-95					
(26)	6	48	50	24.6	9	76					
	6	24	50	17						31	
(27)	4	24	50	9	6	68	15			37.4	2
	4	72	50	18.1							

Fecal elimination of EE₂ has only been reported in a handful of studies.^{20,23,29} Of these, the most comprehensive was that of Speck et al.²³ who, upon studying fecal elimination for 10 days in 8 subjects, demonstrated that approximately 62% of the administered dose of EE₂ was eliminated via this route. Unfortunately, this study did not report on the fraction of the net fecal release that was present in the form of unchanged EE₂. However, Reed et al.²⁰, upon the analysis of fecal collections from a single male subject, suggested that 30% was eliminated via the fecal route in the form of EE₂. Further, it has been suggested that the fecal elimination of EE₂ largely results from biliary excretions.^{20,29} Maggs et al.²⁵ reported that on average 37% (n=5) of biliary excretions were in the form of EE₂ conjugates, which is consistent with the values measured by Reed et al. for the release of EE₂ in a single fecal sample. Overall, in the present study, the fecal elimination was estimated by multiplying the fraction of biliary excretions that is present as conjugated EE₂²⁵ by the net levels of EE₂ eliminated via the fecal route²³ to arrive at an estimate of 22.9%.

By summing the fecal and urinary elimination levels estimated above, it is estimated that 37.2% of an administered dose of EE₂ is eliminated as EE₂ and its conjugates.

S4 Modeling the Load of Natural Estrogens Released over the Course of Unintended Pregnancies that can be Associated with a User's Choice to Use a Particular Contraceptive Option ($J_{f,n}$)

The definitions of all variables used below along with their estimated values are provided in Section S9.

The total load of natural steroidal estrogens released over the course of unintended pregnancies that can be associated with a user's specific choice of a given contraceptive option is estimated as follows:

$$J_{f,n} = \sum_{j=1}^J \frac{A_n}{100} \cdot \left(f_{a,n} \int_{t=0}^{t_a} (U_j(t) + F_j(t)) dt + f_{b,n} \cdot f_u \int_{t=0}^{t_b} (U_j(t) + F_j(t)) dt + f_{m,n} \int_{t=0}^{t_m} (U_j(t) + F_j(t)) dt + f_{e,n} \int_{t=0}^{t_e} (U_j(t) + F_j(t)) dt \right) \cdot P_j \quad (S2)$$

In the equation above, j refers to the individual natural steroidal estrogens E_1 , E_2 , and E_3 . A_n is the annual probability that a typical user for a given contraception option n will experience an unintended pregnancy during the first year of use due to contraception failure⁵¹. $f_{a,n}$, $f_{b,n}$, $f_{m,n}$, $f_{e,n}$ are the fractions of an unintended pregnancy experienced by the users of contraceptive option n that will result in the outcomes of induced abortion, birth, spontaneous abortion and ectopic pregnancy⁵², respectively. f_u is the fraction of all unintended births that are unwanted. Such a correction/adjustment factor is not applied to all other outcomes of unintended pregnancies since these outcomes do not end up satisfying a future need of the parents for a child. t_a , t_b , t_m and t_e are the durations of unintended pregnancies that result in the outcomes of induced abortion, birth, spontaneous abortion and ectopic pregnancy, respectively.^{13,14,41}

$U_j(t)$ and $F_j(t)$ are the gestation age-dependent releases of natural estrogens via the urinary and fecal excretions of pregnant women, respectively. The urinary excretions curves for each estrogen j as function of gestational age, $U_j(t)$, were estimated by multiplying the data reported by Berg and Kuss⁸ for the excretion curves of natural estrogens for women of various gestational ages expressed in units of grams of estrogen per gram of creatinine by the average daily creatinine excretion for pregnant women (g of creatinine/24hr)⁹. To date, only a handful of analyses have been performed for the fecal release of natural estrogens by pregnant women.^{9,12} Therefore, as a best approximation, the limited fecal release data available^{11,12} were used to estimate fecal-to-urinary excretion ratios for each natural estrogen. Subsequently, these estimated ratios were multiplied by their respective $U_j(t)$ values to arrive at best possible estimates for $F_j(t)$. P_j is the potency of estrogen j relative to that of E_2 (see Section S2).

S5 Modeling the Legacy Estrogenic Load Arising from an Unwanted Birth and can be Associated with a User's Choice to Use a Particular Contraceptive Option ($J_{L,n}$)

The definitions of all variables used below along with their estimated values are provided in Section S9.

The legacy estrogen load resulting from an unwanted birth that is manifested over the life span of the resulting child and the duration of its genetic lineage (i.e., that child's progeny) is expressed as follows:

$$J_{L,n} = \frac{A_n}{100} \cdot f_b \cdot f_u \cdot M_L \quad (S3)$$

In Eq. (S3), M_L is the estrogenic legacy load of an unwanted birth and its genetic lineage. This is an inherently difficult parameter to quantify with certainty. For example, consider the work of Murtaugh and Schlax⁵⁵ in which the medium variant fertility projections from the World Population Prospects' 2006 revision⁵⁰ were used to estimate that the duration of a single birth's average genetic legacy in the USA is 470 years, which is nearly six times the average life span of a person in the USA.⁴⁹ Any attempt at quantifying M_L would not only require that one be able to predict all contraceptive options that will be available over such a lengthy duration but also requires the one can establish the mix with which future populations choose to use these available options. As such, we purposefully do not attempt to use this approach to estimate M_L here because we believe any such attempt is likely to be presumptive. However, a defensible estimate for M_L can be made using a highly conservative approach as described by the following expression:

$$M_L = G_L \cdot ((L_{BF} + L_{FT}) \cdot SR_F + L_{BM} \cdot SR_M) \quad (S3a)$$

In this expression, G_L is the duration of a single birth's genetic legacy in the USA, for which Murtaugh and Schlax's estimate of 470 years⁵⁵ is adopted here. L_{BF} and L_{BM} are the life-span averaged loads of natural estrogens basally excreted by females and males, respectively, and are estimated below in section 5.1 and 5.3 respectively. These loads only account for the release of natural estrogens from those anthropogenic excretions that will always be present (i.e., the basal levels excreted as the females and males progress through their various life stages). L_{FT} is the life-span averaged annual load of natural estrogens due to an assumed future total fertility rate (TFR) of 1.85 and is estimated below in section 5.2. The latter TFR of 1.85 was assumed as the basis for an estimate of L_{FT} for several reasons: (1) this estimate for the future fertility rate largely served as the basis for Murtaugh and Schlax's estimate for G_L ; and (2) it is considered to be a conservative estimate for future fertility rates in the USA.^{59, 60} The latter assertion is justified below. SR_F and SR_M are the respective fractions of births in the USA that are females and males, respectively, and are estimated using the at-birth sex ratio currently observed in that country.⁵⁶ The parameterization of variables in Eq. (S3a) yields an estimate of M_L of 2.1 grams of E_{2-eq} per unwanted birth.

The estimate for M_L that the above parameterization yields is highly conservative (i.e., it will result in an underestimate of legacy load) and, hence, is defensible for a number of reasons. Firstly, the uncertain

contribution due to the genetic legacy's use of future contraceptive options and HRT preparations is not included. Also not included, for similar reasons, is the genetic legacy's use of other future estrogenic chemicals. Lastly, both the parameterization for G_L and L_{FT} are likely conservative estimates since more recent future fertility projection developed for the United Nation's World Population Prospects' 2010 revision suggest a medium variant TFR of 2.1 for the USA^{59,60}. This projected level of 2.1 is equal to replacement level fertility and as long as such a fertility rate is maintained within a population the value of G_L , and hence M_L , would not converge to a finite value.

S5.1 Life-span-averaged Basal Estrogen Load of a Female in the USA (L_{BF})

In the USA, the average female will be pre-pubescent for 12.5 years¹, menstruate for another 38.8 years^{1,6} and be menopausal for 29.6 years^{6,49} before death at the age of 80.6 years⁴⁹. As shown in Table S4 below, such a life history can be used to estimate that a female basally releases a minimum of 124 mg of E_2 -eq over her life span to sewers. Given that the average life span of a female is 80.6 years⁴⁹, the life-span-averaged basal estrogen load (L_{BF}) for a female in the USA can be estimated to amount to 1.54 mg of E_2 -eq/yr (i.e., L_{BF}).

Table S4 Estimation of the Life-span Basal Estrogen Load of a Female in the USA.

Life stage	Duration of life stage yr	Daily per capita excretion during the life stage ^(a)			Life-span load ^(b) E_2 -eq mg
		E_1	E_2	E_3	
		$\mu\text{g}/\text{cap-d}$			
Prepubescent girls	12.5	0.08	0.06	0.2	0.43
Menstruating women	38.5	8.69	4.42	9.4	108
Menopausal women	29.6	1.7	0.79	1.9	15.5
					124

Footnotes: (a) See Table S1; (b) $E_2\text{-eq} = [E_1]/3 + [E_2] + [E_3]/25$ where: $[E_2\text{-eq}]$, $[E_1]$, $[E_2]$ and $[E_3]$ are the mass loads of estradiol equivalents, estrone, estradiol and estriol, respectively. The mass loads for all life stages were estimated as follows: daily per capita excretion ($\mu\text{g}/\text{cap-d}$) $\times$ duration of life stage (yr) $\times$ 365 (d/yr) $\times$ $1/10^3$ (mg/ μg).

S5.2 Life-span-averaged Estrogen Load of a Female in the USA due to Total Fertility (L_{FT})

In the present study, as described above, the future fertility rate of a woman in the USA is assumed to be 1.85 (i.e., 1.85 live births over her lifetime), which is the United Nations' 2006 mid-variant estimate for the level to which total fertility rate was projected to converge in the USA by 2050⁵⁰. Pregnancy outcomes other than births were not considered since future trends for these outcomes are difficult to predict. Nevertheless, pregnancies that result in outcomes other than birth are comparatively minor contributors of estrogenic content (see Table S1). For example, consider that a pregnancy resulting in a birth leads to the release of an E_2 -eq load that is 20, 25 and 32 times higher than the levels released had the pregnancy instead resulted in the outcome of spontaneous abortion, induced abortion and ectopic pregnancy, respectively.

The analysis summarized in Table S5 suggests that, with an assumed fertility rate of 1.85, a female would release 520 mg of E_2 -eq to sewer systems over her lifetime. As noted earlier, the average life span of a female in the USA is 80.6 years⁴⁹. This estimate, along with the estimates from Table S6 below, suggest that the life-span-averaged estrogen load due to the fertility of a female in the USA can be estimated to be 6.5 mg of E_2 -eq/yr (i.e., L_{FT}).

Table S5 Estimation of the Life-Span Estrogen Fertility Load for a Female with a Fertility Rate of 1.85.

Events	Fertility rate	Excretion/birth ^(a)			Life-span load ^(b)
		E ₁	E ₂	E ₃	E _{2-Eq}
	Births/women	mg/birth			mg
Pregnancies resulting in births	1.85	259	134	1525	520

Footnotes: (a) See Table S1; (b) $E_{2-Eq} = [E_1]/3 + [E_2] + [E_3]/25$ where $[E_{2-Eq}]$, $[E_1]$, $[E_2]$ and $[E_3]$ are the mass loads of estradiol equivalents, estrone, estradiol and estriol, respectively. The mass loads were estimated as follows: fertility rate (Births/Life) × excretion per birth (mg/birth).

S5.3 Life-span-averaged Basal Estrogen Load of a Male in the USA (L_{BM})

The average male in the USA will be pre-pubescent for 12.2 years¹⁶. For the remainder of his life, it is assumed that he will excrete as an adult male before dying at the age of 75.6 years⁴⁹. This data can be used to estimate the minimum life-span averaged annual load of E_{2-eq} of a male in the USA. Specifically, the analysis in Table S6 below suggests that an American male basally releases a minimum of 79.7 mg of E_{2-eq} over his life span to sewers. Noting that the average life span of an American male is 75.6 years⁴⁹, the life-span averaged basal estrogen load for a male in the USA is estimated to be 1.05 mg of E_{2-eq}/yr (i.e., L_{BM}).

Table S6 Estimate of the Life-span Basal Estrogen Load of a Male in the USA.

Life stages	Duration of life stage	Daily per capita excretion during the life stage ^(a)			Life-span load ^(b)
		E ₁	E ₂	E ₃	E _{2-Eq}
	yr	µg/cap-d			mg
Prepubescent boy	12.2	0.08	0.06	0.2	0.42
Adult Male	63.4	3.6	2.1	2.4	79.3
				Sum	79.7

Footnotes: (a) See Table S1; (b) $E_{2-Eq} = [E_1]/3 + [E_2] + [E_3]/25$ where $[E_{2-Eq}]$, $[E_1]$, $[E_2]$ and $[E_3]$ are the mass loads of estradiol equivalents, estrone, estradiol and estriol, respectively. The mass loads for all life stages were estimated as follows: daily per capita excretion (µg/cap-d) × Duration of life stage (yr) × 365 (d/yr) × $1/10^3$ (mg/µg).

S6 Pregnancy Events and Estrogenic Load Averted by a Population's Collective Use of Contraception

The definitions of all variables used below along with their estimated values are detailed in Section S9.

S6.1 Estrogenic Load Averted by a Population's Collective Use of Contraception

The net estrogenic load averted through the collective use of contraception by a given population was estimated using the following model:

$$E_a = E_p + E_L - E_e \quad (S4)$$

In Eq. (S4), E_a is the net estrogenic averted through a population's collective use of contraception. E_p is the estrogenic load that would have been released over the course of all pregnancies averted due to the population's collective use of contraception. E_L is the estrogenic load represented by all unwanted legacies averted through the population's collective use of contraception. E_e is the estrogenic content directly released via the population's collective use of contraception.

E_p was estimated using the following model

$$E_p = P_T \cdot (IP_e - IP_o) \cdot \left[\sum_{j=1}^J P_j \cdot \left(f_a \int_{t=0}^{t_a} (U_j(t) + F_j(t)) dt + f_b \cdot f_u \int_{t=0}^{t_b} (U_j(t) + F_j(t)) dt + f_m \int_{t=0}^{t_m} (U_j(t) + F_j(t)) dt + f_e \int_{t=0}^{t_e} (U_j(t) + F_j(t)) dt \right) \right] \quad (S4a)$$

In Eq. (S4a), P_T is the total number of women using any form of contraception.⁵ IP_o is the rate at which P_T currently experiences unintended pregnancies.⁵³ IP_e is the unintended pregnancy rate expected to be observed among the user population P_T should they all stop using their respective contraceptive methods. Since the accurate estimation of IP_e represents a significant challenge, it is conservatively estimated here. A conservative estimate for IP_e can be furnished by assuming that it is equal to the level of unintended pregnancies observed among those women who currently do not use any form of contraception and due to their sexual activity are at a risk of experiencing unintended pregnancies.^{47,53} The reason the use of such data is considered to produce a conservative estimate for IP_e , and hence, E_p , is that these sexually active non-users of contraception have been suggested to represent a selected population cohort that experiences lower-than-normal level of sexual activity and fecundity⁵³. f_a , f_b , f_m and f_e are overall levels of all pregnancies averted that are taken to the outcome of induced abortion, birth, spontaneous abortion and ectopic pregnancy, respectively.^{40,47} All other variables are as previously stated.

E_L was estimated using the following model:

$$E_L = P_T \cdot (IP_e - IP_o) \cdot [f_b \cdot f_u \cdot M_L] \quad (S4b)$$

All variables in Eq. (S4b) have been previously defined.

E_e was estimated as in section S1 (see footnote f Table S1).

S6.2 Pregnancy Events Averted by a Population's Collective Use of Contraception

The net number of pregnancy events averted through a population's collective use of contraception was estimated by using the following model:

$$N_{\text{averted}} = P_T \cdot (IP_e - IP_o) \cdot [f_a + f_b \cdot f_w + f_m + f_e] \quad (S5)$$

All variables in Eq. (S5) have been previously defined.

The number of each pregnancy outcome averted by a population's collective use of contraception was estimated using the following simplifications of Eq. (S5):

Number of abortions averted	$N_{\text{a-averted}} = P_T \cdot (IP_e - IP_o) \cdot [f_a]$	(S5a)
Number of unwanted births averted	$N_{\text{ub-averted}} = P_T \cdot (IP_e - IP_o) \cdot [f_b \cdot f_w]$	(S5b)
Number of miscarriages averted	$N_{\text{m-averted}} = P_T \cdot (IP_e - IP_o) \cdot [f_m]$	(S5c)
Number of ectopic pregnancies averted	$N_{\text{e-averted}} = P_T \cdot (IP_e - IP_o) \cdot [f_e]$	(S5d)

S7 Estimating Relative Contributions as Shown in Figure 3 (Main Body).

All loads were estimated on a pre-treatment basis.

The number of events for each pregnancy outcome was estimated from Finer and Henshaw⁴⁷, Hoover et al.⁴⁰ and Ventura et al.⁷.

The resultant estrogenic load released over the course of each pregnancy outcome was estimated as follows: number of events for a pregnancy outcome^{7, 40, 47} multiplied by the estrogenic load excreted over course of the pregnancy outcome (See Table S1).

The estrogenic legacy represented by each birth category was estimated as follows: number of births per category^{7,47} multiplied by M_L (Eq. (S3a)).

S8 Modeling Estrogen Loads Arising from Changes in Contraceptive Use

The definitions of all variables used below along with their estimates values are provided in Section S9.

In order to estimate the changes in steroidal estrogen loads that result from changes in contraceptive use, it is necessary to evaluate the estrogen loads for the *status quo* scenario (i.e., the resulting from the mix of contraceptive options currently in use) and compare them to the loads experienced under alternate scenarios.

S8.1 Modeling Steroidal Estrogens Loads for the *Status Quo* Scenario

The estrogenic load that can be ascribed to a group of first-year EE₂-OC users under the *status quo* scenario is estimated using the following equation:

$$E_{EE2-OC} = P_s \cdot [J_{d,EE2-OC} + J_{f,EE2-OC} + J_{L,EE2-OC}] \quad (S6)$$

In Eq. (S6), for the purpose of the scenario analysis, P_s is chosen here to be a unit population of 1,000 first year users of EE₂-OC. $J_{d,EE2-OC}$, $J_{f,EE2-OC}$ and $J_{L,EE2-OC}$ were estimated using Eq. (S1), (S2) and (S3), respectively.

S8.2 Modeling Steroidal Estrogens Loads for Scenarios Where Users Switch to Non-Estrogen Based Contraceptive Methods

Upon discontinuing the use of EE₂-OC, the switching population, P_s , is expected to either adopt other contraceptive options or discontinue the use of contraception altogether.⁴⁵ Under the *Discontinue EE₂* scenario, the expected load of steroidal estrogens that can be attributed to contraceptive choices made by P_s can be modeled as follows:

$$E_s = P_s \cdot \left[\sum_{m=1}^M f_{s,m} \cdot (J_{f,m} + J_{L,m}) + f_{no-method} \cdot (J_{f,no-method} + J_{L,no-method}) \right] \quad (S7)$$

In Eq. (S7), M is the total number of individual contraceptive options, m , adopted by the P_s after they discontinue the use of EE₂-OC and $f_{s,m}$ is the fraction with which P_s adopts each option m . $f_{no-method}$ is the fraction of P_s that completely abandons the use of contraception after discontinuing the use of the EE₂-OC. Values for $f_{s,m}$ and $f_{no-method}$ are estimated using the data of Rosenberg and Waugh⁴⁵ who reported the contraceptive mix adopted by those individuals who for various reasons discontinued the use of EE₂-OC and still wanted to prevent a pregnancy. $J_{f,m}$ and $J_{f,no-method}$ were estimated using Eq. (S2) and $J_{L,m}$ and $J_{L,no-method}$ using Eq. (S3).

In addition to the most likely switch scenario, we also consider three more explorative scenarios as per the suggestion of Wise et al.¹⁰ in which the entire switching population, P_s , is modeled as switching from EE₂-based oral contraceptives to the use of male condoms or diaphragms or a copper IUD. These scenarios are modeled by simplifying the coefficients of Eq. (S7).

S8.3 Modeling Changes in Flows of Steroidal Estrogens Should EE₂-OC Users Switch to E₂-OC

The pearl index (i.e., number of unintended pregnancies per 100 women-years of contraceptive exposure) for the newly introduced E₂-OC has been reported to be similar to that of EE₂-OC.⁶¹ Perhaps more importantly, since the manner with which the E₂-OC is administered is exactly the same as EE₂-OCs (i.e., one pill a day), the typical failure rate of the E₂-OC is expected to be similar to that of EE₂-OCs. Therefore, the estrogenic loads J_f and J_L for the two forms OCs can be assumed to be comparable. Further, this suggests that the only difference in terms of estrogenic load associated with these two forms of OC, results from the estrogenic content that is released directly via the excretion of the respective users (i.e., J_d). Moreover, it is also important to recognize that, clinically a 2 mg/cap·d dose of estradiol valerate (i.e., the salt form of estradiol used in Natazia) is equivalent to a 20 µg/cap·d dose of ethinylestradiol.⁶¹ This, along with the estimates furnished in Section S4 for the average daily use of E₂ and EE₂ by their respective users of 1.86 mg/cap·d and 21.7 µg/cap·d, suggests that a user of E₂-OC can be approximated as being clinically equivalent to the average EE₂-OC user. Under the *Switch to E₂-OC* scenario, the expected load of steroidal estrogens that can be attributed to contraceptive choices made by P_s can be modeled as follows:

$$E_{E2-OC} = P_s \cdot [J_{d,E2OC} + J_{f,E2OC} + J_{L,E2OC}] \quad (S8)$$

$J_{d,E2OC}$, $J_{f,E2OC}$ and $J_{L,E2OC}$ were estimated using Eq. (S1), (S2) and (S3), respectively. All other variables are as previously stated.

S9 Nomenclature and Specific Estimates for All Variables Used

Table S7 Nomenclature and Specific Estimates for All Variables.

Parameter	Description	Estimate	Units	Data Source	Notes
$A_{\text{Copper-T IUD}}$	Annual probability that a typical user of Copper-T IUD will experience an unintended pregnancy during the first year of use due to contraception failure.	0.8	%	Trussel ¹⁵¹	
$A_{\text{Depo-Provera}}$	Annual probability that a typical user of Depo-Provera will experience an unintended pregnancy during the first year of use due to contraception failure.	6	%	Trussel ¹⁵¹	
$A_{\text{Diaphragm}}$	Annual probability that a typical user of diaphragms will experience an unintended pregnancy during the first year of use due to contraception failure.	12	%	Trussel ¹⁵¹	
$A_{\text{Female condom}}$	Annual probability that a typical user of female condoms will experience an unintended pregnancy during the first year of use due to contraception failure.	21	%	Trussel ¹⁵¹	
$A_{\text{Fertility awareness-based methods}}$	Annual probability that a typical user of fertility awareness-based methods will experience an unintended pregnancy during the first year of use due to contraception failure.	24	%	Trussel ¹⁵¹	
A_{Implanon}	Annual probability that a typical user of Implanon will experience an unintended pregnancy during the first year of use due to contraception failure.	0.05	%	Trussel ¹⁵¹	
$A_{\text{LNG-20 IUS}}$	Annual probability that a typical user of LNG-20 IUS will experience an unintended pregnancy during the first year of use due to contraception failure.	0.2	%	Trussel ¹⁵¹	
$A_{\text{Male condom}}$	Annual probability that a typical user of male condoms will experience an unintended pregnancy during the first year of use due to contraception failure.	18	%	Trussel ¹⁵¹	
$A_{\text{Male sterilization}}$	Annual probability that a typical user of male sterilization will experience an unintended pregnancy during the first year of use due to contraception failure.	0.15	%	Trussel ¹⁵¹	
$A_{\text{No method}}$	Annual probability of experiencing an unintended pregnancy among those who use no method of contraception.	85	%	Trussel ¹⁵¹	
$A_{\text{EE2-OC}}$	Annual probability that a typical user of OC will experience an unintended pregnancy during the first year of use due to contraception failure.	9	%	Trussel ¹⁵¹	
$A_{\text{Progestin-only pill}}$	Annual probability that a typical user of Progestin-only pills will experience an unintended pregnancy during the first year of use due to contraception failure.	9	%	Trussel ¹⁵¹	
$A_{\text{Spermicides}}$	Annual probability that a typical user of spermicides will experience an unintended pregnancy during the first year of use due to contraception failure.	28	%	Trussel ¹⁵¹	
$A_{\text{Sponge-Nulliparous women}}$	Annual probability that a typical nulliparous user of sponges will experience an unintended pregnancy during the first year of use due to contraception failure.	12	%	Trussel ¹⁵¹	
$A_{\text{Sponge-Parous women}}$	Annual probability that a typical parous user of sponges will experience an unintended pregnancy during the first year of use due to contraception failure.	24	%	Trussel ¹⁵¹	
$A_{\text{Tubal ligation (Female sterilization)}}$	Annual probability that a typical user of female sterilization will experience an unintended pregnancy during the first year of use due to contraception failure.	0.5	%	Trussel ¹⁵¹	

Parameter	Description	Estimate	Units	Data Source	Notes
$A_{\text{Withdrawal}}$	Annual probability that a typical user of the withdrawal method will experience an unintended pregnancy during the first year of use due to contraception failure.	22	%	Trussell ¹⁵¹	
E_a	Total estrogenic load averted through a population's collective use of contraception.	4.80	tonnes of $E_{2\text{-eq}}$ Eq. (S4)		
E_p	Estrogenic load that would have been released over the course of all pregnancies averted due to American's collective use of contraception.	0.66	tonnes of $E_{2\text{-eq}}$ Eq. (S4a)		
E_L	Estrogenic load represented by all unwanted legacies averted through American's use of contraception.	4.44	tonnes of $E_{2\text{-eq}}$ Eq. (S4b)		
E_e	Total estrogenic content directly released due to the current contraceptive mix used by Americans.	0.31	tonnes of $E_{2\text{-eq}}$ Section S1		
$E_{\text{EE2-OC}}$	Total estrogenic load that can be associated with 1,000 first year users of $EE_2\text{-OC}$	62	grams of $E_{2\text{-eq}}$ Eq. (S6)		
E_s	Total estrogenic load that can be associated with those who discontinue the use of $EE_2\text{OC}$	107	grams of $E_{2\text{-eq}}$ Eq. (S7)		
$E_{\text{E2-OC}}$	Total estrogenic load that can be associated with 1,000 first year users of $E_2\text{-OC}$	137	grams of $E_{2\text{-eq}}$ Eq. (S8)		
E_{CIUD}	Total estrogenic load that can be associated with 1,000 first year users of Copper IUDs	2.8	grams of $E_{2\text{-eq}}$ Eq. (S7)		
E_{MC}	Total estrogenic load that can be associated with 1,000 first year users of Male Condoms	65	grams of $E_{2\text{-eq}}$ Eq. (S7)		
E_{Di}	Total estrogenic load that can be associated with 1,000 first year users of Diaphragms	43	grams of $E_{2\text{-eq}}$ Eq. (S7)		
f_s	Fraction of wastewater that currently undergoes secondary treatment in the USA.	0.47		US EPA ³⁶	
f_{ad}	Fraction of wastewater that currently undergoes advanced treatment in the USA.	0.53		US EPA ³⁶	
f_a	Fraction of all pregnancies averted that would have resulted in the outcome of induced abortion.	0.42		Ventura et al. ⁷ ; Hoover et al. ⁴⁰	
f_b	Fraction of all pregnancies averted that would have resulted in the outcome of birth.	0.44		Ventura et al. ⁷ ; Hoover et al. ⁴⁰	
f_e	Fraction of all pregnancies averted that would have resulted in the outcome of ectopic pregnancy.	0.006		Ventura et al. ⁷ ; Hoover et al. ⁴⁰	
f_m	Fraction of all pregnancies averted that would have resulted in the outcome of spontaneous abortion.	0.134		Ventura et al. ⁷ ; Hoover et al. ⁴⁰	
$f_{a, \text{all other methods}}$	Fraction of unintended pregnancies experienced by the users of all other methods that will result in the outcome of induced abortion.	0.46		Trussell et al. ⁵²	
$f_{a, \text{Copper-T IUD}}$	Fraction of unintended pregnancies experienced by the users of Copper-T IUD that will result in the outcome of induced abortion.	0.45		Trussell et al. ⁵²	
$f_{a, \text{LNG-20 IUS}}$	Fraction of unintended pregnancies experienced by the users of LNG-20 IUS that will result in the outcome of induced abortion.	0.23		Trussell et al. ⁵²	
$f_{a, \text{Tubal ligation}}$	Fraction of unintended pregnancies experienced by the users of tubal ligation that will result in the outcome of induced abortion.	0.31		Trussell et al. ⁵²	

Parameter	Description	Estimate	Units	Data Source	Notes
$f_{b, \text{all other methods}}$	Fraction of unintended pregnancies experienced by the users of all other methods that will result in the outcome of birth.	0.37		Trussell et al. ⁵²	
$f_{b, \text{Copper-T IUD}}$	Fraction of unintended pregnancies experienced by the users of Copper-T IUD that will result in the outcome of birth.	0.36		Trussell et al. ⁵²	
$f_{b, \text{LNG-20 IUS}}$	Fraction of unintended pregnancies experienced by the users of LNG-20 IUS that will result in the outcome of birth.	0.19		Trussell et al. ⁵²	
$f_{b, \text{Tubal ligation}}$	Fraction of unintended pregnancies experienced by the users of tubal ligation that will result in the outcome of birth.	0.25		Trussell et al. ⁵²	
$f_{e, \text{all other methods}}$	Fraction of unintended pregnancies experienced by the users of all other methods that will result in the outcome of ectopic pregnancy.	0.01		Trussell et al. ⁵²	
$f_{e, \text{Copper-T IUD}}$	Fraction of unintended pregnancies experienced by the users of Copper-T IUD that will result in the outcome of ectopic pregnancy.	0.03		Trussell et al. ⁵²	
$f_{e, \text{LNG-20 IUS}}$	Fraction of unintended pregnancies experienced by the users of LNG-20 IUS that will result in the outcome of ectopic pregnancy.	0.50		Trussell et al. ⁵²	
$f_{e, \text{Tubal ligation}}$	Fraction of unintended pregnancies experienced by the users of tubal ligation that will result in the outcome of ectopic pregnancy.	0.33		Trussell et al. ⁵²	
F_{E1} / U_{E1}	Fecal to urinary ratio with which E_1 is released by pregnant women.	0.13		Adlercreutz et al. ¹¹ , Martin et al. ¹²	
$F_{E1, E2} / F_{E2, E2}$	Fraction of an administered dose of E_2 that is excreted as $E_1/E_2/E_3$ and its conjugates via the user's fecal excretions.	Minor		Assumed	
F_{E2} / U_{E2}	Fecal to urinary ratio with which E_2 is released by pregnant women.	0.84		Adlercreutz et al. ¹¹ , Martin et al. ¹²	
F_{E3} / U_{E3}	Fecal to urinary ratio with which E_3 is released by pregnant women.	0.03		Adlercreutz et al. ¹¹ , Martin et al. ¹²	
$F_{EE2, EE2}$	Fraction of an administered dose of EE_2 that is excreted unchanged and its conjugates via the user's fecal excretions.	0.229 ± 0.03		Section S3	Assumed to be normally distributed.
$f_{m, \text{all other methods}}$	Fraction of unintended pregnancies experienced by the users of all other methods that will result in the outcome of spontaneous abortion.	0.17		Trussell et al. ⁵²	
$f_{m, \text{Copper-T IUD}}$	Fraction of unintended pregnancies experienced by the users of Copper-T IUD that will result in the outcome of spontaneous abortion.	0.16		Trussell et al. ⁵²	
$f_{m, \text{LNG-20 IUS}}$	Fraction of unintended pregnancies experienced by the users of LNG-20 IUS that will result in the outcome of spontaneous abortion.	0.09		Trussell et al. ⁵²	
$f_{m, \text{Tubal ligation}}$	Fraction of unintended pregnancies experienced by the users of tubal ligation that will result in the outcome of spontaneous abortion.	0.11		Trussell et al. ⁵²	
$f_{\text{no-method}}$	Fraction of Ps that completely abandons the use of contraception after discounting the use of the EE_2 -OC.	0.19		Rosenberg and Berg ⁴⁵	

Parameter	Description	Estimate	Units	Data Source	Notes
$f_{s,m}$	Fraction with which P_s adopts each option m (see table at right) after discontinuing the use of EE ₂ -OC.	m			
		Male Condom			
		Rhythm, Withdrawal, or Natural Family Planning			
		Sterilization			
		IUD, Implant, Injectable (DMPA)			
		Other Barrier or Spermicide			
		Other			
f_u	Fraction of unintended births that is unwanted.	0.40		Trussell et al. ⁵² Trussell ⁵³⁻⁵⁴	
G_L	Duration of single birth's genetic legacy in the USA.	470	years	Murtaugh and Schlax ⁵⁵	
IP_0	The rate at which P_T currently experiences unintended pregnancies.	39	Unintended pregnancies per 1000 women	Finer and Henshaw ⁴⁷	
IP_e	The unintended pregnancy rate expected to be observed among the user population P_T should they all stop using their respective contraceptive methods.	354	Unintended pregnancies per 1000 women	Trussell et al. ⁵³	
$J_{d,EE2-OC}$	Steroidal estrogen load released directly via the use of EE ₂ -OC.	29.5	mg of E ₂ -eq/ user. first year of use	Eq. (S1)	
$J_{d,E2-OC}$	Steroidal estrogen load released directly via the use of E ₂ -OC.	105	mg of E ₂ -eq/ user. first year of use	Eq. (S1)	

Parameter	Description	Estimate	Units	Data Source	Notes
$J_{f, \text{no method}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with user's choice to use no method of contraception.	43	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{spermicide}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with user's choice to use spermicides.	14	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{fertility awareness-based methods}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with user's choice to use fertility awareness-based methods.	12	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{withdrawal}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with user's choice to use withdrawal.	11	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{sponge-parous}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a parous user's choice to use sponges.	12	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{sponge-nulliparous}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a nulliparous user's choice to use sponges.	6	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{female condom}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use female condoms.	11	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{male condom}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use male condoms.	9	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{diaphragm}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use diaphragms.	6	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{EE2-OC}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use EE2-OC.	5	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{E2-OC}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use E2-OC.	5	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{progestin-only pill}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use progestin-only pill.	5	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{depo-provera}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use Depo-provera.	3	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{copper IUD}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use Copper IUD.	0.4	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		
$J_{f, \text{IUS}}$	Load of natural estrogens released over the course of unintended pregnancies that	0.1	mg of $E_{2\text{-eq}}$ /user. first year of use Eq. (S2)		

Parameter	Description	Estimate	Units	Data Source	Notes
	can be associated with a user's choice to use Levengestrol IUS.		user. first year of use		
$J_{f, \text{female sterilization}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use female sterilization.	0.2	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S2) of use		
$J_{f, \text{male sterilization}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use male sterilization.	0.1	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S2) of use		
$J_{f, \text{implant}}$	Load of natural estrogens released over the course of unintended pregnancies that can be associated with a user's choice to use the implant.	0.03	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S2) of use		
$J_{L, \text{no method}}$	Legacy estrogenic load for the users of no method of contraception	261	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{spermicide}}$	Legacy estrogenic load for the users of spermicide	87	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{fertility awareness-based methods}}$	Legacy estrogenic load for the users of fertility awareness-based methods.	74	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{withdrawal}}$	Legacy estrogenic load for the users of withdrawal.	68	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{sponge-parous}}$	Legacy estrogenic load for the parous users of sponges.	74	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{sponge-nulliparous}}$	Legacy estrogenic load for the nulliparous users of sponges.	37	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{female condom}}$	Legacy estrogenic load for the users of female condoms.	64	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{male condom}}$	Legacy estrogenic load for the users of male condoms .	56	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{diaphragm}}$	Legacy estrogenic load for the users of diaphragms.	37	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{EE2-OC}}$	Legacy estrogenic load for the users of EE2-OC.	28	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		
$J_{L, \text{E2-OC}}$	Legacy estrogenic load for the users of E2-OC.	28	mg of $E_{2\text{-eq}}$ / user. first year Eq. (S3) of use		

Parameter	Description	Estimate	Units	Data Source	Notes
$J_{L, \text{progestin-only pill}}$	Legacy estrogenic load for the users of progestin-only pill.	28	mg of $E_{2\text{-eq}}$ /user.first year of use Eq. (S3)		
$J_{L, \text{depo-provera}}$	Legacy estrogenic load for the users of Depo provera.	19	mg of $E_{2\text{-eq}}$ /user.first year of use Eq. (S3)		
$J_{L, \text{copper IUD}}$	Legacy estrogenic load for the users of Copper IUD.	2.4	mg of $E_{2\text{-eq}}$ /user. first year Eq. (S3) of use		
$J_{L, \text{IUS}}$	Legacy estrogenic load for the users of IUS.	0.3	mg of $E_{2\text{-eq}}$ /user.first year Eq. (S3) of use		
$J_{L, \text{female sterilization}}$	Legacy estrogenic load for the users of female sterilization.	1.0	mg of $E_{2\text{-eq}}$ /user.first year Eq. (S3) of use		
$J_{L, \text{male sterilization}}$	Legacy estrogenic load for the users of male sterilization.	0.5	mg of $E_{2\text{-eq}}$ /user.first year Eq. (S3) of use		
$J_{L, \text{implant}}$	Legacy estrogenic load of implant users.	0.15	mg of $E_{2\text{-eq}}$ /user.first year Eq. (S3) of use		
k-E1	First order decay constant for E1 in surface waters.	0.3	d^{-1}	Caldwell et al. ¹⁷	
k-E2	First order decay constant for E2 in surface waters.	0.3	d^{-1}	Caldwell et al. ¹⁷	
k-E3	First order decay constant for E3 in surface waters.	5.7	d^{-1}	Caldwell et al. ¹⁷	
k-EE2	First order decay constant for EE2 in surface waters.	0.07	d^{-1}	Caldwell et al. ¹⁷	
L_{BF}	Life-span averaged annual load of natural estrogens basally excreted by females.	1.54	mg of $E_{2\text{-eq}}$ per year	Section S5	
L_{BM}	Life-span averaged annual load of natural estrogens basally excreted by males.	1.05	mg of $E_{2\text{-eq}}$ per year	Section S5	
$L_{E2\text{-OC}}$	Per user daily consumption of E_2 via users of OC.	1419	μg of E_2 /user-d	Section S3	
$L_{EE2\text{-OC}}$	Per user daily consumption of EE_2 via users of OC.	21.7	μg of EE_2 /user-d	Section S3	
L_{FT}	Life-span averaged annual load of natural estrogens due to an assumed total fertility rate of 1.85.	6.5	mg of $E_{2\text{-eq}}$ per year	Section S5	
M_L	Estrogenic legacy load of unwanted births and its genetic lineage	2.1	g of $E_{2\text{-eq}}$ per unwanted Eq. (S3a) birth		
Mw_{E1}	Molecular weight of E_1 .	270.4	g/mole		

Parameter	Description	Estimate	Units	Data Source	Notes
Mw_{E2}	Molecular weight of E_2 .	272.4	g/mole		
Mw_{E3}	Molecular weight of E_3 .	288.4	g/mole		
Mw_{EE2}	Molecular weight of EE_2 .	296.4	g/mole		
N_{averted}	Net number of pregnancy events averted through a population's collective use of contraception.	8.8	Million people Eq. (S5)		
$N_{\text{a-averted}}$	Net number of abortions averted through a population's collective use of contraception.	5.0	Million people Eq. (S5a)		
$N_{\text{ub-averted}}$	Net number of unwanted births averted through a population's collective use of contraception.	2.1	Million people Eq. (S5b)		
$N_{\text{m-averted}}$	Net number of miscarriages averted through a population's collective use of contraception.	1.6	Million people Eq. (S5c)		
$N_{\text{e-averted}}$	Net number of ectopic pregnancies averted through a population's collective use of contraception.	0.07	Million people Eq. (S5d)		
P_{E1}	Potency of E_1 relative to E_2 .	1/3		Section S2	
P_{E2}	Potency of E_2 relative to E_2 .	1		By definition Section S2	
P_{E3}	Potency of E_3 relative to E_2 .	1/25		Section S2	
P_{EE2}	Potency of EE_2 relative to E_2 .	10		Section S2	
P_s	Unit population used a basis for scenario analysis.	1,000	First-year users of contraception	Assumed	
P_T	Total number of American women using any form of contraception.	38,106,259	People	Mosher and Jones ⁵	
$R_{s,E1}/R_{s,E2}$ $/R_{s,E3}/R_{s,EE2}$	Removal of steroidal estrogens in secondary treatment plants.	66.8% ($R_{s,E1}$), 85.0% ($R_{s,E2}$), 97.0% ($R_{s,E3}$), 84.0% ($R_{s,EE2}$)		Caldwell et al. ¹⁷	
$R_{ad,E1}/R_{ad,E2}$ $/R_{ad,E3}/R_{ad,EE2}$	Removal of steroidal estrogens in advanced treatment plants.	87.7% ($R_{s,E1}$), 95.5% ($R_{s,E2}$), 97.0% ($R_{s,E3}$), 84.0% ($R_{s,EE2}$)		Caldwell et al. ¹⁷	
SR_F	Fraction of births in the USA that are females.	0.49		Martin et al. ⁵⁶	
SR_M	Fraction of births in the US that are males.	0.51		Martin et al. ⁵⁶	

Parameter	Description	Estimate	Units	Data Source	Notes

		Weeks	Days	Cumulative Probability (%)	
		0	0	0	
		4	28	31	
		7	49	49	
		8	56	63	
		9	63	72	
		10	70	79	
		11	77	84	
		12	84	88	
		13	91	91	
		14.5	101.5	95	
		16.5	115.5	97	
		19	133	99	
		24	168	100	

t_a Duration of an unintended pregnancy resulting in the outcome of induced abortion.

Weeks/Days Pazol et al.¹³

		Weeks	Days	Cumulative Probability (%)	
		0	0	0	
		30	210	1	
		33.5	234.5	2	
		35	245	3	
		36	252	6	
		37	259	10	
		38	266	21	
		39	273	43	
		40	280	75	
		41	287	90	
		42	294	98	
		43	301	100	
		44	308	100	

t_b Duration of an unintended pregnancy resulting in the outcome of birth.

Weeks/Days Goldhaber and Fireman⁴¹

Parameter	Description	Estimate	Units	Data Source	Notes
t_e	Duration of an unintended pregnancy resulting in the outcome of ectopic pregnancy.				
t_m	Duration of an unintended pregnancy resulting in the outcome of spontaneous abortion.				
t_r	Typical residence time of a wastewater parcel in surface water.	40	Days	Sinclair et al. ³⁷	
	Was modelled by fitting appropriate distribution in @RISK to excretion developed from the data of Berg and Kuss ⁸ and Knuppel et al. ⁹ :				
$\int u_{E1}$	Excretion of E_1 as a function of gestational age	Birth: RiskBetaGeneral(3.4,17.7,18.5,1405) Abortions: RiskLognorm(11.3,5.3) Miscarriage: RiskBetaGeneral(1.36,4.2,6.3,54.8) Ectopic: RiskBetaGeneral(1.24,3.8,6.1,40.3)		mg of E_1	
$U_{E1,E2}$	Fraction of an administered dose of E_2 that is excreted as E_1 and its conjugates via	0.30 ± 0.09		Friel et al. ¹⁵	Assumed to be

Parameter	Description	Estimate	Units	Data Source	Notes
	the user's urinary excretions.				normally distributed.
$\int u_{E_2}$	Excretion of E_2 as a function of gestational age	Was modelled by fitting appropriate distribution in @RISK to excretion developed from the data of Berg and Kuss⁸ and Knuppel et al.⁹: Birth: RiskTriang(29.61,51.5,149.7) Abortions: RiskLognorm(1.91,2.16,RiskShift(0.75)) Miscarriage: RiskLognorm(3.28,3.11,RiskShift(1.12)) Ectopic: RiskLognorm(2.56,2.89,RiskShift(0.95))	mg of E_2	Berg and Kuss ⁸ ; Knuppel et al. ⁹	
u_{E_2,E_2}	Fraction of an administered dose of E_2 that is excreted unchanged and its conjugates via the user's urinary excretions.	0.10 ± 0.04		Friel et al. ¹⁵	Assumed to be normally distributed.
$\int u_{E_3}$	Excretion of E_3 as a function of gestational age	Was modelled by fitting appropriate distribution in @RISK to excretion developed from the data of Berg and Kuss⁸ and Knuppel et al.⁹: Birth: RiskTriang(345.9,12,3020) Abortions: RiskWeibull(1.83,26.3) Miscarriage: RiskLognorm(101,25.7,RiskShift(-54.2)) Ectopic: RiskLognorm(60.3,19.2,RiskShift(-29.9))	mg of E_3	Berg and Kuss ⁸ ; Knuppel et al. ⁹	
u_{E_3,E_2}	Fraction of an administered dose of E_2 that is excreted as E_3 and its conjugates via the user's urinary excretions.	0.06 ± 0.04		Friel et al. ¹⁵	Assumed to be normally distributed.
u_{EE_2,EE_2}	Fraction of an administered dose of EE_2 that is excreted unchanged and its conjugates via the user's urinary excretions.	0.143 ± 0.03		Section S3	Assumed to be normally distributed.

S10 Changes in Flows of Estrogens When Users of EE₂-OC Switch to Male Condoms

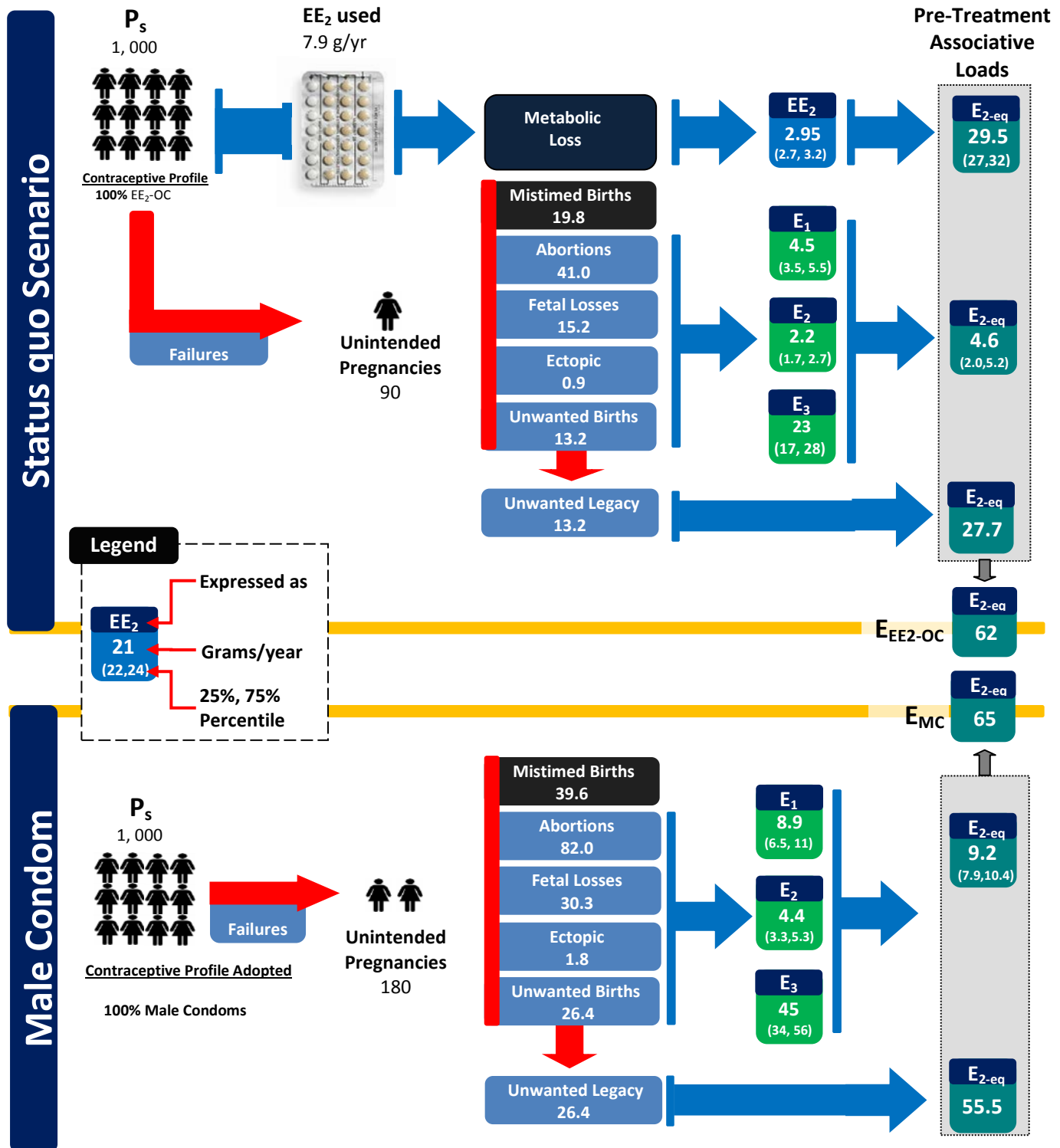


Figure S1: Changes in associative loads of steroidal estrogens when a unit of population of 1,000 first-year EE₂-OC users switches entirely to the use of male condoms. E_{EE2-OC} was estimated using Eq. (S6), while E_{MC} was estimated using the appropriately modified version of Eq. (S7).

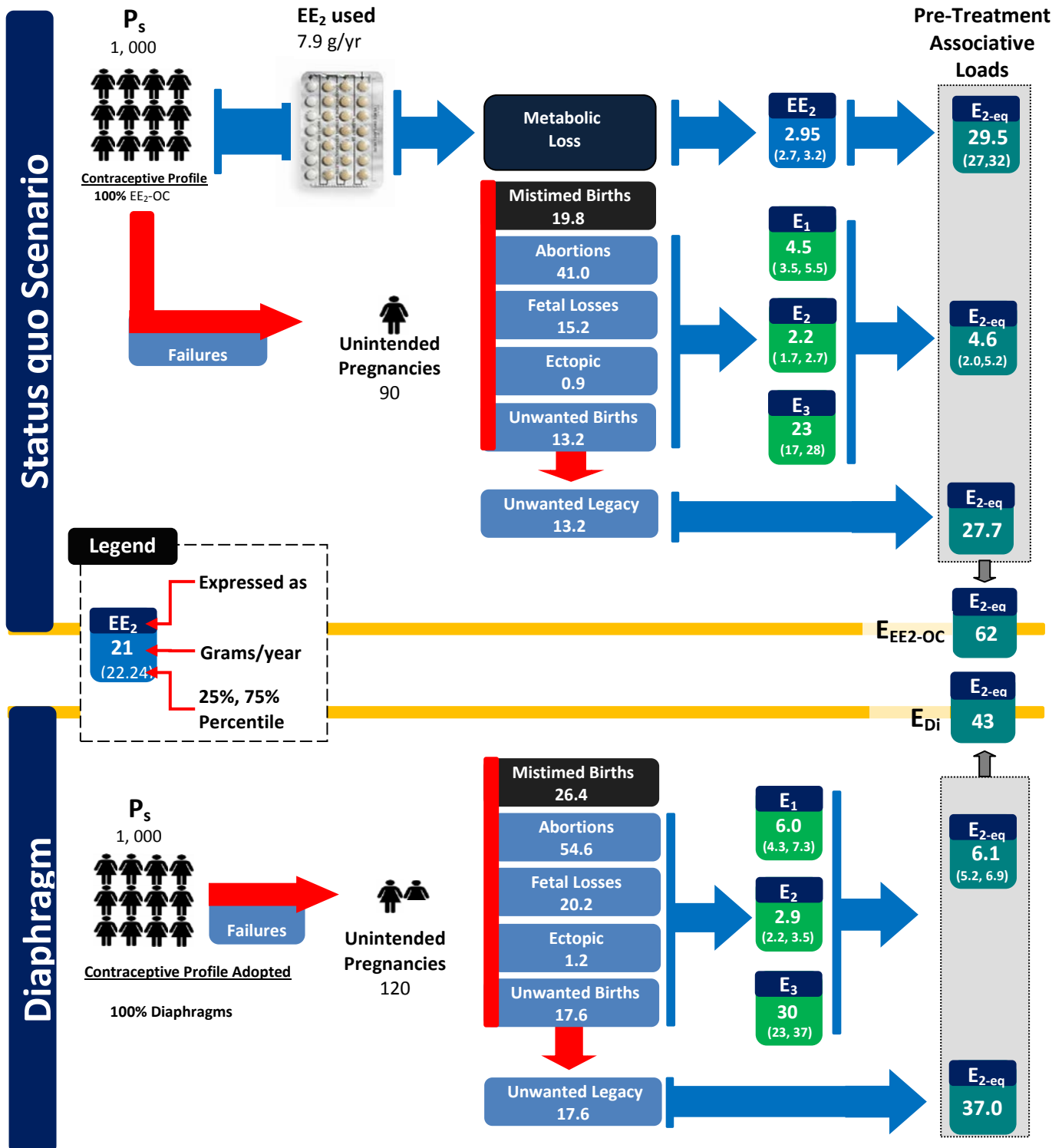
S11 Changes in Flows of Estrogens When Users of EE₂-OC Switch to Diaphragms

Figure S2: Changes in associative loads of steroidal estrogens when a unit of population of 1,000 first-year EE₂-OC users switches entirely to the use of diaphragms. E_{EE2-OC} was estimated using Eq. (S6), while E_{Di} was estimated using the appropriately modified version of Eq. (S7).

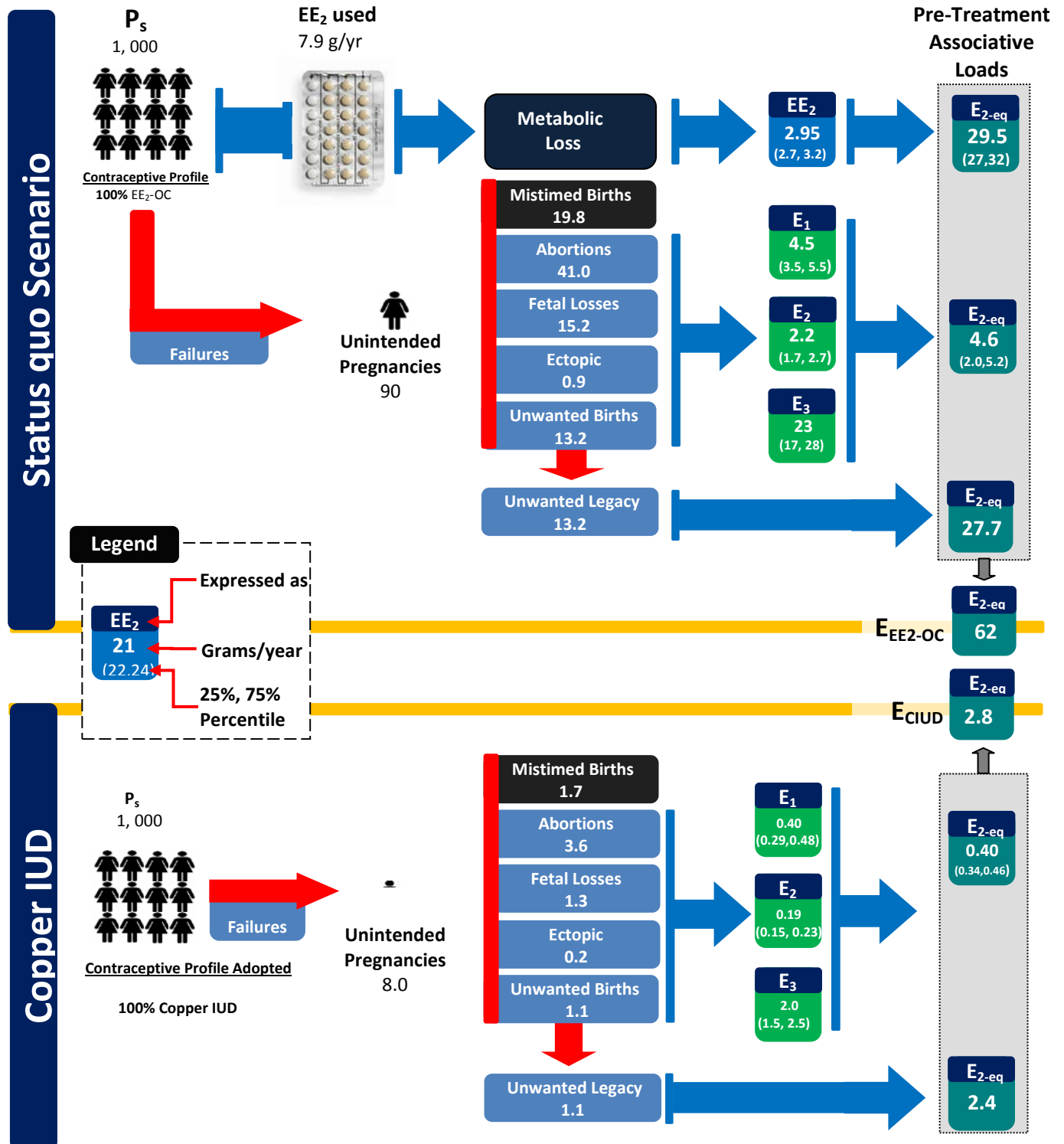
S12 Changes in Flows of Estrogens When Users of EE₂-OC Switch to Copper IUDs

Figure S3: Changes in associative loads of steroidal estrogens when a unit of population of 1,000 first-year EE₂-OC users switches entirely to the use of Copper IUD. E_{EE2-OC} was estimated using Eq. (S6), while E_{CIUD} was estimated using the appropriately modified version of Eq. (S7).

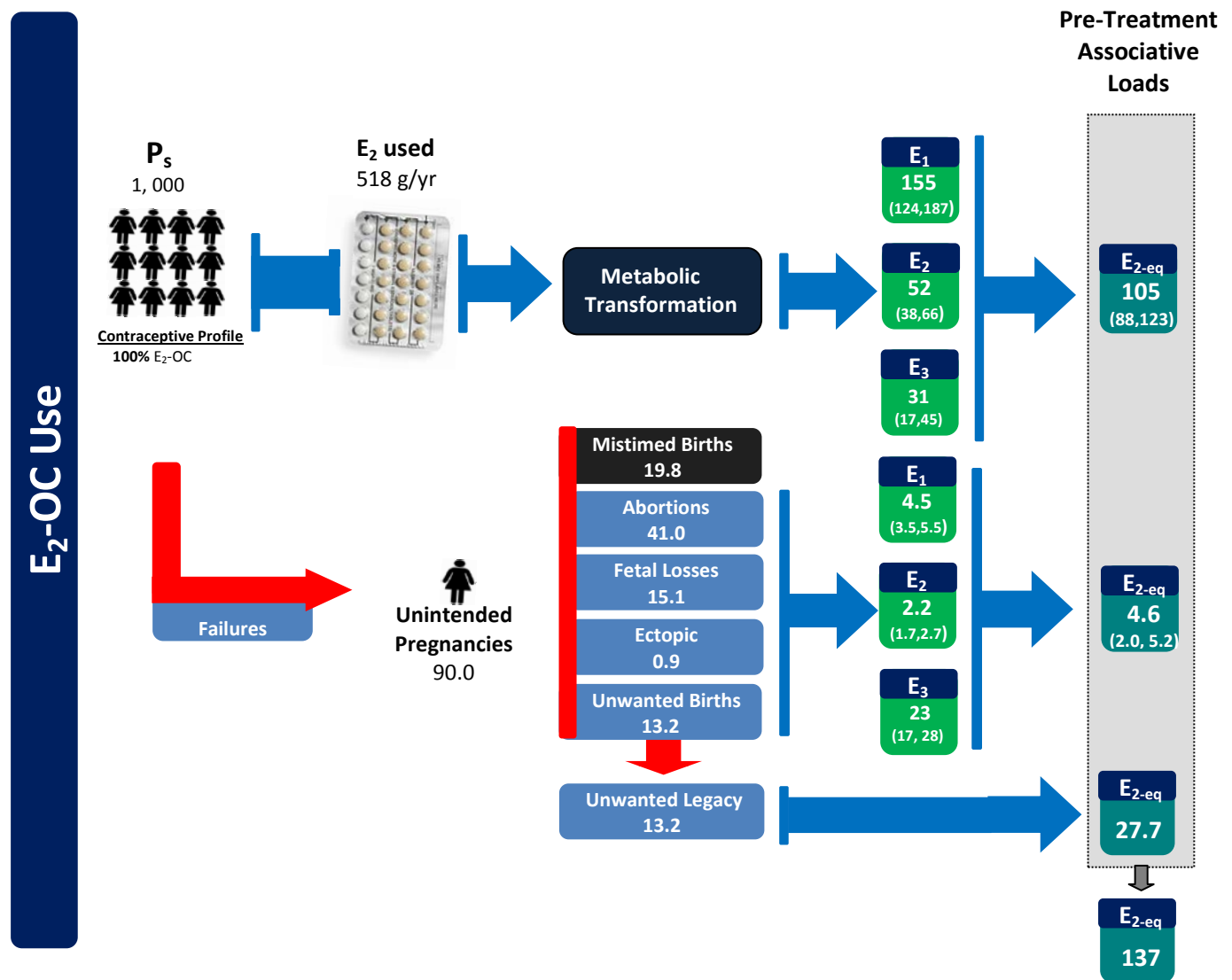
S13 Flow of Estrogens Associated with the Use of E₂-OC

Figure S4: Loads of steroidal estrogens associated with a unit of population of 1000 first-year E₂-OC users. For further details on the estimation methodology used to model this scenario please refer to S8.

S14 Excretion of Equine Estrogens and their Relevance

Even though the potential presence of equine estrogens in human urine has been suspected for more than half a century³⁴, to our knowledge only urine from menopausal women has been analyzed for the endogenous presence of these compounds.^{30,31} Therefore, at present, it is not possible to estimate the release of these estrogens for population cohorts other than menopausal women.

In Table S8, the endogenous release of equine estrogens by menopausal women is estimated. In Table S9, the release of these estrogens from the exogenous use of conjugated and esterified estrogens is estimated where possible.

Table S8 Endogenous release of equine estrogens by menopausal women.

Equine estrogen	Daily per capita excretion ^(a)	Endogenous Load ^(b)
	µg/cap·d	Kg/yr
17αDihydroequilin	1.2	19
17βDihydroequilin	1.2	19
17αDihydroequilenin	3.2	48
17βDihydroequilenin	Interference during analysis	?
Equilin	4.4	66
Equilenin	< level of detection	?

(a) Sample weighted mean^{30,31}; (b) Daily per capita excretion (µg/cap·d) × Number of women above the age of 51 years² × 365 (d/yr) × 1/10⁹ (kg/µg).

Table S9 Release of equine estrogens from the use of HRT preparations.

Equine estrogen	Conjugated Estrogen Metabolism ³⁰	Esterified Estrogen Metabolism	Exogenous Load ^(b)
	g of Estrogen /g of Conjugated Estrogen(%)	g of Estrogen /g of Esterified Estrogen (%)	kg/yr
17αDihydroequilin	0.54	Not Available	>3
17βDihydroequilin	0.86	0.34 ^(a)	5
17αDihydroequilenin	1.57	Not Available	>8
17βDihydroequilenin	Interference	Not Available	?
Equilin	0.34	0.13 ^(a)	2
Equilenin	< level of detection	Not Available	?

(a) Mass fraction of conjugated estrogen excreted as the equine estrogen³⁰ × [Average fraction of Esterified Estrogen (USP) that is equilin / Average fraction of Conjugated Estrogen (USP) that is equilin]; (b) [Annual consumption of conjugated estrogens in the USA⁴ × Conjugated estrogen metabolism] + [Annual consumption of Esterified Estrogens in the USA⁴ × Esterified estrogen metabolism]

In Table S10, the contribution of equine estrogens to the environment from menopausal women is estimated. A comparison of these results with those estimated in Table S1 for traditional estrogens suggests that equine estrogen from menopausal women alone could be significant contributors of estrogenic activity to the environment.

Table S10 Release of equine estrogens by menopausal women.

Equine estrogen	Net Load Released to STPs by only menopausal women in the USA	
	kg of Equine Estrogen/yr ^(a)	kg of E _{2-<i>eq</i>} /yr ^(b)
17 α Dihydroequilin	22	0.6
17 β Dihydroequilin	24	837.6
17 α Dihydroequilenin	56	3.6
17 β Dihydroequilenin	?	?
Equilin	68	17.4
Equilenin	?	?

(a) From Table S8 and S9; (b) Using in-vitro binding potency to the alpha estrogen receptor of Roach ³⁵.

S15 References for All Supporting Information Sections

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Appendices for Chapter 6

Refined sewer epidemiology mass balances and their application to heroin, cocaine and ecstasy

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Abbreviations: 6MAM, 6-monoacetylmorphine; AEEE, anhydroecgonine ethylester; AEME, anhydroecgonine methylester; ATC, anatomical therapeutic chemical classification system; BE, benzoylecgonine; COC, cocaine; COD, codeine; COE, cocaethylene; DDD, defined daily dose; ECD, ecgonidine; EME, ecgonine methylester; EMOR, ethylmorphine, HHMA, 3,4-dihydroxymethamphetamine; HMA, 4-hydroxy-3-methoxy amphetamine; HMMA, 4-hydroxy-3-methoxymethamphetamine; HER, heroin; MDA, 3,4-methylene dioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MOR, morphine; NCOD, norcodeine; NEMOR, norethylmorphine, NMOR, normorphine; SEEB, sewer epidemiology extrapolation mass balances; SEM, sewer epidemiology metabolite; STP, sewage treatment plant.

Appendix A: Nomenclature

Table A.1 Nomenclature of variables used.

Variable	Description	Units
b	A given formulation that can be metabolized to a SEM of interest	-
B	Number of individual formulations b	-
C_{in-s}	Dissolved concentration of a selected SEM in the influent of the STP being monitored	μg of SEM/L
C_{ss}	Average concentration of suspended solids in the influent of a wastewater treatment plant	kg/L
$d_{m,d}$	Net yearly amount of illicit drug demanded/consumed by intensity group m	μg of illicit drug/cap·d
D_{oc-s}	Organic carbon–water distribution coefficient at relevant pH values	-
DDD	Defined daily dose for a particular ATC class	$\mu\text{g}/\text{day}$
E	Number of routes-of-administration typically used to clinically administer an SEM of interest	-
e	A route used to clinically administer SEM of interest	-
$F_{b,i,s}$	Net fraction of L_b that is expected to be excreted as the SEM in the fecal matter of formulation b users when administered via the route i	moles of b/mole of b
f_{e-s}	Per capita endogenous excretion of an SEM of interest on a daily basis in the population's fecal excretions	μg of SEM/cap·d
$F_{h,s}$	Fraction of the illicit drug that is excreted as the SEM in the fecal matter of the abuser when the drug is administered via a typical route-of-administration h	moles of illicit drug/mole of illicit drug
$F_{s,e,s}$	Fraction of L_s that is expected to be excreted as unchanged SEM in the fecal matter of clinical SEM users when administered via the route e	moles of SEM/mole of SEM
G	Total number of individual contaminants, g , that could potentially degrade to the SEM of interest during the sewer transit process	-
g	A contaminant that could potentially degrade to the SEM of interest	-
h	A typical route used to administer an illicit drug	-
H	Total number of individual routes-of-administration typically used for an illicit drug	-
i	A route used to administer formulation b	-
I	Number of routes-of-administration typically used to administer a given formulation b	-

$J_{G,s}$	Amount of $J_{T,s}$ that results from in-transit generation of the SEM due to the degradation of other sewer borne contaminants loads	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{I,s}$	Contribution to $J_{T,s}$ that results exclusively from the use of the illicit drug of interest	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{L,s}$	Amount of $J_{T,s}$ that results from all licit sources of SEM	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{L,s-c}$	Amount of $J_{T,s}$ that results from the clinical use of the SEM itself	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{L,s-end}$	Amount of $J_{T,s}$ that results from the endogenous excretion of the SEM itself	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{L,s-m}$	Amount of $J_{T,s}$ that results from licit uses of other drugs	$\mu\text{g of SEM/cap}\cdot\text{d}$
$J_{T,s}$	Total daily per capita load of the SEM arriving in the influent of the STP being monitored	$\mu\text{g of SEM/cap}\cdot\text{d}$
$k_{d,g}$	First-order degradation constant for the load L_g	d^{-1}
$k_{d,s}$	First-order degradation constant for an SEM of interest	d^{-1}
L_b	Daily per capita mass sold of formulation b that is expected to be metabolized to the SEM upon licit use within the community	$\mu\text{g of b/cap}\cdot\text{d}$
L_g	Daily per capita release of a contaminant g to sewers	$\mu\text{g of g/cap}\cdot\text{d}$
L_s	Daily per capita mass sold of the SEM itself for clinical purposes	$\mu\text{g of SEM/cap}\cdot\text{d}$
m	Individual group of abusers	-
M	Number of individual groups of abusers using a given drug with different intensities that are likely to present within the population	-
Mo_s/Mo_b	Molar stoichiometric ratio of metabolically generating SEM from a given formulation b	moles of SEM/ mole of b
Mo_s/Mo_d	Molar stoichiometric ratio of metabolically generating SEM by abusing the illicit drug of interest	moles of SEM/ mole of illicit drug
Mo_s/Mo_g	Molar stoichiometric ratio of generating SEM due to the degradation of a particular contaminant g	moles of SEM/ mole of g
Mw_b	Molecular weight of formulation b	g of b/mole of b
Mw_d	Molecular weight of the illicit drug	g of illicit drug/mole of illicit drug
Mw_d/Mw_{salt}	Drug content adjustment factor	g of drug /g of salt
Mw_g	Molecular weight of the contaminant g	g of g/mole of g
Mw_s	Molecular weight of the SEM	g of SEM/mole of SEM
N_d	Net daily per capita demand for various illicit drugs in national populations	mg of illicit drug/cap·d
NX	the number of pills consumed on a daily averaged basis by ecstasy abusers who have used the drug within the last year	pills/year
P	Population served by the STP being monitored	People
PIC_{d-s}	Nationally-averaged concentration of a particular SEM in the influents of a country	$\mu\text{g of SEM/L}$

p_{N-d}	Reported national prevalence of all abusers for a particular illicit drug within the 15-64 year age cohort	%
p_{r-d}	Regional prevalence of all abusers for a particular illicit drug within the 15-64 year age cohort of the population being monitored	%
Q_{in}	Daily flow arriving as the influent to the treatment plant	L/d
$R_{I,d}$	Net daily per capita illicit consumption of a particular drug within the population that is connected to the STP being monitored	µg of illicit drug/cap·d
$R_{I,s}$	Daily per capita load of the SEM that is expected to be excreted by the abusers of the drug of interest	µg of SEM/cap·d
t_s	Sewer transit time	d
$U_{b,i,s}$	Net fraction of L_b that is expected to be excreted as the SEM in the urine of formulation b users when administered via the route i	moles of b/mole of b
u_{e-s}	Per capita endogenous excretion of the SEM on a daily basis in the population's urinary excretions	µg of SEM/cap·d
$U_{h,s}$	Fraction of the illicit drug that is excreted as the SEM in the abuser's urine when the drug is administered via a typical route-of-administration h	moles of illicit drug/mole of illicit drug
UN_d	Fraction of the abusers that are likely to under-report their use of a particular drug of abuse	-
$U_{s,e,s}$	Net fraction of L_s that is expected to be excreted as the unchanged SEM in the urine of clinical SEM users when administered via the route e	moles of SEM/mole of SEM
W	Average wastewater produced per capita for the population of a given country	L/cap·d
x_{con}	Fraction of the national population that is connected to wastewater treatment plants	-
x_e	Fraction of the users that administered clinical SEM through the route-of-administration e	-
x_{g-s}	Fraction of k_g that is expected to be converted to the SEM	-
x_h	Fraction of the abusers that administered the illicit drug through the route-of-administration h	-
x_i	Fraction of the users that administered formulation b through the route-of-administration i	-
$x_{m,d}$	Fraction of the total abusers of a particular illicit drug that are likely to use the drug with an intensity of group m	-
xn_{15-64}	Fraction of a national population that is within the 15-64 year age cohort	-
xr_{15-64}	Fraction of the wastewater-contributing population that is within the 15-64 year age cohort	-
x_{s-s}	Fraction of an SEM likely to be sorbed onto influent suspended solids	-
Y_{fs}	Fraction of Y_{ns} that is expected to be flushed down the toilets and/or sinks	-
Y_{nb}	Fraction of formulation b sold that ends up not being used by the population	-
Y_{ns}	Fraction of clinical SEM sold that ends up being not used by clinical SEM users	-

Appendix B: Sample Calculation for Equation (13)

A sample calculation is presented below to illustrate how the net per capita daily demand of various illicit drugs for a national population (N_d) can be estimated. The calculations shown are for Spain using the data sources indicated.

Estimates were performed using Equation (13), reproduced here to aid in illustrating the sample calculation below:

$$N_d = \frac{x n_{15-64} \cdot \frac{p_{N-d}}{100} \cdot \left(\sum_{m=1}^M x_{m,d} \cdot d_{m,d} \right)}{1 - UN_d} \quad (B.1)$$

The quantification of the various variables of Equation (B.1) is summarized in Table B.1. The table also lists the resultant estimates of Spanish N_d values generated by inserting the quantified variables back into Equation (B.1).

Table B.1 Quantification of the variables of Equation (B.1) and the estimates of Spanish N_d values generated as a consequence.

Drug of Abuse	$x n_{15-64}^{(a)}$	$p_{N-d}^{(b)}$ %	$m^{(c)}$	$d_{m,d}$ mg/cap·d	$x_{m,d}^{(f)}$	$UN_d^{(f)}$	$N_d^{(g)}$ mg/cap·d
Heroin	0.69	0.13	Typical last year use	82.2 ^(c)	1	0	0.07
Cocaine		3	Heavy users	274 ^(d)	0.17	0.33	1.9
			Light users	19 ^(d)	0.83		

(a) US Census (2010); (b) UNODC (2010); (c) Kilmer and Pacula (2009), refers to pure heroin; (d) Based on information in Kilmer and Pacula (2009) assumed to refer to pure drug based on recent information available in UNODC (2010); (f) Kilmer and Pacula (2009) (g) Estimated using Equation (B.1) with the parameters listed.

Appendix C: Fraction of SEMs Likely to be Sorbed onto Influent Suspended Solids

Table C.1 x_{s-s} values for candidate SEMs for the various illicit drugs of interest.

Drug of Abuse /Clinical Formulation	Candidate SEM	$D_{OC-S}^{(a)}$		$x_{s-s} (\%)^{(b)}$	
		pH 2.0	pH 7.5	pH 2.0	pH 7.5
Cocaine	COC	1.0	22.6	< 0.01	0.17
	BE	1.0	1.3	< 0.01	0.01
	EME	1.0	1.0	< 0.01	< 0.01
Crack	AEME	1.0	12.2	< 0.01	0.09
	AEEE	1.0	109	< 0.01	0.81
	ECD	1.0	1.0	< 0.01	< 0.01
Cocaine + Ethanol	COE	1.0	36.3	< 0.01	0.27
Heroin	HER	1.0	55.4	< 0.01	0.42
	6MAM	1.0	10.9	< 0.01	0.08
	MOR	1.0	15.9	< 0.01	0.12
	NOM	1.0	1.0	< 0.01	< 0.01
MDMA	MDMA	1.0	1.4	< 0.01	0.01
	HMMA	1.0	1.0	< 0.01	< 0.01
	HMA	1.0	1.1	< 0.01	< 0.01
	MDA	1.0	1.6	< 0.01	0.01
Codeine	COD	1	1.7	< 0.01	0.01
Ethylmorphine	EMOR	1.0	3.3	< 0.01	0.02
	NEMOR	1.0	3.4	< 0.01	0.03

(a) ACD Labs (2010); (b) Estimated using the model of Deo and Haldin's (2010) expressed as Equation (2) in the main text using D_{OC-S} and x_{s-s} as listed above in Table C.1 with x_{oc} and C_{SS} values suggested by Braga et al. (2005) and Qasim (1999).

Appendix D: “Unaccounted-for” Sources of Cocaine to Sewers

Metabolic disposition data (see Table 1 in main text) suggest that cocaine is extensively metabolized and that only small amounts (i.e., 1 - 2% of the administered dose) are excreted unchanged in the urine of abusers. However, cocaine in the influent of STPs will not only originate from the un-metabolized cocaine from a population's consumption of illicit cocaine but also from its clinical use; e.g., cocaine is often used by otolaryngologists and plastic surgeons as a topical anesthetic (Long et al., 2004; Verlander and Johns, 1981). However, such clinical contributions to the net cocaine loads are expected to be small (see Figure D.1). On average, the net cocaine loads are expected to collectively amount to no more than 0.04 - 0.06 of the BE load (see Figure D.2); however, monitoring data suggests otherwise, where currently available data suggests a typical range of COC/BE load ratio of 0.2 - 0.3, with most data clustering around the 0.25-0.30 range (Figure D.2).

Of the two loads (COC and BE), it was demonstrated (see main text) that the magnitude of the predicted loads of BE matched up reasonably well with the measured data; hence, the discrepancy in the load ratio likely originates from a lack of understanding of cocaine release sources to wastewaters. Such an assertion is further supported by a comparison of predicted nationally-averaged concentrations of cocaine with measured sub-national data for a number of countries where such data is available (see Figure D.3). Such discrepancies between predicted and measured loads/concentrations of cocaine, from multiple lines of evidence, suggest the existence of one or more significant sources of cocaine to wastewater influents that may have not been accounted for. As described below, five sources can be suggested, an unlikely one previously suggested in literature and four other ones suggested here.

Kasprzyk-Hordern et al. (2009a) suggested that the high ratio of to COC/BE load ratio in wastewater influents may be the result of direct dumping of cocaine by abusers and dealers. Since dumping is expected to be a low frequency event compared to the gradual excretion of unchanged cocaine by abusers (e.g., with an elimination half-life of 1.5 hrs according to Ambre et al., (1985)), it is expected to only originate in an a few distinct pulses (i.e., toilet flushes) and the probability of these pulses being captured by current day sampling norms is uncertain (Ort et al., 2010). Further, consider the data arising with the largest spatial extent of sampling (i.e., approximately 40% of the Belgian population sampled) reported by van Nuijs et al. (2009) (Figure D.2). They reported, after monitoring 37 STPs for several days each on 29 distinct dates in a sampling campaign spanning 5 months, an average influent COC/BE ratio of 0.28 ± 0.07 (σ). Such values would suggest that cocaine dumping was consistently happening in Belgium. However, due to the inherent value of the cocaine to the abusers and dealers, in reality, the probability that cocaine was continuously being dumped at all these locations over the monitoring duration is low.

It is suggested that there are other more plausible sources that would result in cocaine being released to sewers on a more continuous basis. Four such plausible sources are suggested that warrant investigation.

Firstly, it is known that un-metabolized cocaine is released in the abuser's sweat (Cone et al., 1994; Preston et al., 1999; Uemura et al., 2004). That is, for drugs such as cocaine that are extensively metabolized, the contribution of the excreted unchanged drug through sweat may be just as important as the amounts released through traditional excretory routes via urine and feces (Daughton and Ruhoy, 2009). Although some data is available on the cumulative amounts excreted onto sweat-patches after administering cocaine through various routes (Cone et al., 1994), the data cannot readily be used to predict with confidence the net fraction of the consumed cocaine that is excreted via sweat. Even though evidence would seem to indicate that significant amounts of unchanged cocaine are released through sweat and therefore likely to end up in wastewater through the bathing or laundering activities of abusers, at present due to lack of suitable disposition data, it is not possible to fully establish cocaine loads expected to be released through such an elimination route.

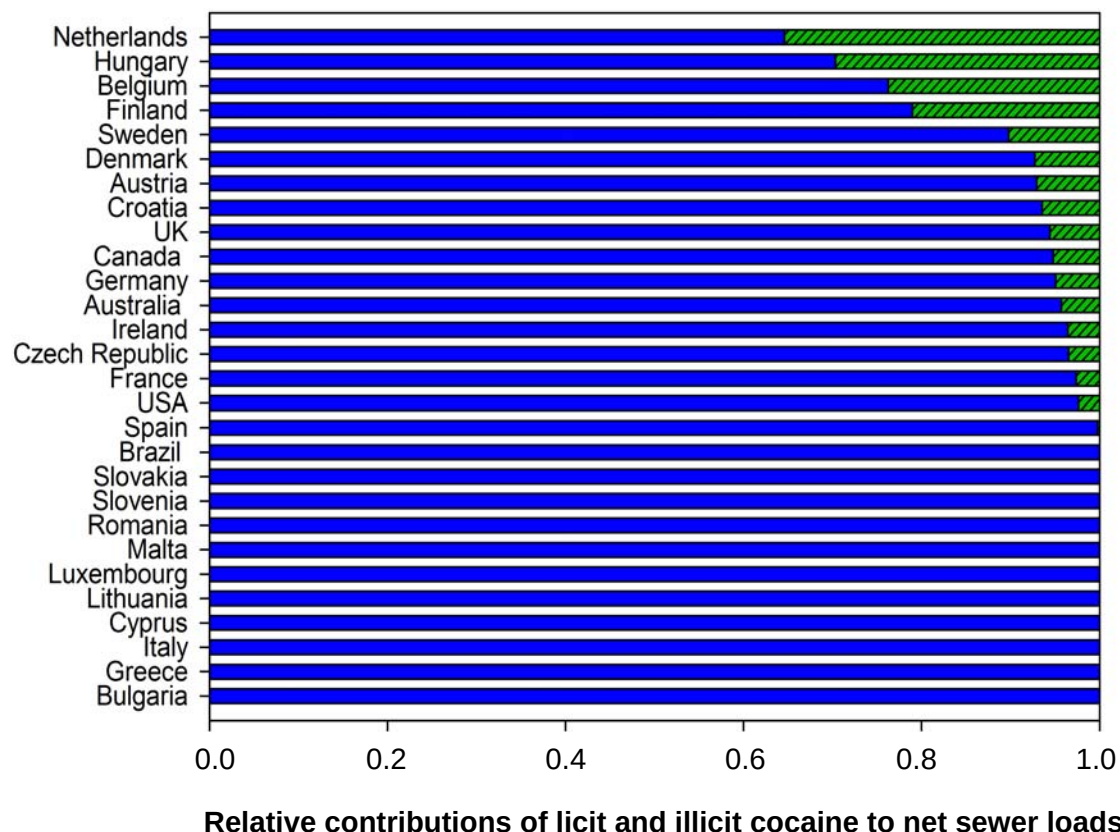


Figure D.1 Relative contributions of illicit (■) and licit (▨) cocaine to theoretically-estimated net sewer loads. Licit cocaine consumption data were assumed to be equal to the values reported by INCB (2010). Since licit cocaine is topically applied and expected to be minimally absorbed once applied (Baselt et al., 1990), it was conservatively assumed that the consumed load of clinical cocaine enters the sewers un-metabolized. Hence, in this way, licit contributions have likely been overcompensated for. Illicit contribution, due to excretion of unchanged cocaine, were estimated for each country using: $N_d \times \sum (U_{h,COC} + F_{h,COC}) \cdot x_h$ where: N_d values were derived using Equation (13); $U_{h,COC} + F_{h,COC}$ values for each route-of-administration, h , were obtained from the compiled data presented in Table 1 (see main text). For most cases, x_h values for a given national population were assumed to be similar to the routes-of-administration of abusers reported for the respective country's substance-abuse treatment programs (SAMHSA, 2007; EMCDDA, 2009). Exceptions to the latter were for Australia where route-of-administration trends from domestic household survey were used (Ross, 2007), for Brazil where route-of-administration trends reported by Ferri and Gossop (1999) were used, and for Canada where x_h values were assumed to be equal to those of the USA (SAMHSA, 2007).

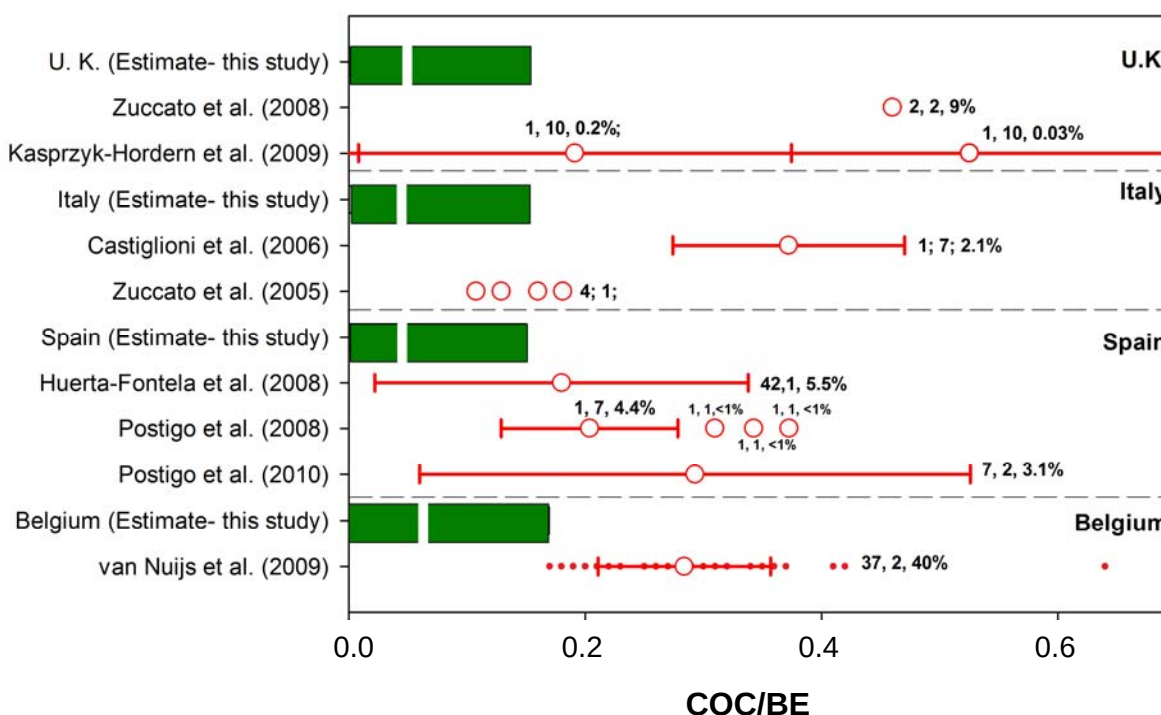


Figure D.2 Comparison of theoretically-estimated (■) ratios of sewer-borne cocaine to BE (COC/BE) to those reported in monitoring investigations (○). For theoretically-estimated COC/BE ratios, the range of the filled bars represents the 95% confidence interval, while the vertical white line represents the mean. These estimates were generated using the expression $(\sum(U_{h,COC}+F_{h,COC}) \cdot x_h) / (\sum(U_{h,BE}+F_{h,BE}) \cdot x_h)$; where: $U_{h,COC}+F_{h,COC}$ and $U_{h,BE}+F_{h,BE}$ for each route-of-administration, h , were obtained from the compiled data presented in Table 1 (see main text) and for most cases, x_h values for a given national population were assumed to be similar to the routes-of-administration reported for abusers in the respective country's substance-abuse treatment programs (EMCDDA, 2009). For monitored C/BE ratios, means (○) reported by each study are indicated and the error bars represent standard deviations of the monitored ratios. Where available, individual measured ratios from a given study were plotted (●). The numerical values reported next to the monitored data represent, respectively: spatial extent of the data as represented by the number of sewage treatment plants (STPs) monitored in the investigation, temporal extent of the data as represented by the number of days each STP was monitored; and percentage (%) national coverage of the data as represented by percentage of the national population that was contributing wastewater to the STPs that were monitored by a given study.

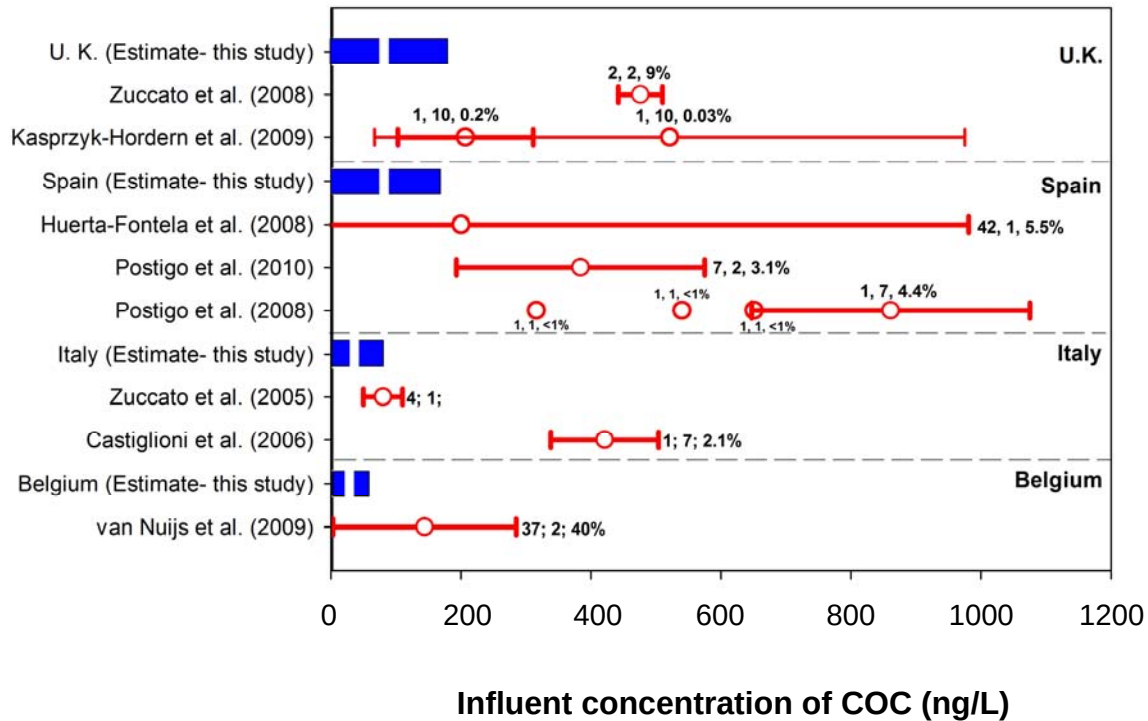


Figure D.3 Comparison of theoretically-estimated (■) nationally-averaged influent concentrations of cocaine (COC) to those reported in sub-national monitoring studies (○). For theoretically-derived estimates, the range of the filled bars represents one standard deviation ($\pm\sigma$), while the vertical white line represents the mean. Estimates were generated using Equation (14) where: N_d was estimated using Equation (13); $U_{h,COC}+F_{h,COC}$ values for each route-of-administration, h , were obtained from the compiled data presented in Table 1 (see main text). And, for most cases, x_h values for a given national population were assumed to be similar to the routes-of-administration used by abusers in the respective country's substance-abuse treatment programs (EMCDDA, 2009); $J_{L,COC}$, licit cocaine consumption data were taken from INCB (2010) and since licit cocaine is typically applied and expected to be minimal absorbed once applied (Baselt et al., 1990), it was conservatively assumed that consumed load of clinical cocaine enters the sewers un-metabolized; $J_{G,COC}$ was assumed to be equal to be zero since no evidence is available in literature to suggest otherwise; k_{d-COC} was also conservatively set equal to zero and W for the various countries were estimated using Eurostat (2010) and the national variation (σ) in W was modeled based on Belgian data (van Nuijs et al., 2009). For monitored data, means reported by each study are indicated (○) and error bars represent standard deviations of the reported values. The numerical values reported next to the monitored data represent, respectively: spatial extent of the data as represented by the number of sewage treatment plants (STPs) monitored in the investigation, temporal extent of the data as represented by the number of days each STP was monitored; and percentage (%) national coverage of the data as represented by percentage of the national population that was contributing wastewater to the STPs that were monitored by a given study.

A second continuous source of cocaine to wastewaters may be un-metabolized cocaine in the fecal excretions of abusers. Overall, fecal elimination is a minor release pathway compared to the elimination of cocaine metabolites in net urinary excretions (Jeffcoat et al., 1989). However, the fraction of unchanged cocaine in the net urinary load is minor (see Table 1, main text); hence, small contributions from other elimination pathways could substantially factor into the net amounts of cocaine released (Daughton and Ruhoy, 2009). Particularly, in cases where cocaine is abused by low bioavailability routes, the probability that a significant fraction of the fecal excretions is un-metabolized cocaine is high, since such routes are likely to yield higher proportions of unabsorbed cocaine. The lone report on the fecal disposition of cocaine (Jeffcoat et al., 1989) did not contain an analysis of the fecal excretory profile but only reported on the net amounts excreted through such a route. In particular, it is interesting to note that the net fecal elimination reported in this study when cocaine was smoked was considerably higher than the net fecal excretions recorded when cocaine was administered through higher bioavailability routes (i.e., through intravenous administration or nasal insufflation). Nevertheless, the hypothesis that fecal loads contribute significant amounts of unchanged cocaine to wastewaters needs to be confirmed.

The third metabolic source worth investigating further could be the increased excretion of unchanged cocaine in urinary excretions when cocaine is co-administered with ethanol. Cami et al. (1998) reported that urine excretion of unchanged cocaine was two to three times higher when cocaine was co-abused with ethanol. Considering that co-abuse of cocaine and ethanol is quite common (Cami et al., 1998; Jatlow, 1993), the more relevant proportion of unchanged cocaine in urinary excretions may be the increased levels released after incidences of co-abuse. Again, it seems plausible that co-abuse may be resulting in increased excretion of unchanged cocaine in an abuser's urine but more concrete data is desirable before one can fully evaluate the significance of such an increased contribution. That is, it remains unclear how the levels of unchanged cocaine released in urinary excretions changes as the dose of ethanol that is co-abused is varied. Further, to-date, only levels of unchanged cocaine in urinary excretions of co-abusers that nasally insufflated and injected cocaine with oral ethanol have been reported (Cami et al., 1998; Harris et al., 2003), therefore it remains unclear whether the increased excretion of unchanged cocaine is also to be expected in cases where co-abused cocaine is administered via smoking. And, finally, the potential importance of unchanged cocaine in fecal excretions of co-abusers also remains uncertain.

A fourth possible source of high sewer loads of cocaine could be due to the processing of the influent samples that are analyzed for cocaine content. Numerous investigations have reported on the presence of cocaine in ambient air (Cecinato and Balducci, 2007; Cecinato et al., 2009; Viana et al., 2010). Hence, conceivably, the actual sewer cocaine loads may be increased when SPE columns are dried by pulling liters of ambient air through them. While, it is hypothesized that this contribution would be relatively small compared to other sources described above, the importance of such a contribution to actual cocaine loads measured in samples remains unclear and, therefore, is in need of further study.

Appendix E: Importance of Sweat Contributions to Net Sewer Loads of SEMs

E.1 BE

BE that is excreted in the abuser's sweat is expected to end up in sewers through the abuser's bathing and/or laundering activities. Contrary to the observed urinary excretory profile, BE is a minor metabolite in released sweat (Cone et al., 1994; Uemura et al., 2004). Specifically, 24-hr collected loads ranging between 0.0 to 7.8 ng/per sweat-patch placed on the backs and abdomens of abusers has been reported (Cone et al., 1994). In this investigation, abusers were administered with 25-42 mg of cocaine via various routes. These measured patch loads can be used to generate a conservative "order-of-magnitude" estimate of the net load of the administered cocaine dose that is expected to be collectively released in sweat as BE (Daughton and Ruhoy, 2009). Such a calculation must assume that the whole body excretes the same quantities as the regions of the body for which monitoring data is available. Further, recognizing that a typical sweat-patch has an area of 1480 mm² and a typical value upper limit for human skin surface area is 2.0 m² (Daughton and Ruhoy, 2009), each sweat patch samples 1/1352 of the total body area. Therefore, the factor of 1352 multiplied by the reported patch loads suggests that a total of 0 to 10.5 µg of BE can be expected to be released in the sweat of abusers who administer 25-42 mg of cocaine via various routes. This low value should be compared to the 3.1 - 15.9 mg of BE that would be expected in the urine of such abusers; i.e., 25 - 42 mg $\times U_{h,BE}$ (see Table 1 in main text) $\times MW_{BE}/MW_{COC}$. Hence, for all practical purposes, the sweat of cocaine abusers is not expected to significantly contribute to the net sewers loads of BE.

E.2 MOR

Twenty-four hour sweat-patch data from Kintz et al. (1997) suggests that abusers released 0 to 11.2 ng of MOR via sweat onto their respective patches when they were intravenously administered from 80-1000 mg of heroin. Using the methodology described above (see Appendix E.1 above), such data can be used to estimate that 0-15 µg of MOR is approximated to be collectively released through the sweat of abusers who have been intravenously administered 80 -1000 mg of heroin. Compare this to 44-548 mg of MOR that would be expected in the urine of such abusers; i.e., 80-1000 mg $\times U_{I.V.,MOR}$ (see Table 2 in main text) $\times MW_{MOR}/MW_{HER}$. Hence, for all practical purposes, the sweat of heroin abusers is not expected to significantly contribute to the net sewers loads of MOR.

E.3 6MAM

Kintz et al. (1997) reported that abusers in a maintenance program, who were being intravenously administered 80 -1000 mg of heroin daily, released 0 to 24.6 ng of 6MAM onto their respective sweat patches after 24 hours of collection. Using the methodology described above, such data can be used to estimate that 0 - 33.2 µg of 6MAM is collectively released through the sweat of abusers who have been intravenously administered 80 -1000 mg of heroin. Compare this to 1.2 - 12.1 mg of 6MAM that would be expected in the urine of such abusers; i.e., 80-1000 mg $\times U_{I.V.,6MAM}$ (see Table 2 in main text) $\times MW_{6MAM}/MW_{HER}$. Hence, the contribution of sweat to the net sewer loads of 6MAM is expected to be of a negligible importance.

E.4 HMMA

To-date three communications have reported on the levels of HMMA in the sweat of subjects that had been administered MDMA orally (Barnes et al., 2009; De Martinis et al., 2007; Pichini, et al., 2003). All three reports suggested that the level of HMMA released via the sweat of MDMA abusers was below the respective detection limits of the analytical methods used. Even if one conservatively assumes that the release of HMMA via sweat is equal to the respective detection limits, the relative contribution of HMMA via sweat is expected to be of negligible importance. As an example, consider the work of Pichini, et al. (2003), where the authors reported that upon administering 100 mg of MDMA to subjects, the net amount of HMMA released, over a period of 24 hrs, was below their detection limit of 0.96 ng/patch. Using the approach detailed above and conservatively assuming that the per patch release of HMMA is equal to its detection limit of 0.96 ng/patch, it can be estimated that the full body load of HMMA via sweat is at most 1.3 µg. Compare this minute amount to 19.7 mg of HMMA that would be expected in the urine of such abusers; (see Table 3 in main text). Hence, the sweat of MDMA abusers is not expected to contribute significantly to the net sewer loads of HMMA.

E.5 MDMA

Pichini, et al. (2003) estimated that of the 100 mg of MDMA that was orally administered to their subjects approximately 0.6 mg was collectively released unchanged via sweat. In comparison, Table 3 (main text) suggests urine of such abusers would be expected to contain 21.9 mg of unchanged MDMA. Hence, the sweat of MDMA abusers is not expected to contribute significantly to the net sewer loads of MDMA.

Appendix F: Nationally-Averaged BE Concentrations: Sample Calculation

A sample calculation is presented below to illustrate how the nationally-averaged concentration of BE in influents can be estimated. The calculations are shown for Spain using the data sources indicated. Estimates were calculated using Equation (14) from the main text, which is repeated here to aid in the sample calculation discussion below:

$$PIC_{COC-BE} = \frac{\left(N_{COC} \cdot \left(\sum_{h=1}^H (U_{h,BE} + F_{h,BE}) \cdot x_h \right) \frac{Mw_{BE}}{Mw_{COC}} + J_{L,BE} + J_{G,BE} \right) (1 - k_{d,BE}) \cdot x_{con}}{W_{Spain}} \quad (F.1)$$

$k_{d,BE}$; $J_{L,BE}$ and $J_{G,BE}$ were assumed to be approximately zero (see justification in main text) and hence the above equation could be simplified to the following:

$$PIC_{COC-BE} = \frac{\left(N_{COC} \cdot \left(\sum_{h=1}^H (U_{h,BE} + F_{h,BE}) \cdot x_h \right) \frac{Mw_{BE}}{Mw_{COC}} \right) \cdot x_{con}}{W_{Spain}} \quad (F.2)$$

The molecular weight ratio (Mw_{BE}/Mw_{COC}) is equal to 0.95.

x_h values for the national cocaine-abusing population within Spain were assumed to be equal to the routes-of-administration reported for abusers in Spanish substance-abuse treatment programs. According to EMCDDA's statistical bulletin (EMCDDA, 2009) 2.2, 16.1, 0.6 and 66.5% of cocaine abusers in Spanish substance-abuse treatment programs reported primarily injecting, smoking, orally ingesting and nasally insufflating cocaine, respectively. The remaining 14.6% used other routes to administer their cocaine. The proportions of known routes were scaled to 100% in light of the limitation that no detailed information was available for how the abusers in the "other" routes category abused cocaine and the fact that such abusers constitute a minor fraction of the abusing population in treatment. Such scaling results in the route-of-administration distribution among cocaine abusers to be approximated as 2.5, 18.9, 0.8 and 77.8% of abusers primarily injected, smoking, orally ingesting or nasally insufflating cocaine, respectively. Further, this also allows one to establish H (i.e., total number of individual routes-of-administration typically used to administer cocaine) to be equal to 4, while individual h 's (i.e., a given route used to administer cocaine) become: intravenous injection, smoking, oral ingestion and nasal insufflation. $U_{h,BE}$ and $F_{h,BE}$ for the identified routes-of-administrations, h , can themselves be obtained from the compiled data presented in Table 1 (see main text).

N_{COC} was estimated in Appendix B to be 1.9 mg/cap-d and x_{con} for Spain was suggested to be 0.98 (Eurostat, 2010).

W_{Spain} was approximated as 349 L/cap-d by dividing the total daily amount of water abstracted for public water supply by the net population of Spain that is connected to public water supply (Eurostat, 2010; US Census, 2010). The national variation (σ) in W_{Spain} was assumed to be equal to 40% of its magnitude. This is, at best, an order of magnitude estimate of this variation based on the spatial variation in daily flow arriving at Belgian STPs serving 40% of the national population as reported by van Nuijs et al. (2009).

Following substitution of the quantified variables into Equation (F.2), the concentrations of BE in the national influents of Spain is estimated to be: $PIC_{COC-BE} = 1513 \pm 741$ ng/L

Appendix G: Methods Used to Estimate Theoretical Parameters in Figures 1 and 2

G.1 Data in Figure 1(A)

Estimates were generated using Equation (14), where N_d was estimated using Equation (13) and $U_{h,BE}+F_{h,BE}$ values for each route of administration were obtained from the compiled data presented in Table 1. For most cases, x_h values for a given national population were assumed to be the same as the routes-of-administration of abusers reported for the respective country's substance-abuse treatment programs (EMCDDA, 2009; SAMHSA, 2007). As exceptions to the latter, for Australia route-of-administration trends from domestic household survey were used (Ross, 2007) while for Brazil route-of-administration trends reported by Ferri and Gossop (1999) were used, and Canadian x_h 's values were assumed to be equal to those available for the USA (SAMHSA, 2007); $J_{L,BE}$, $J_{G,BE}$ and $k_{d,BE}$ were assumed to be equal to zero (see main text for details); W for the various countries were compiled from various sources (Beeton et al., 2006; DANVA, 2009; Environment Canada, 2004; Eurostat, 2010; EUREAU, 2009; Hutson et al., 2004; Statistical Office of the Republic of Slovenia, 2010; van Nuijs et al., 2009; WRI, 2005). When not available, the national variation (σ) in W was modeled for all countries using Belgian data (van Nuijs et al., 2009) with the exception of USA, for which Canadian data was used (Environment Canada, 2004).

G.2 Data in Figure 2(A)

For morphine contribution calculated using Equation (4); L_{MOR} values originated from the compilation in Appendix K; $Y_{n,mor}$ and $Y_{f,mor}$ was assumed to be equal to data for painkillers reported by Bound and Voulvoulis (2005); $\sum(U_{s,MOR}+F_{s,MOR})\cdot x_e$ were based on the excretion profiling of oral morphine presented in Appendix I; relative contributions due to the consumption of codeine, ethylmorphine, pholcodine and nicomorphine were estimated using Equation (3); respective L_b values were derived from the compilation in Appendix K; $Y_{n,b}$ was assumed to be equal to the data reported by Bound and Voulvoulis (2005) for painkillers; $\sum(U_{b,MOR}+F_{b,MOR})\cdot x_c$ were based on the excretion profiling in Appendix I; the relative contribution for endogenous morphine was derived using Equation (5); u_{e-MOR} and f_{e-MOR} were based on the endogenous excretion profiling detailed in Appendix I.

G.3 Data in Figure 2(B)

The illicit contribution was due to respective national population's demand for heroin and was estimated using $N_d \cdot (\sum(U_{h,MOR}+F_{h,MOR})\cdot x_h) \cdot (Mw_{MOR}/Mw_{HER})$ where: N_d was estimated using Equation (13); $U_{h,MOR}+F_{h,MOR}$ for each route-of-administration h were obtained from the compiled data presented in Table 2. For most cases, x_h values for a given national population were assumed to be the same as the routes of administration used by abusers in the countries substance-abuse treatment programs (Broz and Ouellet, 2008; EMCDDA, 2009a) with the exception to the latter being Australia, Norway and Portugal for which administration trends reported in relevant literature were used (AIHW, 2002; Bretteville-Jensen and Amundsen, 2009; Marsden, 2009) and for Canada where x_h values were assumed to be equal those of the USA (Broz and Ouellet, 2008).

G.4 Data in Figure 2(C)

Estimates were generated using Equation (14) where: N_d was estimated using Equation (13); $U_{h,MOR} + F_{h,MOR}$ values for each route-of-administration were obtained from the compiled data presented in Table 2; and x_h values were from sources as identified for Figure 2(B) (AIHW, 2002; Bretteville-Jensen and Amundsen, 2009; Broz and Ouellet, 2008; EMCDDA, 2009a; Marsden, 2009). $J_{L,MOR}$ were calculated in similar manner as detailed for Figure 2(A) above. $J_{G,BE}$ and $k_{d,BE}$ were assumed to be equal to zero (see main text for details). W for the various countries were compiled from various sources (i.e., Beeton et al., 2006; DANVA, 2009; Environment Canada, 2004; Eurostat, 2010; EUREAU, 2009; Hutson et al., 2004; Statistical Office of the Republic of Slovenia, 2010; van Nuijs et al., 2009; WRI, 2005) and, when not available, the national variation (σ) in W was modeled for all countries using Belgian data with the exception of USA, for which Canadian data was used (Environment Canada, 2004).

Appendix H: Effect of Ethanol Co-abuse on the Levels of BE Excreted

It is not often recognized in the field of sewer epidemiology that the co-abuse of ethanol and cocaine is quite common (Cami et al., 1998, Harris et al., 2003; Pennings et al., 2002). Hence, it is necessary to discuss any effects that ethanol co-abuse may have on the urinary elimination of BE. Two studies have reported on the effects of ethanol co-abuse on the cumulative urinary excretions of BE (Cami et al., 1998; Harris et al., 2003). Before the results from these studies are discussed, it should be recognized that the order in which ethanol is co-abused with cocaine has been suggested to be of significance (Perez-Reyes, 1994). Such an assertion stems from the recognition that when ethanol is used prior to and/or simultaneously with cocaine, the co-abused ethanol could competitively inhibit the liver's cocaine-metabolizing enzymes, but such inhibition is not expected when ethanol is administered following cocaine abuse (Pennings et al., 2002).

Cami et al. (1998) reported little effect of co-abused ethanol on the cumulative fractions of BE excreted in 48-hour urinary collections of abusers that had nasally insufflated cocaine. Hence, the current data seem to suggest that ethanol co-abuse has little effect on the urinary excretions of BE when the commonly used route of nasal insufflation is used to co-administer cocaine. However, two key knowledge gaps need to be addressed before this can be definitively accepted. First, Cami et al. (1998) reported little effect after simultaneously administering ethanol and cocaine to their subjects and hence it remains unknown if the lack of effect is also expected if ethanol is administered before the cocaine is nasally insufflated. Such considerations are of importance since the reported behavior of nasally insufflating co-abusers is such that they prefer co-abusing ethanol at all stages of their usage episodes (i.e. before, during and after) (Gossop et al., 2006). Secondly, Cami et al. (1998) administered ≈ 56 g of ethanol and 100 mg of cocaine to their subjects; both of these doses are substantially lower than the typical usage reported by nasally-insufflating co-abusers which was 116 g and 900 mg for ethanol and cocaine (Gossop et al., 2006), respectively. Hence, it is of interest to establish the effect of ethanol co-abuse on the excreted cumulative fractions of BE at these reported usage levels for nasally insufflating co-abusers.

For the typically minor route-of-administration of injecting cocaine, Harris et al. (2003) reported a decrease in the cumulative fraction of BE excreted in 24-hour urine collections of their subjects. The subject in this study co-abused ethanol an hour before injecting cocaine. However, compared to the levels of the two substances administered by Harris et al. (2003) to their subjects, data from Gossop et al. (2006) suggests that on typical occasions cocaine injectors administered half as much and almost an order of magnitude higher levels of ethanol and cocaine, respectively. Hence, it remains unclear if the decrease in BE excretions due to the co-abuse of ethanol as reported by Harris et al. (2003) is still to be expected at the typical dosage levels reported by Gossop et al. (2006); i.e., substantially higher levels of cocaine and lower levels of ethanol.

For smoking co-abusers, no data are currently available as to the effects of ethanol co-abuse on the urinary levels of BE. However, several behavioral characteristics of such co-abusers may mitigate any effect ethanol co-abuse may have on their excreted fractions of BE. For one, cocaine smokers have been reported to consume significantly lower amounts of ethanol than their nasally-insufflating counterparts, specifically by a factor of 4.2 times less (Gossop et al., 2006). Further, cocaine smoking co-abusers tended to use ethanol towards the end of their crack-using session (Gossop et al., 2006). Taken together, these behavioral trends suggest that cumulative BE excretions from cocaine smoking co-abusers are less likely to be affected by the concurrent use of alcohol because they prefer co-abusing lower amounts of ethanol and even then their overall tendency is to co-abuse ethanol towards the end of their usage session (Gossop et al., 2006). Nevertheless, it is of interest to establish the effect of ethanol co-abuse on the cumulative fractions of BE excreted by cocaine smoking co-abusers; in particular, the trends reported by

Gossop et al. (2006) would allow one to pragmatically establish the significance of any such effects.

Appendix I: Excretion Profiling for Licit Sources of Morphine

Medicinal sources of morphine include the use of morphine, codeine, ethylmorphine, nicomorphine and pholcodine (Brunk et al., 1974; Hedenmalm et al., 1997; Koopman-Kimenai et al., 1987; Maurer and Fritz, 1990; Ripel et al., 1992). Furthermore, morphine can also be present in humans excretions through the consumption of poppy seeds (Rohrig and Moore, 2003). Lastly, a basal level of morphine is expected to be naturally present in human excretions since it is endogenously produced (Mikus et al., 1994). From a sewer epidemiology perspective, since the interest lies in quantifying the illicit contributions to the net sewer loads of morphine, excretion profiling must be conducted for each of the aforementioned sources to identify their potential contribution to metabolites found in influents.

I.1 Morphine

On a mass basis, medicinal morphine is predominately consumed orally (Garcia del Pozo et al., 1999). Hence, for excretion profiling, interest lies in those studies where morphine was orally administered to subjects. In total, three suitable studies reporting on the urinary disposition of orally administered morphine were identified (Table I.1).

Table I.1 Urinary morphine following administration of oral morphine.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Fraction of administered dose (%)	
					MOR	
					Free	Glucuronide Conjugated
Brunk et al. (1974)	10	6	34-60	48	3.4 ± 0.7	69.0 ± 8.2
Hasselstrom and Sawe (1993)	15.2	7	28-55	72	2.6 ± 0.5	65.8 ± 11.6
Mitchell et al. (1991)	8.5	4	26-36	108	6.8 ± 0.8	59.0 ± 1.4
$U_{\text{morphine,oral,MOR}}$					69.2 ± 9.1	

The compiled data suggests that 69.2 ± 9.1 % of orally-administered morphine is expected to be excreted in urine as morphine. Of this net morphine load, a minor fraction is present as free morphine whereas the majority of the load is conjugated to glucuronide moieties (Table I.1). Nevertheless, research conducted primarily with glucuronides of endogenous estrogens suggests that such conjugates are deconjugated to the free form during the sewer transit process (D'Ascenzo, 2003; Gomes et al., 2009). These assertions are assumed to hold true here for the glucuronide conjugated fraction of excreted morphine, as is supported by limited monitoring data available in this respect (Castiglioni et al., 2006).

Limited data is available with respect to the fecal disposition of morphine. Available data suggests that the net level of fecal excretions amount to 7 - 10% of the administered dose (Abbott Labs, 2006). However, it remains unclear what fraction of this net fecal load is morphine. Recognizing that the fecal load of morphine originates in the biliary excretions of the users (Abbott Labs, 2006), a reasonable assumption would be that the fecal excretory profile closely resembles the urinary excretion profile. Since the urinary excretion profile almost exclusively consists of free and conjugated morphine (Hasselstrom and Sawe, 1993), it is assumed here that the majority of the net fecal excretions is morphine. Further, the fecal load of morphine is expected to be predominately present as free morphine, since any conjugated

fractions present in biliary excretions are expected to be deconjugated to the free form due to the action of intestinal flora (Johnson and Williams, 2005). Hence, $F_{oral,MOR}$ was assumed to be equal to 8.5% , the mean value of the available net fecal excretion data.

Therefore, the sum of the urinary and fecal excretions, being 77.7 ± 9.1 % of the orally-administered morphine, is expected to end up in sewers as morphine.

I.2 Codeine

Codeine for clinical purposes is primarily administered orally (Khan and Nicell, in preparation). The excretion profiling of codeine suggests that $6.0 \pm 2.6\%$ of an orally administered dose is expected to be excreted in the urine of users as free and glucuronide conjugated morphine (see Table I.2). As with morphine (see section I.1), assuming that the glucuronide fraction will revert to the free form, it is expected that $6.0 \pm 2.6\%$ of orally administered codeine will end up in sewers as morphine.

Table I.2 Urinary morphine following administration of oral codeine.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Fraction of administered dose (%)	
					MOR	
					Total	
					Free	Glucuronide Conjugated
Ammon et al. (2002)	73.6	12	26-42	36	0.2 ± 0.05	5.6 ± 0.8
Redmond and Parker (1963)	45.5	6	-	14		14 ± 1.4
Hedenmalm et al. (1997)	18.4	4	21-39	15		6.5 ± 3.9
Dutt et al. (1983)	22.6	10	19-37	72 +		3.2 ± 1.6
Somogyi et al. (1991)	22.8	6	18-44	48		5.0 ± 4.8
Adler et al. (1955)	20.2-21.5	3	26-38	24		7.7 ± 4.4
Lafolie et al. (1996)	18.4-36.8	13	22-61	96		5.4 ± 2.9
Vree and Wissen (1992)	22	5	20-50	48	0.5 ± 0.4	2.9 ± 1.5
$U_{codeine,oral,MOR}$					6.0 ± 2.6	

Negligible amounts of morphine are expected in the fecal excretions of codeine users since it has been reported that only 0.02 - 0.17% of an administered dose of codeine is eliminated via this route by humans (Adler et al., 1955).

I.3 Ethylmorphine

Excretion profiling of oral ethylmorphine suggests that 14.5 ± 5.4 % of orally-administered ethylmorphine will appear in the urinary excretions of users as morphine (see Table I.3). Data on the fecal disposition of ethylmorphine is currently not available in literature. Nevertheless, the evidence from structurally similar compounds such as codeine and morphine (Abbott Labs, 2006; Adler et al., 1955), suggests that fecal elimination of ethylmorphine is expected to be of minor importance. Hence, it assumed here that 14.5 ± 5.4 % of orally administered ethylmorphine ends up in sewers as morphine.

Table I.3 Urinary morphine following administration of oral ethylmorphine.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Fraction of administered dose (%)	
					MOR	
					Total	
Popa et al. (1998)	22.4-44.8	10	22-53	48	14.1 ± 5.9	
Aasmundstad et al. (1995)	94	8	24	48	16.7 ± 3.4	
Hedenmalm et al. (1997)	22.4	4	21-39	15	11.0 ± 7.3	
$\overline{U}_{\text{ethylmorphine,oral,MOR}}$					14.5 ± 5.4	

I.4 Pholcodine

Pholcodine is typically used orally and the majority of the administered dose is excreted via urinary excretions, with primary excretory metabolites being unchanged and conjugated pholcodine (Chen et al., 1988; Johansen et al., 1990; Maurer and Fritz, 1990; Neuvonen et al., 1980). Urinary morphine, essentially all present as glucuronide conjugates, was reported to amount to 0.5 – 1.0 % of the orally-administered dose of pholcodine (Johansen et al., 1990). Fecal elimination of administered pholcodine has been suggested to be a minor elimination pathway (Neuvonen et al., 1980) and hence unlikely to significantly contribute to the urinary loads of morphine. Hence, it is estimated that 0.75% (i.e., the mean of the reported range) of an orally-consumed pholcodine dose ends up in sewers as morphine.

I.5 Nicomorphine

Nicomorphine is another clinically-used drug that is metabolized to morphine (Koopman-Kimenai et al., 1987; Koopman-Kimenai et al., 1994; Koopman-Kimenai et al., 1995). Clinical preparations of nicomorphine can be administered by injection, orally ingestion, or rectally as a suppository (DKMA, 2010). Data on the disposition of rectally and intramuscularly administered nicomorphine published in literature (Koopman-Kimenai et al., 1994; Koopman-Kimenai et al., 1995) suggests that 49 to 63 % of an administered nicomorphine dose is excreted as morphine in the urine of users (see Table I.4). Recognizing that the predominant fraction (i.e., 85%) of nicomorphine is typically administered via injections (Clausen et al., 1995), it can be assumed that $\overline{U}_{\text{Nicomorphine,injection,MOR}} = 62.7 \pm 9.1\%$. Data on the fecal disposition of nicomorphine is currently not available in literature. Nevertheless, the evidence from structurally similar compounds such as codeine, pholcodine and morphine suggests that fecal elimination of nicomorphine is expected to be of minor importance (Abbott Labs, 2006; Adler et al., 1955; Neuvonen et al., 1980). Hence, it is estimated here that $62.7 \pm 9.1\%$ of the consumed nicomorphine ends up in sewers as morphine.

Table I.4 Urinary morphine following administration of nicomorphine.

					Fraction of administered dose (%)	
Reference	Dose (mg)	n	Age (yr)	Duration (hr)	MOR	
					Total	
Injection						
Koopman-Kimenai et al. (1995)	20	8	24	48	10.6 ± 1.9	52.1 ± 8.9
				U _{nicomorphine, inj., MOR}	62.7 ± 9.1	
Rectal						
Koopman-Kimenai et al. (1994)	30	8	21-39	48	3.6 ± 1.6	45.0 ± 6.0
				U _{nicomorphine, rec., MOR}	48.6 ± 6.2	

I.6 Endogenous morphine

Morphine is also produced endogenously (Mikus et al., 1994). Hence, a basal level of morphine is expected in all anthropogenic excretions (Hofmann et al., 1999; Mikus et al., 1994). The excretion profiling of endogenous urinary levels (see Table I.5) suggests that $0.64 \pm 1.84 \mu\text{g}/\text{cap}\cdot\text{d}$ of endogenous morphine is expected to be released to the sewers through this source. No data has been reported to date on the fecal disposition of endogenous morphine, however disposition of exogenous morphine (Abbott Labs, 2006) suggests that elimination of endogenous morphine through such a route would be expected to be comparatively minor.

Table I.5 Endogenous excretion of morphine.

Reference	n	Age (yr)	Endogenous Excretion ($\mu\text{g}/\text{cap}\cdot\text{d}$)
Mikus et al. (1994)	40	21-62	0.65 ± 1.84
Hofmann et al. (1999)	1	-	0.09
		$u_{\text{e-MOR}}$	0.64 ± 1.84

I.7 Poppy seeds

Morphine could also be present in the excretions of those who consume poppy seeds as food products. The morphine content of ingested poppy seeds is excreted unchanged in the urine of consumers (i.e., $U_{\text{oral, MOR}} = 100\%$) (Lachenmeier et al., 2010; Pettitt, et al., 1987), as will be explored in detail in Appendix J.

Appendix J: Importance of Poppy Seeds as a Source of Morphine to Sewers

Typically, the mass of poppy seeds consumed by the population of a nation as food products is not available in the literature. Hence, the analysis of the importance of poppy seeds as a contributor to the net sewer loads of morphine was only conducted for Austria and Germany, where such data was readily available. In addition, since these countries are considered to be among the highest consumers of poppy seeds (Beráth, 1998; FAOSTAT, 2010), these countries are good case studies to establish the significance of poppy seeds as a contributor of morphine loads in sewers.

Germany and Austria report the use of 1,020-1,380 and 10,000 tonnes per annum of poppy seeds, respectively, for food and baking needs (Beráth, 1998; Sproll et al., 2006). Further it has been reported that 60% of the poppy seeds on the German market had an average morphine content of 4 -12 mg/kg while the remaining 40% had a content of 0-4 mg/kg (Lachenmeier et al., 2010). Using the midpoint of the content ranges it can be assumed that an average poppy seed on the German market contains 7.2 mg of morphine/kg of seed. Similar data was not available for poppy seeds available on the Austrian market. However, import data for Austria tracked by the Food and Agriculture Organization of the United Nations (FAO) suggests that approximately 60% of the imported poppy seeds were from the Czech Republic, with an additional 10% each, originating from Germany, Turkey and the Netherlands (FAOSTAT, 2010). The remaining 10% of the imported seeds were of Polish and Slovakian origin (FAOSTAT, 2010). Such information can be used along with the average reported morphine content of poppy seeds originating from the various geographical regions to estimate the net morphine content of raw poppy seeds on the Austrian market (see Table J.1).

Table J.1 Estimated morphine content of raw poppy seeds.

Country	Poppy seed consumption (MT/yr)	Geographical origin of seeds	Fraction of Poppy seed market	Average morphine content (mg/kg)	Morphine content of raw poppy seeds (kg/yr) ^(b)	Morphine content of raw poppy seeds (µg/cap·d) ^(c)
Germany	10,000 ¹	Various	1	7.2 ¹	72	2.4
		Czech	≈ 0.6 ³	61 ^{4,5}	43-58	14-19
		Germany	≈ 0.1 ³	7.2 ¹		
Austria	1,020-1,380 ²	Netherlands	≈ 0.1 ³	33 ⁵		
		Turkey	≈ 0.1 ³	5.7 ⁴⁻⁶		
		Poland & Slovakia	≈ 0.1 ³	7.4 ^{(a); 4,5}		

(a) No data was available for morphine content of Slovakian poppy seeds, hence it was assumed to be equal to morphine content of Polish seeds^{4,5}; (b) Poppy seed consumption × Σ(fraction of poppy seed market × average morphine content); (c) Morphine content of raw poppy seeds (kg/yr) / (365 × National population of the country⁷)

Sources: (1) Sproll et al. (2006); (2) Beráth (1998); (3) FAOSTAT (2010); (4) BfR (2006); (5) Moeller et al. (2004); (6) Thevis et al. (2003); (7) US Census (2010).

The analysis suggests that 72 and 43-58 kg of morphine are present in raw German and Austrian poppy seeds, respectively, used for baking and food needs within a given year. In most instances, the raw seeds are further processed before actually being consumed. Such processing can substantially reduce the

morphine content of the raw poppy seeds (Lachenmeier et al., 2010; Sproll et al., 2006; Sproll et al., 2007). For example, washing, grinding and baking of raw poppy seeds can reduced their morphine content by 40-73%, 25-34% and 30-90%, respectively (Lachenmeier et al., 2010). Further, if the seeds are used to prepare commercial baking mix, a 100% reduction in morphine content of the seeds can be expected (Lachenmeier et al., 2010). Therefore, the actual load of morphine consumed by the German and Austrian populations, within a given day on a per capita basis, is expected to be substantially lower than raw seed content of 2.4 and 14-19 $\mu\text{g}/\text{cap}\cdot\text{d}$ (see Table J.1), respectively. Even if one assumes no reduction due to processing, the amount of morphine that is expected to be released to German and Austrian sewers due to poppy seed consumption is minor compared to the cumulative morphine load released due to other licit and illicit sources (see Table J.2). Hence, it is likely that the consumption of poppy seeds does not significantly add to the sewer loads of morphine. It is assumed that this assertion would also be valid for others countries considered in this communication; since Germany and Austria are considered to be among the highest consumers of poppy seeds (Beráth, 1998; FAOSTAT, 2010) and hence relative contribution from such a source are expected to be even smaller in other countries.

Table J.2 Net morphine per capita sewer loads ($\mu\text{g}/\text{cap}\cdot\text{d}$) and its various sources.

Country	Sewer borne morphine from various sources ($\mu\text{g}/\text{cap}\cdot\text{d}$)								Raw poppy seeds ⁽ⁱ⁾
	Heroin ^(a)	Morphine	Ethylmorphine	Codeine	Pholcodine	Nicomorphine	Endogenous ^(e)	Net ^(h)	
Germany	58	27 ^(b)	- ^(c)	2.5 ^(d)	- ^(c)	- ^(c)	0.64	88	2.4
Austria	105	> 283 ^(f)	?	> 0.2 ^(g)	- ^(c)	- ^(c)	0.64	>389	14-19

(a) Estimated using $N_d \cdot (\sum (U_{h,MOR} + F_{h,MOR}) \cdot x_h) \cdot (Mw_{MOR}/Mw_{HER})$ where: N_d was estimated using equation 13; $U_{h,MOR} + F_{h,MOR}$ for each route-of-administration, h , were obtained from the compiled data presented in Table 2 (see main text); x_h values for a given national population were assumed to be equal to the routes-of-administration reported for abusers in the respective country's substance-abuse treatment programs (EMCDDA, 2009a); and Mw_{MOR}/Mw_{HER} is equal to 0.77.

(b) Estimated using Equation (4); L_{MOR} for Germany was based on consumption data reported in Schwabe and Paffrath (2007); $Y_{n,mor}$ and $Y_{f,mor}$ was assumed to equal to be equal to data for painkillers reported by Bound and Voulvoulis (2005); $\sum (U_{s,MOR} + F_{s,MOR}) \cdot x_e$ were based on the excretion profiling of oral morphine presented in I.1.

(c) These active ingredients are currently not sold in Germany or Austria for clinical consumption (Schwabe and Paffrath, 2007; Sweetman, 2009).

(d) Estimated using Equation (3); $L_{codeine}$ was based on consumption data reported in Schwabe and Paffrath (2007); $Y_{n,codeine}$ was assumed to be equal to the data reported by Bound and Voulvoulis (2005) for painkillers; $\sum (U_{b,MOR} + F_{b,MOR}) \cdot x_i$ were based on the excretion profiling detailed for codeine in I.2; $Mw_{MOR}/Mw_{codeine}$ is equal to 0.95.

(e) Estimated using Equation (5); $u_{e,MOR}$ and $f_{e,MOR}$ were based on the endogenous excretion profiling detailed in I.6.

(f) Estimated using Equation (4); L_{MOR} for Austria was based on consumption data reported by INCB (2010); $Y_{n,mor}$ and $Y_{f,mor}$ was assumed to be equal to data for painkillers reported by Bound and Voulvoulis (2005); $\sum (U_{s,MOR} + F_{s,MOR}) \cdot x_e$ were based on the excretion profiling of oral morphine presented in I.1. Data reported by INCB (2010) for the consumption of morphine, does not include the mass of the drug sold within a given country as formulations listed under the Schedule III of the 1961 convention on narcotic drugs and hence the calculated value represents an ``at minimum`` contribution.

(g) Estimated using Equation (3); $L_{codeine}$ was based on consumption data reported by INCB (2010); $Y_{n,codeine}$ was assumed to be equal to the data reported by Bound and Voulvoulis (2005) for painkillers; $\sum (U_{b,MOR} + F_{b,MOR}) \cdot x_i$ were based on the excretion profiling detailed for codeine in I.2; and $Mw_{MOR}/Mw_{codeine}$ is equal to 0.95. Data reported by INCB (2010) for the consumption of codeine does not include the mass of the drug sold within a given country as formulations listed under Schedule III of the 1961 convention on narcotic drugs and since a predominate fraction of codeine is sold as such formulations (INCB, 2010) the calculated value represents a minimum contribution to morphine loads due to the consumption of codeine.

(h) All sources but the consumption of poppy seeds.

(i) Table J.1; assumes no processing losses.

Appendix K: Clinical Consumption of Morphine-related Active Ingredients in Various Countries

Per capita daily consumption values for morphine, codeine, ethylmorphine, nicomorphine and pholcodine for various countries were compiled from a number of literature sources and national databases. In almost all instances, consumption data available used the Anatomical Therapeutic Chemical classification of drugs/Defined Daily Dose (ATC/DDD) methodology (WHO, 2010) to report the national consumption levels in one of the following units: $DDD/1000 \text{ cap}\cdot\text{d}$ or $DDD/1000 \text{ cap}\cdot\text{yr}$ or DDD/yr , where DDD is the defined daily dose of particular ATC classification.

The DDD for the various ATC classes as suggested by the WHO (2010) were used to convert reported data into the desired units of $\mu\text{g}/\text{cap}\cdot\text{d}$ using one of the following equations to estimate either L_b or L_s :

$$L_b \text{ or } L_s (\mu\text{g}/\text{cap}\cdot\text{d}) = DDD/1000 \text{ cap}\cdot\text{d} \times 1/1000 \times \mu\text{g}/DDD \times M_{w_{\text{drug}}}/M_{w_{\text{salt}}} \quad (\text{K.1})$$

$$L_b \text{ or } L_s (\mu\text{g}/\text{cap}\cdot\text{d}) = DDD/1000 \text{ cap}\cdot\text{yr} \times 1/1000 \times \mu\text{g}/DDD \times 1/365 \text{ DDD} \times M_{w_{\text{drug}}}/M_{w_{\text{salt}}} \quad (\text{K.2})$$

$$L_b \text{ or } L_s (\mu\text{g}/\text{cap}\cdot\text{d}) = DDD/\text{yr} \times 1/\text{National Population} \times \mu\text{g}/DDD \times M_{w_{\text{drug}}}/M_{w_{\text{salt}}} \quad (\text{K.3})$$

National population data were derived from the IDB database (US Census, 2010) for the year 2006, since this year was chosen as base year for the evaluation.

Typically, DDD 's are expressed as the mass of the drug's salt as present in a given clinical formulation (i.e., codeine phosphate) rather than the anhydrous drug itself (i.e., codeine). The molecular weight ratio $M_{w_{\text{drug}}}/M_{w_{\text{salt}}}$ is the adjustment factor that corrects DDD for the actual drug content of a prescribed formulation.

Codeine is typically prescribed as its phosphate salt, hence its drug content adjustment factor is 0.78, whereas morphine is typically prescribed as its sulphate salt hence its drug content adjustment factor is 0.75 (Khan and Nicell, in preparation). Ethylmorphine and Nicomorphine are typically prescribed as their HCl salts and hence their respective drug content adjustment factors are 0.81 and 0.93 (Sweetman, 2009). Pholcodine is present in clinical formulations as itself; hence its consumption reported as DDD does not need to be adjusted.

The various national estimates of per capita consumption, L_b values, for the selected base year 2006 and the sources used to compile the data are summarized in Table K.1.

Table K.1 Clinical consumption of relevant active ingredients (morphine, codeine, ethylmorphine, nicomorphine and pholcodine) in various countries. (Note: All consumption is for the year 2006, unless otherwise indicated)

Country	L _{codeine}	L _{morphine}	L _{ethylmorphine}	L _{pholcodine}	L _{nicomorphine}	Reference
	(µg/cap·d)					
Australia	595.1	129.7	-	0.5	-	DUSC (2009)
Belgium	91.7 ^(a)	6.4 ^(a)	≈ 15.0 ^(b)	≈ 10.6 ^(b)	-	De Conno et al. (2005); INCB (2010)
Canada	996.9	161.0	-	-	-	Khan and Nicell (in preparation)
Czech Republic	≈ 44.4	14.4	6.2	-	-	State Institute for Drug Control (2006)
Denmark	507.6	156.2	-	-	2.4	Danish Medicines Agency (2010)
Estonia	< 0.8	15.0	-	-	-	State Agency of Medicines-Estonia (2007)
Finland	796.4	14.3	16.2	1.5	-	FIMEA (2009)
Germany	55.0	42.4	-	-	-	Schwabe and Paffrath (2007)
Holland	128.2	24.6	-	-	0.1	GIP (2010)
Iceland	666.1 ^(c)	76.5 ^(c)	-	-	-	IMA (2008)
Ireland	217.7 ^(a)	8.5 ^(a)	-	≈ 93.5 ^(b)	-	De Conno et al. (2005); INCB (2010)
Italy	8.3 ^(a)	1.0 ^(a)	-	-	-	De Conno et al. (2005); INCB (2010)
Latvia	-	2.3 ^(d)	-	-	-	State Agency of Medicines-Latvia (2008)
Malaysia	15.1	13.9	-	-	-	Ministry of Health Malaysia (2009)
Norway	1099.8	106.7	64.0	32.0	-	Norwegian Inst. of Public Health (2010); Grung et al. (2007)
Portugal	21.8 ^(a)	1.4 ^(a)	≈ 0.3 ^(b)	-	-	De Conno et al. (2005); INCB (2010)
Slovenia	1.6	9.8	-	6.0	-	IVZ RS (2009)
Spain	76.9 ^(a)	5.0 ^(a)	≈ 0.1 ^(b)	≈ 0.2 ^(b)	-	De Conno et al. (2005); INCB (2010)
Sweden	383.2	65.7	100.2	-	-	Apoteket AB (2009); Grung et al. (2007); INCB (2010)
UK	1490 ^(e)	19.7 ^(a)	-	≈ 34.5 ^(b)	-	De Conno et al. (2005); DEFRA (2007); INCB (2010)
USA	172.1	160.6	-	-	-	DEA (2008)

“-” drug (i.e., active ingredient) not sold in the respective countries; (a) Consumption for the year 2003; (b) Approximate consumption based on data from INCB (2010) for the year 2006; (c) Consumption for the year 2008; (d) Consumption for the year 2007; (e) Consumption for the year 2004.

Appendix L: Nationally-Averaged MOR Concentrations: Sample Calculation and Comparison

L.1 Sample Calculation

A sample calculation is presented below to illustrate how the nationally-averaged concentration of morphine (MOR) in influents can be estimated. The calculations shown are for Spain using the data sources indicated.

Estimates were performed using Equation (14), which is reproduced here to aid in the sample calculation discussion below:

$$\text{PIC}_{\text{HER-MOR}} = \frac{\left(N_{\text{HOR}} \cdot \left(\sum_{h=1}^H (U_{h,\text{MOR}} + F_{h,\text{MOR}}) \cdot x_h \right) \frac{Mw_{\text{MOR}}}{Mw_{\text{HOR}}} + J_{L,\text{MOR}} + J_{G,\text{MOR}} \right) (1 - k_{d,\text{MOR}}) \cdot x_{\text{con}}}{W_{\text{Spain}}} \quad (\text{L.1})$$

$k_{d,\text{MOR}}$ and $J_{G,\text{MOR}}$ were assumed to be approximately zero, as justified earlier (see main text). The molecular weight ratio ($Mw_{\text{MOR}}/Mw_{\text{HOR}}$) is equal to 0.77. Substituting these into Equation (L.1) yields:

$$\text{PIC}_{\text{HER-MOR}} = \frac{\left(N_{\text{HOR}} \cdot \left(\sum_{h=1}^H (U_{h,\text{MOR}} + F_{h,\text{MOR}}) \cdot x_h \right) 0.77 + J_{L,\text{MOR}} \right) \cdot x_{\text{con}}}{W_{\text{Spain}}} \quad (\text{L.2})$$

$J_{L,\text{MOR}}$ can be expanded to its three component using Equation (6):

$$J_{L,\text{MOR}} = J_{L,\text{MOR-c}} + J_{L,\text{MOR-m}} + J_{L,\text{MOR-end}} \quad (\text{L.3})$$

In turn, each of the respective contributions of Equation (L.3) can be expanded using Equations (3) to (5), yielding:

$$J_{L,\text{MOR-m}} = \sum_{b=1}^B L_b \cdot \frac{Mw_{\text{MOR}}}{Mw_b} \cdot \frac{Mo_{\text{MOR}}}{Mo_b} \cdot \left((1 - Y_{nb}) \left(\sum_{i=1}^I (U_{b,i,s} + F_{b,i,s}) \cdot x_i \right) \right) \quad (\text{L.4})$$

$$J_{L,\text{MOR-c}} = L_{\text{MOR}} \cdot \left((1 - Y_{n,\text{MOR}}) \left(\sum_{e=1}^E (U_{\text{MOR},e,\text{MOR}} + F_{\text{MOR},e,\text{MOR}}) \cdot x_e \right) + Y_{n,\text{MOR}} \cdot Y_{f,\text{MOR}} \right) \quad (\text{L.5})$$

$$J_{L,\text{MOR-end}} = (u_{e-\text{MOR}} + f_{e-\text{MOR}}) \quad (\text{L.6})$$

The values for each of the variables of Equations (L.4) to (L.6) are summarized in Table L.1 along with their respective literature sources.

The values in Table L.1 can be substituted into Equations (L.4) to (L.6) resulting in estimates for $J_{L,\text{MOR-c}}$, $J_{L,\text{MOR-m}}$ and $J_{L,\text{MOR-end}}$ as 3.52 ± 1.52 , 3.22 ± 0.36 and 0.64 ± 1.84 $\mu\text{g MOR/cap}\cdot\text{d}$, respectively. The net

daily release of licit MOR to Spanish sewers on a per capita basis ($J_{L,MOR}$) can then be estimated by substituting these values back into Equation (L.3):

$$J_{L,MOR} = J_{L,MOR-C} + J_{L,MOR-m} + J_{L,MOR-end} = (3.52 \pm 1.52) + (3.22 \pm 0.36) + (0.64 \pm 1.84) = 7.38 \pm 2.41 \text{ } \mu\text{g of MOR/cap}\cdot\text{d}$$

x_h values for the national heroin-abusing population within Spain were assumed to correspond to the routes-of-administration reported by abusers in Spanish substance-abuse treatment programs. According to EMCDDA's statistical bulletin (EMCDDA, 2009a), 21.8, 66.1, 5.1 and 4.3% of opiate abusers in Spanish substance-abuse treatment programs reported primarily injecting, chasing, orally ingesting, and nasally insufflating opiates, respectively. The remaining 2.8% used other routes to primarily administer their opiates. In light of the limitation that no detail information was available for how the abusers in the "other" routes category abused opiate and the fact that such abusers are a minor fraction of the net abusing population in treatment, the proportions of known routes were scaled to 100%. Such scaling, results in the route-of-administration distribution among opiate abusers to be approximated as 22.4, 67.9, 5.3, and 4.4% of them primarily injected, chasing, orally ingesting, or nasally insufflating opiates, respectively.

Further, since opiate abusers are primarily heroin abusers in Spain (EMCDDA, 2009b), the derived route-of-administration distribution can safely be assumed to be representative of a heroin-abusing population. Hence, 22.4, 67.9, 5.3 and 4.4% of heroin abusers were assumed to be injecting, chasing, orally ingesting, or nasally insufflating their heroin, respectively. This also allows one to establish H (i.e., the total number of individual routes-of-administration typically used to administer heroin) to be equal to four, while the individual routes used to administer heroin, h , become: intravenous injection, chasing, oral ingestion and nasal insufflation. $U_{h,BE}$ and $F_{h,BE}$ for the individual identified the routes-of-administrations, h , can themselves be obtained from the compiled data presented in Table 2 (see main text).

N_{HER} was estimated in Appendix B to be 0.07 mg/cap·d.

W_{Spain} was approximated as 349 L/cap·d by dividing the total daily amount of water abstracted for public water supply by the net population of Spain that is connected to public water supply (Eurostat, 2010; US Census, 2010). The national variation (σ) in W_{Spain} was assumed to be equal to 40% of its magnitude. This is, at best, an order of magnitude estimate of this variation based on the spatial variation in daily flow arriving at Belgian STPs serving 40% of the national population as reported by van Nuijs et al. (2009).

x_{con} for Spain was suggested to be 0.98 (Eurostat, 2010).

Substituting the quantified variables back into Equation (L.2), the concentrations of MOR in the national influents of Spain can be estimated to be: $PIC_{HER-MOR} = 89.6 \pm 37.7 \text{ ng/L}$

Table L.1 Quantification of the variables of Equations (L.4) to (L.6).

		Various licit sources of MOR to sewers							
Variables		Codeine	Ethylmorphine	Pholcodine	Nicomorphine	Morphine	Endogenous MOR	Units	Notes
Eq. L.4	L _b	76.9	0.1	0.2	0			µg/cap·d	(a)
	M _W _{MOR} /M _W _b	0.95	0.91	0.71	0.58			g/mole	
	M _O _{MOR} /M _O _b	1	1	1	1			moles of MOR/ mole of <i>b</i>	(b)
	Y _{nb}	0.2	0.2	0.2	0.2			-	(c)
	I	1	1	1	1			-	(d)
	i	oral	oral	oral	Injection			-	(d)
	U _{b,i,s} + F _{b,i,s}	6.0 ± 2.6	14.5 ± 5.4	0.75 ± 0.12	62.7 ± 9.1			%	(d)
Eq. L.5	L _{MOR}					5		µg/cap·d	(a)
	Y _{n,MOR}					0.2		-	(c)
	Y _{f,MOR}					0.11		-	(c)
	E					1		-	(d)
	e					oral		-	(d)
	U _{MOR,e,MOR} + F _{MOR,e,MOR}					77.7 ± 9.1		%	(d)
Eq. L.6	u _{e-MOR}						0.64 ± 1.84	µg/cap·d	(d)
	f _{e-MOR}						≈ 0	µg/cap·d	(d)

(a) Table K.1; (b) the metabolic stoichiometry of generating MOR upon administering each of the relevant drug was confirmed to be equal to one by considering the respective structures of MOR and the parent drugs; (c) Approximated to be similar to the painkiller data reported by Bound and Voulvoulis (2005); (d) See analysis presented in Appendix I.

L.2 Comparison of Generated Estimate to Those Reported in Spanish Monitoring Studies

The national estimate from section L.1 is compared to Spanish monitoring data for MOR in Figure L.1. The figure suggests that the derived national for Spain estimates match up reasonably well with the sub-national measured levels.

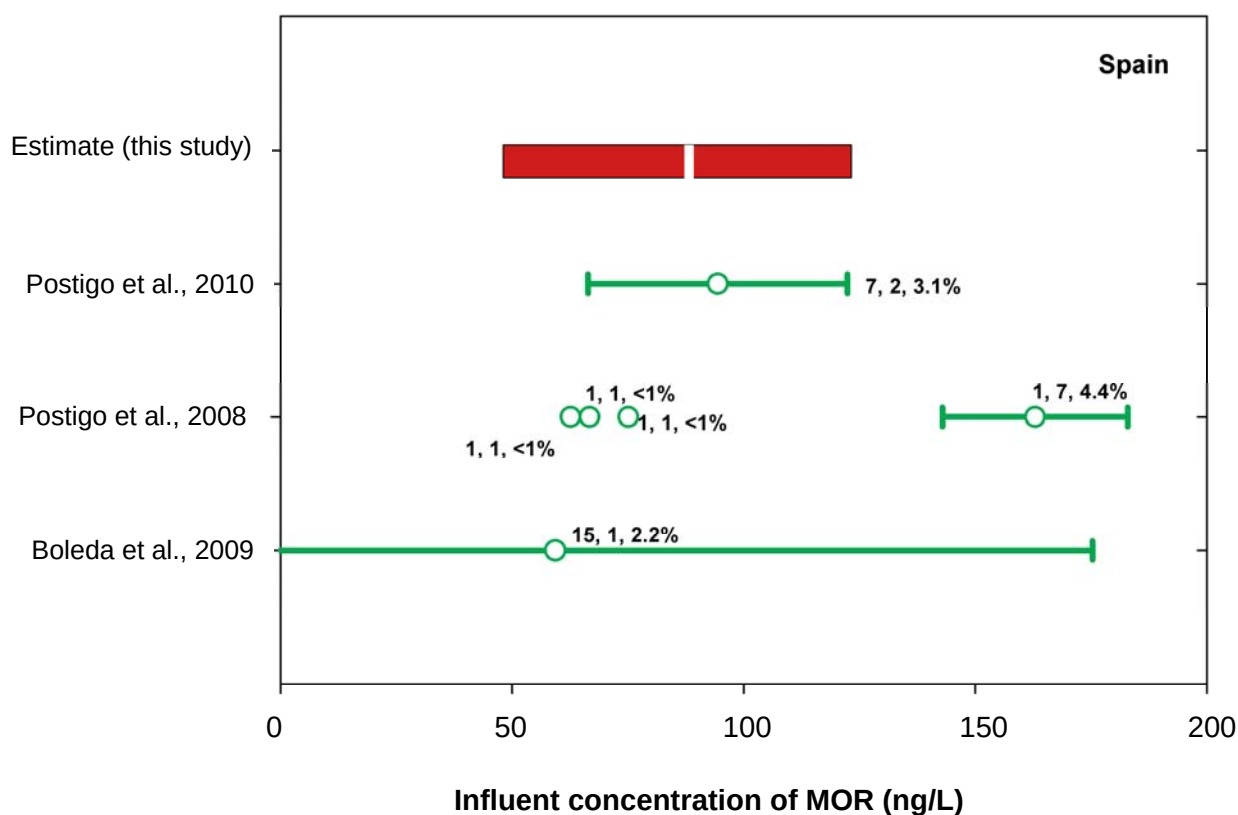


Figure L.1 Comparison of theoretically-estimated (■■) nationally-averaged influent concentrations of morphine (MOR) for Spain to those reported in sub-national Spanish monitoring studies (—○—). The theoretical estimate is from the sample calculation detailed in Appendix L.1. The numerical values reported next to the monitored data represent, respectively: spatial extent of the data as represented by the number of sewage treatment plants (STPs) monitored in the investigation; temporal extent of the data as represented by the number of days each STP was monitored; and percentage (%) national coverage of the data as represented by percentage of the national population that was contributing wastewater to the STPs that were monitored by a given study.

Appendix M: Relative Quantity of Codeine Sold Over-the-Counter in the United Kingdom

Approximately, 32,700 kg of codeine base were sold in 2004 to the British population through filling prescriptions (DEFRA, 2007).

For codeine sold in over-the-counter formulations in the United Kingdom, the Proprietary Association of Great Britain (PAGB, 2010) estimates that on average approximately 27.5 million “packs” are sold per year. Regulatory requirements limit each pack of such over-the-counter formulations to contain no more than 32 pills (MHRA, 2009), which according to the PAGB (2010) is also the most commonly bought pack-size by the British population. Each pill in relevant over-the-counter formulations contains between 6.2 -10 mg of codeine base (MHRA, 2009). Using all the aforementioned information, one can estimate the net amount of codeine sold through over-the-counter channels is between 5,500 and 8,800 kg/yr; i.e., codeine sold (kg/yr) = 27.5 million pack/yr $\times$ 32 pills/pack $\times$ 6.2 – 10 mg codeine/pill $\times$ 1/10⁶ kg/mg = 5,456 to 8,800 kg/yr.

Further, the mass of codeine sold in over-the-counter cough syrups has been suggested to be of minor importance (PAGB, personal communication).

Overall, over-the-counter purchases is estimated to account for 14 to 21% of the net mass of codeine sold to the British population within a given year.

Appendix N: Average Content of Ecstasy Tablets in Various Countries

The variation in MDMA base content of pills sold as ecstasy in various countries is summarized in Figure N.1 below.

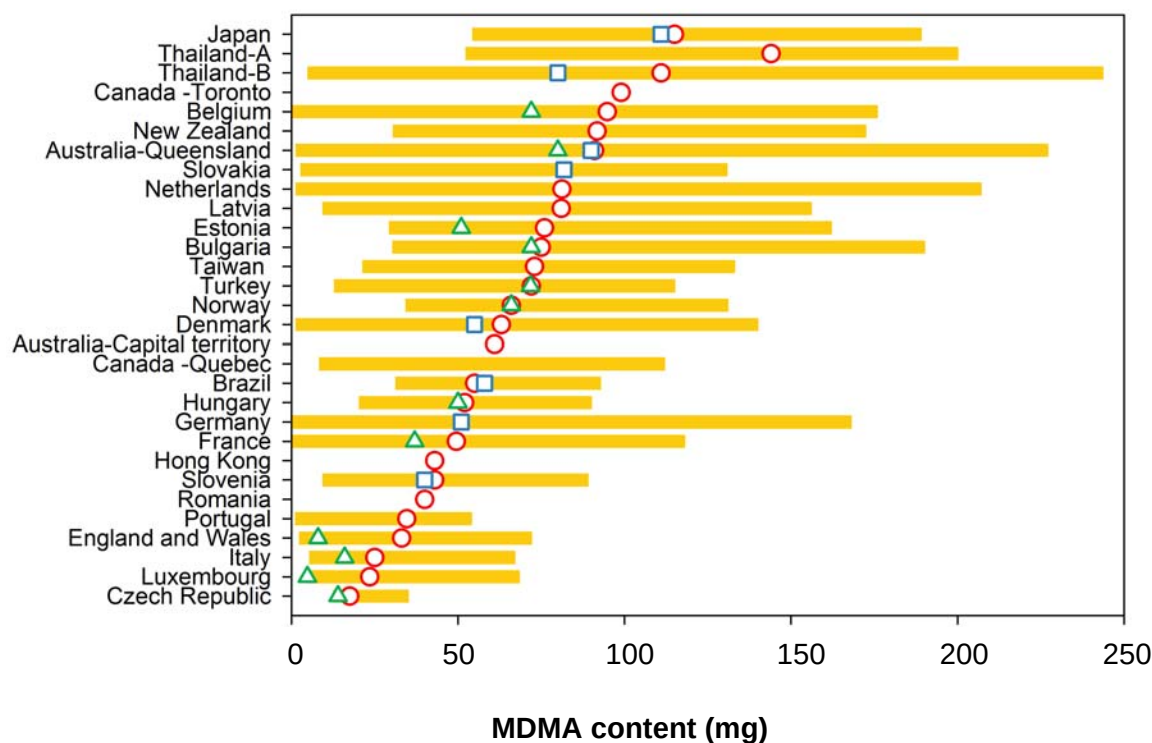


Figure N.1 Free base MDMA content (mg) of pills sold as ecstasy in various countries. The extent of the bars (■) represents the minimum and maximum of the content range reported. The mean (○), median (□) and mode (△) are plotted when reported. Data sources: All European data (EMCDDA, 2010) for seizures during the year 2008; Japanese data for seizures during the year 2002 (Makino et al., 2003); Thailand – B (Phonchai et al., 2010) for 2007/08 Thai seizures; Thailand – A (Thai Bureau of Drug and Narcotic, 2010) for 1995-2002 Thai seizures; Canada-Toronto (RGDU, 2004) for seizures in the city of Toronto during the year 2000; Canada-Quebec (Health Canada, 2008) for seizures in the province of Quebec during 2007-2008; Australia-Queensland (Fowler et al., 2007) for seizures during the year 2003-2004; Australia-Capital territory (NDARC, 2004) for seizures during the year 2003; New Zealand (Noller, 2009) for seizures during the year 2000; Brazil (Lapachinske et al., 2004) for seizures in the city of Sao Paulo during the years 1996-2001; Taiwan (Teng et al., 2006) for seizures during the year 2005 and Hong Kong (Cheng et al., 2006) for seizures during the years 2002-2004.

Appendix O: Excretion Profiling of Codeine and Estimation of its Consumption using Measured Concentrations of Relevant SEMs in STP Influent

O.1 Selection of an Appropriate Sewer Marker for Clinical Codeine Use

Codeine is metabolized *in vivo* to codeine, morphine (as discussed earlier in the Appendices above and the main text), norcodeine and normorphine, where all four metabolites are excreted in free form as well as a further fraction conjugated to glucuronide moieties (see Table O.1). Of these, the predominant fraction of the ingested dose is excreted as free and glucuronide conjugated codeine; while both normorphine and norcodeine are minor metabolites (see Table O.1). Further neither normorphine nor norcodeine are unique metabolites of codeine. Besides the use of codeine, minor amounts of normorphine can also be released to sewers through the consumption of morphine, heroin and ethylmorphine (Aasmundstad et al., 1995; Hasselstrom and Sawe, 1993; Yeh et al., 1976), whereas norcodeine's presence in sewer wastewaters can also be attributed to the use of morphine (Boerner and Roe, 1974). Hence, of all the *in vivo* metabolites, codeine (free + glucuronide conjugated) itself maybe the most suitable excretory marker to establish the net mass of codeine being consumed within a population of interest.

O.2 Excretion Profiling of Codeine

Sources of codeine in anthropogenic excretions, and hence sewers, include its clinical consumption (Table O.1), endogenous production (Mikus et al., 1994) and lastly, consumption via poppy seeds (BfR, 2006).

O.2.1 Clinical Consumption of Codeine

Codeine is primarily administered orally when used for clinical purposes (Khan and Nicell, in preparation). The excretion profiling of codeine suggests that $63.8 \pm 13.6\%$ of an orally administered dose is expected to be excreted in the urine of users as free and glucuronide conjugated codeine (Table O.1). Assuming that the glucuronide fraction would revert to the free form (D'Ascenzo, 2003; Gomes et al., 2009), $63.8 \pm 13.6\%$ of orally administered codeine will end up in sewers as codeine via the urinary excretions of the users. Negligible amounts of codeine are to be expected in the fecal excretions of codeine users since humans only eliminate 0.02 - 0.17% of an administered dose of codeine via such a route (Adler et al., 1955).

Therefore, overall, $U_{oral,codeine} + F_{oral,codeine}$ can be assumed to be equal to $63.8 \pm 13.6\%$.

O.2.2 Establishing the Importance of Sweat as a Source of Codeine to Sewers

Sweat-patch data from Kintz et al. (1996) suggest that subjects that were orally administered 70.2 mg of codeine released 24.9 to 127.2 ng of it onto their respective patches. Using the methodology described in Appendix E, such data can be used to estimate that 34 – 172 μg of codeine is released through the sweat of such users. Compare this to 44.8 mg of codeine that would be expected in the urine of such subjects; i.e., $70.2 \text{ mg} \times U_{oral,codeine}$ (Table O.1). Hence, for practical purposes, sweat of codeine users is not likely to be a significance source of codeine to the net sewers loads.

Table O.1 Urinary profiling of orally administered codeine.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Fraction of administered dose (%)					
					Codeine (COD)		Norcodeine (NCOD)		Normorphine (NMOR)	
					Total		Total		Total	
					Free	Glucuronide Conjugated	Free	Glucuronide Conjugated	Free	Glucuronide Conjugated
Ammon et al. (2002)	73.6	12	26-42	36	3.7 ± 0.2	62.2 ± 3.3	1.8 ± 0.2	3.9 ± 0.4	1.6 ± 0.2	2.3 ± 0.3
Redmond and Parker (1963)	45.5	6	-	14		55 ± 5.5		-		-
Hedenmalm et al. (1997)	18.4	4	21-39	15		97 ± 9.9		4.2 ± 2.2		-
Dutt et al. (1983)	22.6	10	19-37	72 +		48 ± 15		-		-
Somogyi et al. (1991)	22.8	6	18-44	48		56 ± 19		2.6 ± 2.6		-
Adler et al. (1955)	20.2-21.5	3	26-38	24		51 ± 13		16.3 ± 5.7		-
Lafolie et al. (1996)	18.4-36.8	13	22-61	96		66 ± 18		2.8 ± 1.2		-
Vree and Wissen (1992)	22	5	20-50	48	4.0 ± 1.0	80.7 ± 11.0		2.2 ± 1.4		2.4 ± 2.4
Caraco et al. (1996)	93.6	9	28-38	48	4.5 ± 2.9	53.0 ± 18.0	2.8 ± 1.7	2.8 ± 2.1	2.2 ± 0.3	-
Yue et al. (1991)	39	8		48	3.3 ± 1.5	68.4 ± 7.7	2.3 ± 1.6	4.7 ± 0.7	1.5 ± 0.9	-
U _{codeine,oral,s}						63.8 ± 13.6		5.1 ± 2.1		3.4 ± 1.3 ^(a)

(a) Only considers complete data available from Ammon et al. (2002) and Vree and Wissen (1992).

0.2.3 Endogenous Codeine

A basal level of codeine has been reported to be naturally present in human excretions (Mikus et al., 1994). The excretion profiling of endogenous urinary levels suggests that $0.25 \pm 0.52 \mu\text{g}/\text{cap}\cdot\text{d}$ of endogenous codeine is expected to be released to the sewers through this source (Mikus et al., 1994). No data have been reported to date on the fecal disposition of endogenous codeine; however, the disposition of exogenous codeine (Adler et al., 1955) suggests that elimination through such a route would be expected to be comparatively minor.

0.2.4 Codeine Release Due to the Consumption of Poppy Seeds

Typically, the codeine content of raw poppy seeds is an order of magnitude smaller than their morphine content (BfR, 2006). Further, much like the morphine content of raw poppy seeds, the codeine content of raw seeds is substantially reduced through pre-consumption processing (Lachenmeier et al., 2010; Sproll et al., 2006; Sproll et al., 2007). Noting these trends and the analysis presented for morphine in Appendix J, the contribution to the net sewer loads of codeine due to the excretions from poppy seed consumers is expected to be of negligible significance.

0.3 Estimating the Consumption of Codeine using Measured Concentrations of Unchanged Codeine in the STP Influent

As mentioned in the main text, in some countries codeine is sold in formulations that are available over-the-counter. Unfortunately, such sales are difficult to track and may not necessarily be captured by national prescription tracking databases or other sources. In such cases, it is suggested that a sewer epidemiology approach can be used to estimate the net mass of codeine consumed by a population of interest (i.e., $L_{\text{codeine}} \cdot (1 - Y_{n,\text{codeine}})$). Such an approach would require measuring the concentration of codeine in the influent of a STP of interest (C_{codeine}). An expression is derived below to allow the sewer epidemiologist to readily estimate $L_{\text{codeine}} \cdot (1 - Y_{n,\text{codeine}})$ (i.e., mass of the codeine actually consumed by a population of interest) from C_{codeine} (i.e., measured concentration of codeine in the influent of the STP connected to a population of interest).

In an analogous manner to Equations (1) and (9), the measured concentration of codeine (C_{codeine}) in the influent can be converted to a daily mass load using the following equation:

$$R_{T,\text{codeine}} = \frac{J_{T,\text{codeine}}}{\text{EXP}(-k_{d,\text{codeine}} \cdot t_s)} = \frac{C_{\text{codeine}} \cdot Q_{\text{in}}}{P \cdot \text{EXP}(-k_{d,\text{codeine}} \cdot t_s) \cdot (1 - x_{\text{codeine}})} \quad (\text{O.1})$$

where: $R_{T,\text{codeine}}$ represents the daily per capita load of codeine that is excreted by all users of clinical codeine (μg of codeine/cap·d); $k_{d,\text{codeine}}$ is first-order decay constant for codeine in sewers (hr^{-1}); t_s is the sewer transit time (hr); $J_{T,\text{codeine}}$ is the total daily per capita load of codeine arriving in the influent of the STP being monitored (μg of codeine/cap·d); C_{codeine} is the dissolved concentration of codeine in the influent of the STP being monitored (μg of codeine/L); Q_{in} is daily flow arriving as the influent to the treatment plant (L/d); P is the population served by the STP and x_{codeine} is the typical fraction of codeine likely to be sorbed on to suspended solids (dimensionless), which can be estimated using Deo and Halden's model (see Equation (2) in main text).

The analysis presented in Appendix O.2 suggests that codeine could result in anthropogenic excretions, and hence sewers loads, due to the medicinal consumption of codeine and its endogenous release. Hence, $R_{T,\text{codeine}}$ can be expressed as the sum of these two sources:

$$R_{T,codeine} = R_{endo,codeine} + R_{clinical,codeine} \quad (O.2)$$

where $R_{endo,codeine}$ is the amount of $R_{T,codeine}$ that results from the endogenous excretion of codeine (μg of codeine/cap·d) and $R_{clinical,codeine}$ is the amount of $R_{T,codeine}$ that results from the medicinal use of codeine (μg of codeine/cap·d).

$R_{endo,codeine}$ can be expanded in an analogous manner to Equation (5), yielding:

$$R_{endo,codeine} = (u_{e,codeine} + f_{e,codeine}) \quad (O.3)$$

where $u_{e,codeine}$ and $f_{e,codeine}$ are the per capita endogenous excretions of codeine on a daily basis in the populations' urinary and fecal excretions, respectively (μg of codeine/cap·d).

$R_{clinical,codeine}$ can be expanded in an analogous manner to Equation (4), yielding:

$$R_{clinical,codeine} = L_{codeine} \cdot ((1 - Y_{n,codeine}) \cdot (U_{codeine,oral,COD} + F_{codeine,oral,COD}) + Y_{n,codeine} \cdot Y_{f,codeine}) \quad (O.4)$$

where: $L_{codeine}$ is the daily per capita mass of codeine sold for medicinal purposes (μg of codeine/cap·d); $Y_{n,codeine}$ is the fraction of clinical codeine sold that ends up not being used by users (dimensionless); $U_{codeine,oral,COD}$ is the molar fraction of $L_{codeine}$ that is expected to be excreted as codeine in the urine of users when administered orally (moles of codeine/ moles of codeine); $F_{codeine,oral,COD}$ is the molar fraction of $L_{codeine}$ that is expected to be excreted as codeine in the fecal matter of users when administered orally (moles of codeine/moles of codeine); and $Y_{f,codeine}$ is the fraction of $Y_{n,codeine}$ that is expected to be flushed down the toilets and/or sinks (dimensionless).

Substitution of Equations (O.4) and (O.3) into Equation (O.2) yields:

$$R_{T,codeine} = (u_{e,codeine} + f_{e,codeine}) + L_{codeine} \cdot ((1 - Y_{n,codeine}) \cdot (U_{codeine,oral,COD} + F_{codeine,oral,COD}) + Y_{n,codeine} \cdot Y_{f,codeine}) \quad (O.5)$$

Further, based on the analysis presented in Appendix O.2, $f_{e,codeine}$ and $F_{codeine,oral,COD}$ can reasonably be approximated as zero. This allows one to simplify Equation (O.5) to the following:

$$R_{T,codeine} = (u_{e,codeine}) + L_{codeine} \cdot ((1 - Y_{n,codeine}) \cdot (U_{codeine,oral,COD}) + Y_{n,codeine} \cdot Y_{f,codeine}) \quad (O.6)$$

Substituting (O.6) into (O.1) allows $L_{codeine}$ to be isolated, as follows:

$$L_{codeine} = \frac{1}{((1 - Y_{n,codeine}) \cdot (U_{codeine,oral,COD}) + Y_{n,codeine} \cdot Y_{f,codeine})} \cdot \left[\frac{C_{codeine} \cdot Q_{in}}{P \cdot (1 - x_{codeine}) \cdot \text{EXP}(-k_{d,codeine} \cdot t_s)} - u_{e,codeine} \right] \quad (O.7)$$

In Equation (O.7), the combined variable of interest $L_{codeine} \cdot (1 - Y_{n,codeine})$, can only be isolated in the above equation if the contribution from the term $Y_{n,codeine} \cdot Y_{f,codeine}$ (i.e., the fraction of sold codeine that ends up being flushed down the sinks and/or toilets) can be ignored. Before this can be done with confidence, it is important to establish that the relative contribution of $Y_{n,codeine} \cdot Y_{f,codeine}$ to the whole term $((1 - Y_{n,codeine}) \cdot U_{codeine,oral,COD} + Y_{n,codeine} \cdot Y_{f,codeine})$ is minor of importance and hence can be neglected. Such an analysis has been attempted in Figure O.1. Plotted in this graph are percent contribution contours (i.e., expressed as $[Y_{n,codeine} \cdot Y_{f,codeine} / ((1 - Y_{n,codeine}) \cdot U_{codeine,oral,COD} + Y_{n,codeine} \cdot Y_{f,codeine})] \cdot 100$) as a function of $Y_{n,codeine}$ and $Y_{f,codeine}$. It worth noting that this plot is unique to the value of $U_{codeine,oral,COD}$ derived in Section O.2 of 0.64. Also plotted on the figure (indicated with a cross symbol) is the most relevant data available thus-far for $Y_{n,codeine}$ and $Y_{f,codeine}$; that is the data reported by Bound and Voulvoulis (2005) for painkillers. If the data of Bound and Voulvoulis (2005) are somewhat representative of what the actual

situation is within a population of interest with regards to the fraction of unused codeine and the further fraction of that is flushed, the contribution of the term $Y_{n,codeine} \cdot Y_{f,codeine}$ can safely be neglected without a significant loss in accuracy (see Figure O.1). However, if codeine-specific data suggest a substantially different value than those suggested by Bound and Voulvoulis (2005) for painkillers, such values could be plotted on Figure O.1 to assess if $Y_{n,codeine} \cdot Y_{f,codeine}$ can indeed be reasonably neglected. Nevertheless, since the data of Bound and Voulvoulis (2005) is the best available to date, the contribution due to $Y_{n,codeine} \cdot Y_{f,codeine}$ is neglected here. This allows one to isolate the desired variables as follows:

$$L_{codeine} \cdot (1 - Y_{n,codeine}) = \frac{1}{(U_{codeine,oral,COD})} \left[\frac{C_{codeine} \cdot Q_{in}}{P \cdot (1 - x_{codeine}) \cdot (EXP(-k_{d,codeine} \cdot t_s))} - u_{e,codeine} \right] \quad (O.8)$$

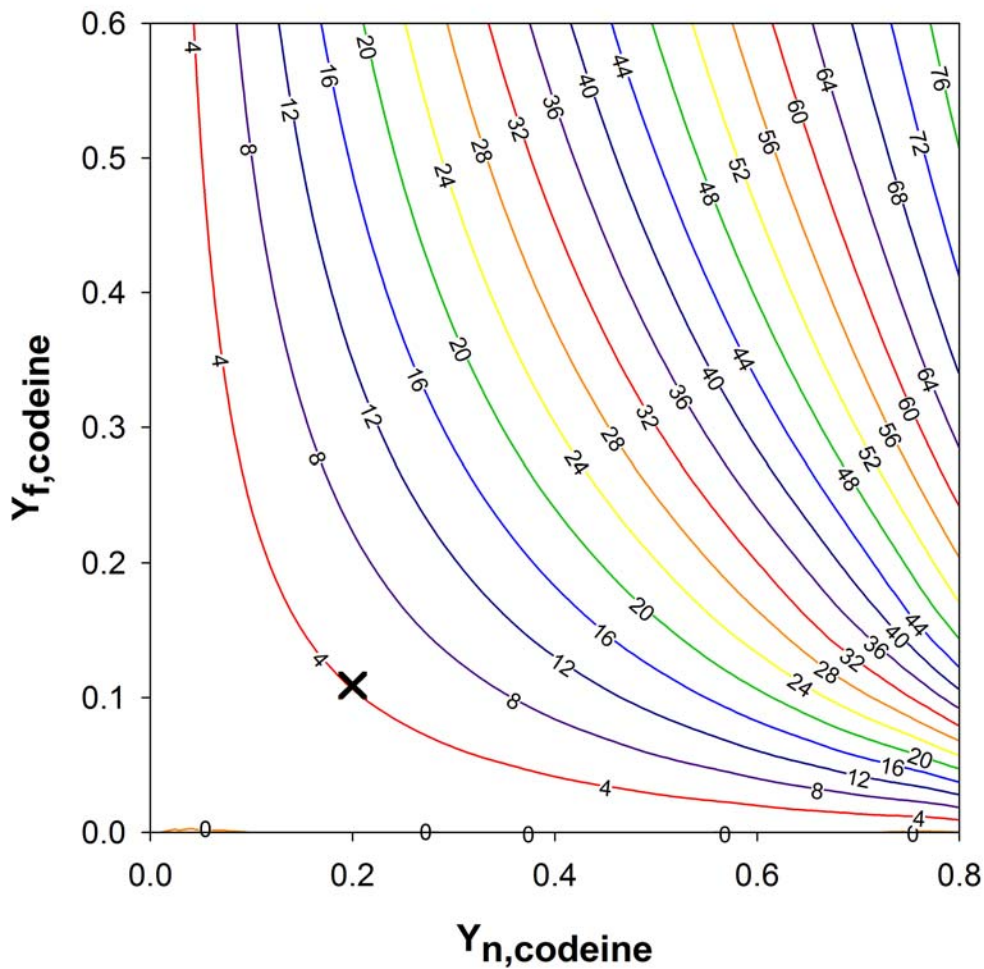


Figure O.1 Contribution contours of $Y_{n,codeine} \cdot Y_{f,codeine}$ to the term $(1 - Y_{n,codeine}) \cdot U_{codeine} + Y_{n,codeine} \cdot Y_{f,codeine}$ as a function of $Y_{n,codeine}$ and $Y_{f,codeine}$. Contribution contours were calculated using the function $[Y_{n,codeine} \cdot Y_{f,codeine} / ((1 - Y_{n,codeine}) \cdot U_{codeine,oral,COD} + Y_{n,codeine} \cdot Y_{f,codeine})] \cdot 100$ with $U_{codeine,oral,COD} = 0.64$ (see Table O.1). The cross symbol (x) represents the data for painkillers reported by Bound and Voulvoulis (2005).

The excretion profiling detailing in Appendix O.2 for medicinal and endogenous codeine allows one to further develop (O.8) to the following:

$$L_{\text{codeine}} \cdot (1 - Y_{\text{n,codeine}}) = \frac{1}{(0.64 \pm 0.14)} \left[\frac{C_{\text{codeine}} \cdot Q_{\text{in}}}{P \cdot (1 - x_{\text{codeine}}) \cdot (\text{EXP}(-k_{\text{d,codeine}} \cdot t_s))} - 0.25 \pm 0.52 \right] \quad (\text{O.9})$$

Additionally, x_{codeine} was established to be at most 0.2% (see Appendix C) and hence can be assumed to be equal to zero. Recognizing this, Equation (O.9) can be simplified to the following:

$$L_{\text{codeine}} \cdot (1 - Y_{\text{n,codeine}}) = \frac{1}{(0.64 \pm 0.14)} \left[\frac{C_{\text{codeine}} \cdot Q_{\text{in}}}{P \cdot \text{EXP}(-k_{\text{d,codeine}} \cdot t_s)} - 0.25 \pm 0.52 \right] \quad (\text{O.10})$$

Equation (O.10) is the suggested mass balance equation that can be used to estimate the mass of codeine that is actually consumed on a daily per capita basis by a population of interest, whether through prescriptions and/or as over-the-counter purchases, provided that the term that accounts for the fraction of sold codeine that ends up being flushed down the sinks and/or toilets can indeed be neglected.

Appendix P: Excretion Profiling of Ethylmorphine and Estimation of its Consumption using Measured Concentrations of Relevant SEMs in STP Influent

P.1 Excretion Profiling of Ethylmorphine

Administered ethylmorphine is eliminated in urine as free and glucuronide conjugates of ethylmorphine itself, morphine, norethylmorphine and normorphine (Aasmundstad et al., 1995). Of these, ethylmorphine (EMOR) and norethylmorphine (NEMOR) are unique to the consumption of ethylmorphine and are therefore good candidates as SEMs. Of the two, ethylmorphine (free + glucuronide conjugate fraction) is the major excretory metabolite, while norethylmorphine is released in lesser amounts (see Table P.1).

Table P.1 Urinary profile following administration of oral ethylmorphine.

Reference	Dose (mg)	n	Age (yr)	Duration (hr)	Fraction of administered dose (%)			
					Ethylmorphine (EMOR)		Norethylmorphine (NEMOR)	
					Total		Total	
					Free	Glucuronide Conjugated	Free	Glucuronide Conjugated
Popa et al. (1998)	22-45	10	22-53	48	33.3 ± 16.5		-	
Aasmundstad et al. (1995)	94	8	24	48	4.4 ± 1.7	41.1 ± 6.5	4.3 ± 1.4	4.6 ± 1.5
Hedenmalm et al. (1997)	22.4	4	21-39	15	32.3 ± 8.7		-	
$U_{EMOR,oral,s}$					37.5 ± 12.5		8.9 ± 1.9	

To our knowledge, data on the fecal disposition of ethylmorphine are currently not available in the literature. Nevertheless, the evidence from structurally and chemically similar compounds such as codeine and morphine (Abbott Labs, 2006; Adler et al., 1955) suggest that fecal elimination of ethylmorphine is expected to be of minor importance. Further, no data to our knowledge have been published reporting on the release of ethylmorphine or its metabolites through sweat. Nevertheless, the analysis in Appendix E suggests that such contributions are expected to be of negligible importance.

P.2 Estimating the Consumption of Ethylmorphine using Measured Concentrations of Relevant SEMs in STP Influent

EMOR and NEMOR are both SEM candidates that could potentially be used to estimate the mass of ethylmorphine consumed within a population of interest; however, to date, no attempts have been reported of measurements of either compound in STP influents. Of the two, NEMOR offers the advantage that its sewer loads are likely to be exclusive markers of ethylmorphine consumption. However, since it is excreted in lower quantities than EMOR, the consistent detection of NEMOR may be problematic. The disadvantage with choosing EMOR as a SEM is that its presence in sewers could either be due to the consumption of ethylmorphine and/or the direct flushing of unused ethylmorphine. Since both potential SEMs offer advantages and disadvantages and, further, the presence of neither has been investigated in STP influents, expressions to estimate $L_{EMOR}(1-Y_{n,EMOR})$ will be developed for both of these potential SEMs.

P.2.1 EMOR as a SEM

If EMOR is considered as a potential SEM, a theoretical development analogous to the one presented in Appendix O.3 allows one to suggest the following mass balance expression relating L_{EMOR} (i.e., mass of ethylmorphine sold to the population of interest) to C_{EMOR} (the measured concentration of ethylmorphine in the influent of a STP):

$$L_{EMOR} = \frac{1}{((1 - Y_{n,EMOR}) \cdot (U_{EMOR,oral,EMOR}) + (Y_{n,EMOR} \cdot Y_{f,EMOR}))} \left[\frac{C_{EMOR} \cdot Q_{in}}{P \cdot (1 - x_{EMOR}) \cdot \text{EXP}(-k_{d,EMOR} \cdot t_s)} \right] \quad (\text{P.1})$$

where: L_{EMOR} the daily per capita mass of ethylmorphine sold for medicinal purposes (μg of ethylmorphine/cap·d); $Y_{n,EMOR}$ is the fraction of clinical ethylmorphine sold that ends up not being used by the users (dimensionless); $U_{EMOR,oral,EMOR}$ is the molar fraction of L_{EMOR} that is expected to be excreted as ethylmorphine in the urine of users when administered orally (moles of ethylmorphine/mole of ethylmorphine); $Y_{f,EMOR}$ is the fraction of $Y_{n,EMOR}$ that is expected to be flushed down the toilets and/or sinks (dimensionless); $k_{d,EMOR}$ is first-order decay constant for ethylmorphine in sewers (hr^{-1}); C_{EMOR} is the dissolved concentration of ethylmorphine in the influent of the STP being monitored (μg of ethylmorphine/L); Q_{in} is daily flow arriving as the influent to the treatment plant (L/d); P is the population served by the STP; and x_{EMOR} is the typical fraction of ethylmorphine likely to be sorbed on to suspended solids (dimensionless), which can be estimated using Deo and Halden's model (see Equation (2) of main text).

The interest is in estimating the actual mass of ethylmorphine consumed by a population ($L_{EMOR} \cdot (1 - Y_{n,EMOR})$), rather than the mass sold to the population. $L_{EMOR} \cdot (1 - Y_{n,EMOR})$ can only be isolated from Equation (P.1) if the term $Y_{n,EMOR} \cdot Y_{f,EMOR}$ can be neglected without a significant loss in accuracy. Hence, it is worth considering the relative importance of such a term ($Y_{n,EMOR} \cdot Y_{f,EMOR}$) to the collective term ($Y_{n,EMOR} \cdot Y_{f,EMOR} / ((1 - Y_{n,EMOR}) \cdot U_{EMOR,oral,EMOR} + Y_{n,EMOR} \cdot Y_{f,EMOR})$). This has been attempted in Figure P.1. Again if the data of Bound and Voulvoulis (2005) is representative of the level of ethylmorphine flushed down the toilet, the term $Y_{n,EMOR} \cdot Y_{f,EMOR}$ can be neglected without a significant loss in accuracy (Figure P.1). Hence, the mass of ethylmorphine consumed by a population of interest ($L_{EMOR} \cdot (1 - Y_{n,EMOR})$) can be estimated from the measured influent concentrations of ethylmorphine (C_{EMOR}) using the following equation:

$$L_{EMOR} \cdot (1 - Y_{n,EMOR}) = \frac{1}{U_{EMOR,oral,EMOR}} \left[\frac{C_{EMOR} \cdot Q_{in}}{P \cdot (1 - x_{EMOR}) \cdot \text{EXP}(-k_{d,EMOR} \cdot t_s)} \right] \quad (\text{P.2})$$

Noting that ethylmorphine is expected to negligibly absorb on to suspended solids (see Appendix C) and the excretion profiling of unchanged EMOR detailed in Table P.1 suggests $U_{EMOR,oral,EMOR} = 0.375 \pm 0.125$, Equation (P.2) can be further simplified to the following:

$$L_{EMOR} \cdot (1 - Y_{n,EMOR}) = \frac{1}{0.375 \pm 0.125} \left[\frac{C_{EMOR} \cdot Q_{in}}{P \cdot \text{EXP}(-k_{d,EMOR} \cdot t_s)} \right] \quad (\text{P.3})$$

Equation (P.3) is the suggested mass balance equation that can be used to estimate the mass of ethylmorphine that is actually consumed on daily per capita basis by a population of interest provided that the term $Y_{n,EMOR} \cdot Y_{f,EMOR}$ can be neglected and that EMOR is indeed detectable in STP influents.

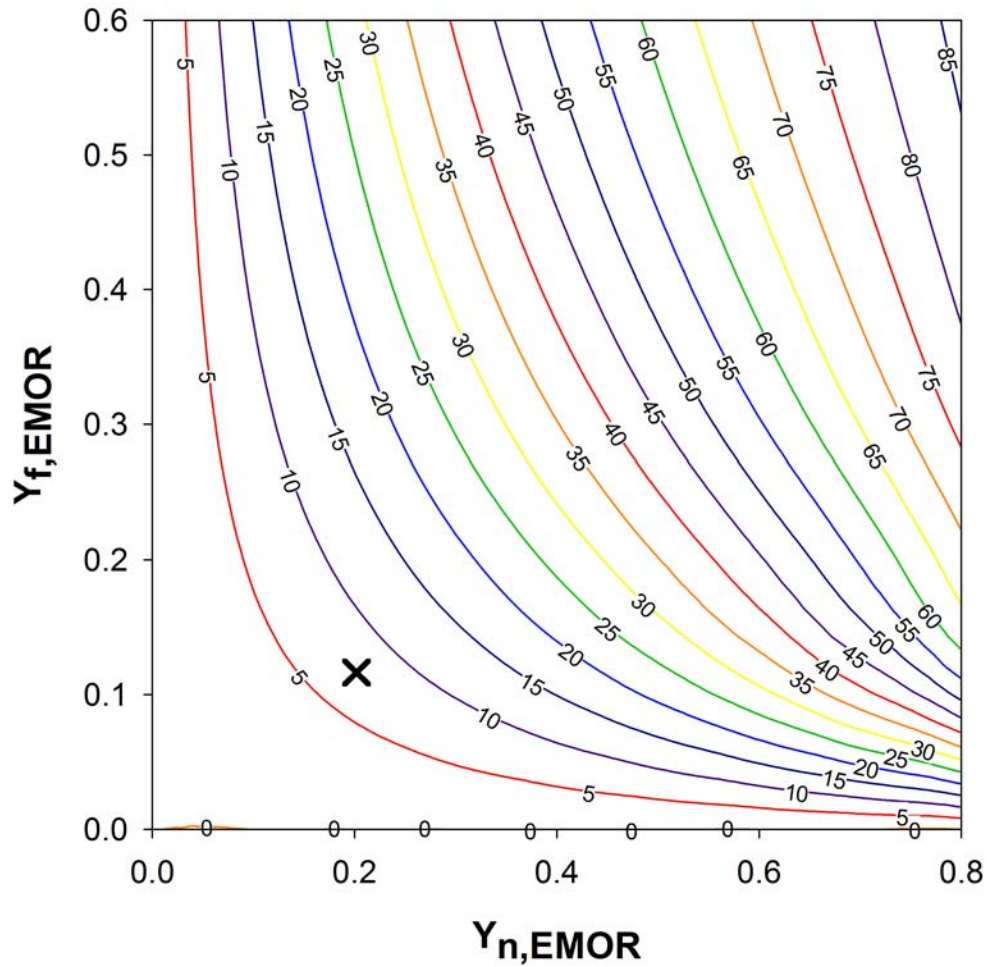


Figure P.1 Contribution contours of $Y_{n,EMOR}$ and $Y_{f,EMOR}$ to the term $(1 - Y_{n,EMOR}) \cdot U_{EMOR,oral,EMOR} + Y_{n,EMOR} \cdot Y_{f,EMOR}$ as a function of $Y_{n,EMOR}$ and $Y_{f,EMOR}$. Contribution contours were calculated using the function $[Y_{n,EMOR} \cdot Y_{f,EMOR} / ((1 - Y_{n,EMOR}) \cdot U_{EMOR} + Y_{n,EMOR} \cdot Y_{f,EMOR})] \cdot 100$ with $U_{EMOR,oral,EMOR} = 0.375$ (see Table P.1). The cross symbol (×) represents the data for painkillers reported by Bound and Voulvoulis (2005).

P.2.1 NEMOR as a SEM

If NEMOR is chosen as a sewer marker to establish the level of ethylmorphine actually consumed within a population, the following equation can be suggested:

$$L_{EMOR} \cdot (1 - Y_{n,EMOR}) = \frac{C_{NEMOR,in} \cdot Q_{in}}{P \cdot (\text{EXP}(-k_{d,NEMOR} \cdot t_s)) \cdot (1 - x_{NEMOR})} \cdot \frac{1}{U_{EMOR,oral,NEMOR}} \cdot \frac{MO_{EMOR}}{MO_{NEMOR}} \cdot \frac{Mw_{EMOR}}{MW_{NEMOR}} \quad (\text{P.4})$$

where: $U_{EMOR,Oral,NEMOR}$ is the molar fraction of L_{EMOR} that is expected to be excreted as norethylmorphine in the urine of users when administered orally (moles of ethylmorphine/moles of ethylmorphine); $k_{d,NEMOR}$ is first-order decay constant for norethylmorphine in sewers (hr^{-1}); $C_{NEMOR,in}$ is the dissolved concentration of norethylmorphine in the influent of the STP being monitored (μg of norethylmorphine/L); x_{NEMOR} is the fraction of norethylmorphine likely to be sorbed onto suspended solids (dimensionless), which can be estimated using Deo and Halden's model (see Equation (2) of main text); MO_{EMOR}/MO_{NEMOR} is the *in vivo* molar stoichiometry of metabolically converting EMOR to NEMOR (moles of ethylmorphine/mole of norethylmorphine); Mw_{EMOR} is the molecular weight of EMOR (g of moles ethylmorphine/ mole of ethyl morphine); and Mw_{NEMOR} is the molecular weight of NEMOR (g of moles norethylmorphine/mole of norethylmorphine).

Equation (P.4) can be further simplified if one recognizes that x_{NEMOR} is of negligible importance (see Appendix C), the respective structures of NEMOR and EMOR suggest that MO_{EMOR}/MO_{NEMOR} is equal to one, Mw_{EMOR}/MW_{NEMOR} is equal to 1.05, and that Table P.1 suggests that $U_{EMOR,Oral,NEMOR}$ is equal to $8.9 \pm 1.9\%$:

$$L_{EMOR} \cdot (1 - Y_{n,EMOR}) = \frac{C_{NEMOR,in} \cdot Q_{in}}{P \cdot (\text{EXP}(-k_{d,NEMOR} \cdot t_{sewer}))} \cdot \frac{1}{0.09 \pm 0.02} \cdot 1.05 \quad (\text{P.5})$$

Equation (P.5) is the proposed mass balance equation that can be used to estimate the mass of ethylmorphine that is actually consumed on daily per capita basis by a population of interest provided that NEMOR can be consistently detected in STP influents. Further, since NEMOR is a minor urinary metabolite, the unaccounted for fecal release of such an SEM could be important. If this is indeed established to be the case in the future, such fractions must be accounted for in the above equation.

Appendix Q: Parameterization of Inputs of Equation (12)

At present, the level of detailed knowledge that Equation (12) requires as inputs may not be fully available for a particular region; hence it is of particular interest to further discuss the approach that should be used for the parameterization of the variables and constants of the equation. The aim of the discussion below will be to identify: (i) the manner in which variables can be quantified; (ii) knowledge gaps that currently prevent the reliable quantification of certain inputs and variables into the equations and, in doing so, to develop a list of research needs to be addressed, and (iii) the best available approximations that can be made for the inputs and variables that we cannot confidently quantify at present. In the latter case, it is important to that one should be aware of the limitations when making such approximations and these are discussed. The variables and inputs required to convert measured concentrations of an SEM to prevalence measures will be discussed in the logical sequence presented in Figure Q.1.

A first step that is required is to assess the total daily per capita load ($J_{T,s}$) of the SEM arriving in the influent of the STP being monitored using Equation (1). A sewer epidemiology investigation must ensure that the samples that have been collected are indeed representative; in this respect, the critical review of Ort et al. (2010) is invaluable for guidance. Once representative samples have been collected, the reliability of the influent concentration of the selected SEM, C_{in-s} , is dependent on the reproducibility and the robustness of the analytical methods used. Thus far, for most potential SEMs of interest here (i.e., BE, MOR, 6MAM, ECD, COE and MDMA), robust analytical methods that allow for the detection of trace concentrations (i.e., ng/L) of these SEMs in STP influents have already been developed and are being used in the field; e.g., see Positgo et al. (2008) and Bisceglia et al. (2010). In contrast, the development of analytical techniques may be required for other potential SEMs. For example, a major knowledge gap in need of attention is to establish the methods for the reliable detection and quantification of HMMA in wastewaters, which is theoretically the most suitable SEM for MDMA.

The daily flow to the treatment plan (Q_{in}) in most instances can be accurately measured. Direct measurement of the population served by the treatment plant (P) is often known or easily estimated, but in instances where this is not the case, it can be estimated through the use of anthropogenic markers. Some markers that have been used in the field include phosphorus, nitrogen, chemical and biological oxygen demand measurements (van Nuijjs et al., 2011) and creatinine levels (Chiaia et al., 2008). Another interesting marker, in this respect, may be the use of artificial sweeteners (Buerge et al., 2009). Preferably, the chosen anthropogenic marker should be such that it demonstrates reasonable stability during the sewer transit process. It is also worth noting that the use of an appropriate anthropogenic marker to estimate P is particularly advantageous in towns that experience a large daytime influx of commuters.

When selecting an appropriate SEM, it is desirable that it not have a tendency to adsorb onto suspended solids found in wastewaters, as was the case for all SEMs explored in this paper in which the fraction of an SEM likely to be sorbed onto influent suspended solids, x_{s-s} , is expected to be of negligible importance (see Appendix C). In cases where this is not possible, x_{s-s} can be estimated by spiking samples with an internal standard before the samples are filtered off for further analysis. As an alternative, the model of Deo and Halden (2010) may be used to estimate the fraction adsorbed. Both of the latter approaches introduce their own additional errors into estimates of the prevalence of illicit drug use.

Overall, by ensuring that representative samples are taken and accurately quantifying C_{in-s} , Q_{in} , P and x_{s-s} , Equation (1) can be used to reliably establish $J_{T,s}$ (g of SEM detected/day per inhabitant) for an SEM of interest. However, depending on the selected SEM, $J_{T,s}$ may need to be further adjusted to account for the degradation of the SEM ($k_{d,s}$) during sewer transit and the amount of SEM detected in the influent that

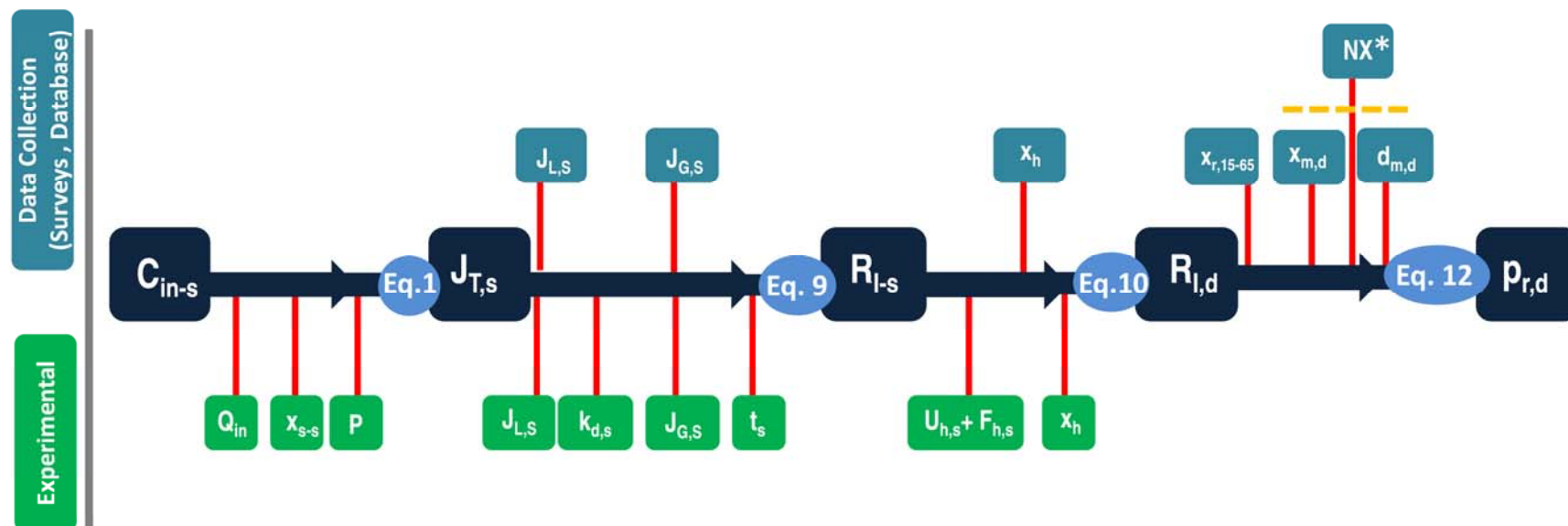


Figure Q.1 Variable parameterization required, as well the means (experimental and/or surveys/databases) to do so, to convert measure measured influent concentration of an SEM (C_{in-s}) into the prevalence of parent drug abuse ($p_{r,d}$) within a population being monitored. See Appendix A for the definition and units of each variable represented in the figure.

(*) only relevant for the SEM HMMA.

may result from licit uses of other drugs ($J_{L,s}$) and from in-transit generation of the SEM due to the degradation of other sewer-borne contaminants loads ($J_{G,s}$) to yield the amount of the SEM excreted per day per inhabitant, $R_{L,s}$. As demonstrated in the main body, for the specific SEEBs for cocaine, heroin and MDMA, the lack of definitive data forced us to rely on plausible deductions to establish the sewer behaviour of the selected SEMs (i.e., $k_{d,s}$ and $J_{G,s}$). Hence there is a need to concretely verify the assumptions made here by further studying the sewer behaviour of the selected SEMs. If the degradation and generation of a SEM in the sewer is established to be of significance, a sewer epidemiology investigation must also ensure that sewer transit times (t_s) can be reasonably estimated.

Of the potential SEMs, $J_{L,s}$ is a major issue for the heroin metabolite MOR. The analysis in Section 3.4.3 suggests that important licit contributions to the net sewer loads of MOR include the clinical use of morphine, codeine and ethylmorphine. Excretion profiling in Appendix J comprehensively established the fractions of these clinical formulations that are converted to MOR (i.e., $U_{b,i,s} + F_{b,i,s}$ and $U_{s,e,s} + F_{s,e,s}$). Besides these, to fully quantify and hence correct for licit contributions to the net sewer loads of MOR, five variables needed to be parameterized: i.e., L_s , L_b , $Y_{n,s}$, $Y_{f,s}$, $Y_{n,b}$. Specifically, the population's consumption of morphine ($L_{\text{morphine}} \cdot (1 - Y_{n,\text{morphine}})$), codeine ($L_{\text{codeine}} \cdot (1 - Y_{n,\text{codeine}})$) and ethylmorphine ($L_{\text{ethylmorphine}} \cdot (1 - Y_{n,\text{ethylmorphine}})$) and the fraction of morphine sold that ends up being flushed down toilets and/or sinks ($Y_{n,\text{morphine}} \cdot Y_{f,\text{morphine}}$) need to be established. Data for relevant L_b values (ethylmorphine and codeine) and L_s (morphine) are available for most countries either through national databases (e.g., DEA (2008) and/or IMS Health (2010)) as shown in the compilation presented in Appendix K. Further, IMS Health (2010) and certain national databases can provide data on a regional scales relevant to sewer epidemiology investigations. However, to use such sales data, knowledge of a population's $Y_{n,b}$, $Y_{n,s}$ and $Y_{f,s}$ values is required. Further, as introduced earlier, codeine is available over-the-counter in certain countries and such sales may be difficult to track. An interesting sewer-based approach to establish a population's consumption of codeine and ethylmorphine ($L_{\text{codeine}} \cdot (1 - Y_{n,\text{codeine}})$ and $L_{\text{ethylmorphine}} \cdot (1 - Y_{n,\text{ethylmorphine}})$) could be through the use of relevant sewer markers. Specifically, unchanged codeine and unchanged ethylmorphine and/or norethylmorphine could be used to establish a population's direct consumption of ethylmorphine and codeine (see Appendices O and P for relevant equations and development). Such an approach assumes that the fraction of ethylmorphine and codeine that is not used and is subsequently flushed down the toilet and/or sinks can be neglected without a significant loss in accuracy, which seems to be the case based on the best available information we have thus far (see Appendices O and P). Such a marker-based measurement of clinical morphine loads is not possible since no unique marker currently exists that is produced exclusively due to the consumption of clinical morphine. Hence, one has no choice but to rely on national prescription databases and IMS Health data to establish L_{morphine} . In the case of $Y_{n,\text{morphine}}$ and $Y_{f,\text{morphine}}$, the best available data is that of Bound and Voulvoulis (2005), who report such values for painkillers collectively. Hence, to-date, specific data for morphine has not been published, therefore there is a need to firmly establish such information. Encouragingly, more and more work is being done to better understand the disposal of unused medications by various national populations (Tong et al., 2011). Such data, which in most instances looks at pharmaceutical disposal from a collective perspective, suggests that flushing of medications is lesser of an issue in European countries than others (Tong et al., 2011). Lastly, the error analysis summarized in Appendix R suggests that if the values reported by Bound and Voulvoulis (2005) are somewhat representative of the magnitudes of $Y_{n,\text{morphine}}$ and $Y_{f,\text{morphine}}$, the fraction of morphine sold that is flushed down toilets and/or sinks (i.e., $Y_{n,\text{morphine}} \cdot Y_{f,\text{morphine}}$) can be neglected in Equation (18b) without introducing an appreciable error in the fraction of clinical morphine released to sewers. Overall, it is important to recognize that a detailed understanding of the aforementioned considerations related to the licit sources of MOR are of more importance to countries where a less-than-predominant fraction of the net sewer load of MOR is expected to arise due to the consumption of heroin.

Once $R_{I,s}$ (g of SEM excreted/day per inhabitant) has been established, the next step involves estimating $R_{I,d}$ (g of parent illicit drug consumed/day per inhabitant) through the use of Equation (10). At this stage, three key pieces of information are required: first, the specific disposition data for each route-of-administration of the parent illicit drug for the SEMs of interest (i.e., $U_{h,s} + F_{h,s}$ values); secondly, the various routes used to administer an illicit drug of interest (i.e., h); and, lastly, the relative proportions (i.e., mix) with which the various route-of-administrations are preferred by abusers (i.e., x_h values). The importance of accounting for route-of-administration considerations can be demonstrated by recognizing that, all else being equal, a predominately cocaine-smoking population would need to abuse 2.2 times more cocaine to yield similar sewer loads of BE (i.e., cocaine's SEM) to a population that predominantly consumes cocaine through nasal insufflation (see excreted fractions for BE in Table 1). Coincidentally, 2.2 times more heroin would also need to be abused to generate similar levels of MOR in STP influents in regions where chasing of heroin predominates compared to regions where intravenous injection of heroin is the predominant route (see excreted fractions for MOR in Table 2).

When considering excreted fractions of an SEM of interest for all relevant routes-of-administration (i.e., $U_{h,s} + F_{h,s}$ values), a sufficient level of data is available for BE and MOR (Tables 1 and 2). That being said, a need exists to further explore the significance of the effect of ethanol co-abuse on the excretion of BE. For other SEMs of interest, certain key disposition data still needs to be established; i.e., 6MAM (urinary and fecal disposition following nasal insufflation and chasing of heroin and fecal disposition following intravenous injection), HMMA (the lowest MDMA dosage at which the urinary HMMA excretions level off), ECD (cumulative urinary and fecal fractions excreted), MDMA (urinary disposition at low dose levels) and COE (route-of-administration and dose-response effects on the cumulative urinary and fecal excretions).

Typical routes-of-administration (h) for illicit drugs are quite well established. As examined earlier in Section 3, MDMA is primarily administered orally. Cocaine use for most populations can be accounted for by only considering those who nasally insufflate and smoke the drug, whereas the routes-of-administration of significance for heroin abuse include its intravenous injection, chasing and nasal insufflation.

The mix of routes-of-administration that an abusing population chooses to administer a drug (x_h) is a more difficult parameter to directly quantify. Ideally such information would be obtained by surveying the abusing population but, when this is not possible due to study limitations, approximations can be made. For example, MDMA is a relatively simple case since it is predominately abused orally (Battisti et al., 2006; EMCDDA, 2010; Topp et al., 1999; White et al., 2006). In contrast, for cocaine and heroin, the route-of-administration mix reported by the respective treatment populations was considered to be a reasonable approximation of the preferences of abusers in the general population. The rationale for this is explained below.

A given heroin-abusing population can be broadly classified into two subpopulations; those that are chronic users and those that are occasional/experimental users (Bretteville-Jensen and Amundsen, 2009; Moore et al., 2005). When heroin prevalence measures are furnished by monitoring agencies such as EMCDDA (2010) and UNODC (2010), they are typically reported for the chronic abusing subpopulation, since it is this sub-population which is of particular interest. In addition, chronic heroin abusers are reported to consume between 90 and 98% of the total mass of heroin in countries where such estimates are available (Bretteville-Jensen and Amundsen, 2009; Moore et al., 2005). Such considerations are of importance since it is the mass load of a relevant SEM (i.e., MOR and 6MAM) which is being back-extrapolated in sewer epidemiology investigations. Hence, for heroin, it is the chronic abusers which is the population of interest and which consumes the predominate mass of heroin. Estimates from the Netherlands suggest that approximately 71% of the problem heroin users in that country were in contact with treatment services at least once in the previous year (Blanken et al., 2010). Further, EMCDDA

(2010b) and UNODC (2010a) often use treatment population data as one measure for estimating the size of opioid abuse within a national population. Hence, the population of heroin abusers within a treatment program appears to be a reasonably representative subset of the relevant heroin-abusing population. Therefore, to quantify x_h values for heroin abuse, the readily available route-of-administration mix reported by heroin abusers undergoing treatment may be the best possible approximation one can make without explicitly conducting a survey of the population of interest. Nevertheless, it is of interest to firmly establish whether the route-of-administration mix reported by a heroin population in treatment programs can be considered as a suitable surrogate for the whole abusing population.

In comparison to heroin, cocaine has a fairly large recreational population of users, with estimates suggesting that 83% and 71% of abusers in Europe and the USA, respectively, are light users of cocaine, while the remaining can be considered to be heavy or chronic users (Kilmer and Pacula, 2009). However, it is the minor fractions of heavy abusers in both regions that are responsible for abusing 75% of the net amount of cocaine consumed within a given year (Kilmer and Pacula, 2009). Such mass considerations are important since it is the total mass of BE (i.e., cocaine's SEM) that is measured downstream at STP influents. Hence, from a mass load perspective, the routes-of-administration used by chronic abusers is expected to have the predominant influence on the mass load found in the sewers. Recognizing this and the fact that the population in substance-abuse treatment programs are predominantly expected to be a subset of the chronic abusing population, a first approximation that can be made for the x_h values for cocaine is that the route-of-administration mix reported by abusers undergoing treatment is representative of the routes used by the abusing population as a whole. This assumption for x_h values for cocaine was used to predict the influent concentrations of BE in Figure 1, for which it must be reiterated that the aim of this analysis was to generate estimates so that one could assess the detectability selection criteria for BE rather than develop a predictive model. Arguably, another approach to estimating the values of x_h for cocaine abuse would be to assume that all chronic abusers use cocaine with the routes-of-administration mix reported by those in treatment, while all recreational users tend to nasally insufflate cocaine. If such an assumption is made for x_h values, as opposed to the one where the whole cocaine population abuses the drug with the route-of-administration mix reported for the treatment population, the European influent concentration of BE would be altered by -4% to +8% (see Figure S.3). A more significant effect of 18% would result for the USA and, hence, Canadian estimates, since the route-of-administration mix for Canada was assumed to be similar to those reported for the USA (see Figure S.3). Regardless of the assumptions made to evaluate x_h , discussed above, the conclusion about the detectability of BE in various national influents is still valid, as is the comparison of generated estimates to measured data (see Figures S.1 and S.2). Nevertheless, it remains uncertain whether either of the aforementioned approximations for the x_h values for cocaine are suitable surrogates. But what is certain is that, since chronic abusers are expected to use the predominant amount of cocaine within a region, a detailed understanding of their route-of-administration carries more significance than those of light users. It is worth noting that sewer epidemiology itself might provide the best solution to concretely estimate x_h values for a cocaine-abusing population of interest in that, if one limits the x_h values to nasal insufflation and smoking of cocaine (i.e., the two major routes reported in most populations), then the level of cocaine smokers within a population (x_{smoke}) could conceivably be deduced from levels of ECD (i.e., the sewer marker for smoked cocaine) in STP influents.

Based on the above, the value of $R_{l,d}$ (g of illicit drug consumed/day per inhabitant) can be derived using Equation (10). This value is an established measure of the prevalence of drug use (e.g., Zuccato et al, 2008), which can be compared with other estimates conducted over geographical and temporal scales.

The last step in estimating the prevalence of an illicit drug within a population of interest from $R_{l,d}$ involves using Equation (12). In order to do this, the parameterization of xr_{15-64} , m , $x_{m,d}$ and $d_{m,d}$ is needed.

Further, it is worth recalling that if HMMA is chosen as the SEM of choice to track ecstasy abuse, the parameterization of NX is sought rather than the combination of m , $x_{m,d}$ and $d_{m,d}$.

The fraction of the population that is 15-64 years of age, xr_{15-64} , is a parameter that ensures that data are appropriately standardized to the population cohort that is largely responsible for abusing illicit drugs. The xr_{15-64} value for a given population can be estimated through census data.

When considering the different abusing groups (m) for the various illicit drugs of interest, our present understanding supports treating heroin and ecstasy abusers as a single population (Kilmer and Pacula, 2009). The case of cocaine is slightly more complicated in that the abusing population is typically considered to be composed of heavy and light abusers (Kilmer and Pacula, 2009). If one is willing to accept the nature of heroin and ecstasy abusers as a single population, the value of $x_{m,d}$ by definition becomes equal to one. However, the net yearly amount of illicit drug demanded/consumed by the group, $d_{m,d}$, is a more difficult parameter to estimate for both. Ideally such a parameter would be obtained by surveying the relevant populations on their consumption trends and establishing the street level purity of the drug. The latter dataset may be available through local police forensic services. In the absence of such data, regional average numbers (i.e., on national scales) that are available through such sources as Kilmer and Pacula (2009), UNODC (2010) or Paoli et al. (2009) may be used as surrogates. Similarly, to establish $x_{m,cocaine}$ and $d_{m,cocaine}$ values for a cocaine-abusing population, preference should be given to surveying the population of interest for such consumption trends and establishing the purity of street level cocaine, but as a last resort, regional estimates furnished by UNODC (2010) or Kilmer and Pacula (2009) can be used instead.

Appendix R: Relative Importance of Flushing Clinical Morphine to the Net Fraction of Such a Formulation Released to Sewer

In Figure R.1 below, the percent contribution contours (i.e., expressed as $[Y_{n,MOR} \cdot Y_{f,MOR} / ((1 - Y_{n,MOR}) \cdot (U_{MOR} + F_{MOR}) + Y_{n,MOR} \cdot Y_{f,MOR})] \cdot 100$) are plotted as a function of $Y_{n,MOR}$ and $Y_{f,MOR}$. The purpose of this plot is to establish at what values of $Y_{n,MOR}$ and $Y_{f,MOR}$ the relative contribution of the morphine flushed down the toilet ($Y_{n,MOR} \cdot Y_{f,MOR}$) is of insignificance relative to the net fraction of sold morphine that is expected to be released to sewers (i.e., $(1 - Y_{n,MOR}) \cdot (U_{MOR} + F_{MOR}) + Y_{n,MOR} \cdot Y_{f,MOR}$). Also plotted as a single data point is the best available data for $Y_{n,MOR}$ and $Y_{f,MOR}$ available thus far; that is, the data of Bound and Voulvoulis (2005) for painkillers.

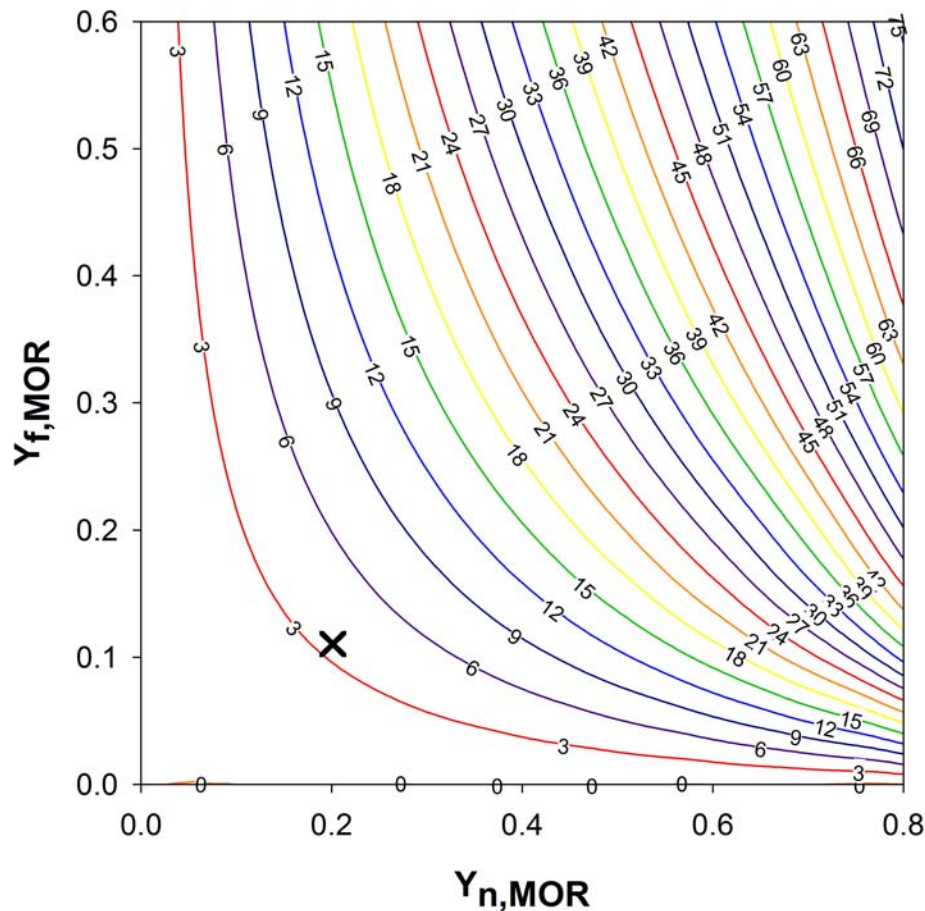


Figure R.1 Contribution contours of $Y_{n,MOR} \cdot Y_{f,MOR}$ to the term $(1 - Y_{n,MOR}) \cdot U_{MOR} + Y_{n,MOR} \cdot Y_{f,MOR}$ as a function of $Y_{n,MOR}$ and $Y_{f,MOR}$. Contribution contours were calculated using the function $[Y_{n,MOR} \cdot Y_{f,MOR} / ((1 - Y_{n,MOR}) \cdot (U_{MOR} + F_{MOR}) + Y_{n,MOR} \cdot Y_{f,MOR})] \cdot 100$ with $U_{MOR} + F_{MOR} = 0.777$ (see Table I.1). The cross symbol (x) represents data for painkillers reported by Bound and Voulvoulis (2005).

If the data of Bound and Voulvoulis (2005) can be considered to be somewhat representative of what the actual situation is within a population of interest with regards to the fraction of unused morphine and the further fraction of that is flushed (see Figure R.1), it is concluded that the contribution of the term $Y_{n,MOR} \cdot Y_{f,MOR}$ can be neglected without a significant loss in accuracy. Furthermore, if local data suggest otherwise, the plot also can be used to suggest at what combinations of $Y_{n,MOR}$ and $Y_{f,MOR}$ the contribution of the term $Y_{n,MOR} \cdot Y_{f,MOR}$ can become significant and hence cannot be neglected from the analysis.

Appendix S: Effect of Route-of-Administration Mix Chosen for a Particular National Cocaine-Abusing Population on the Influent Concentrations of BE

For Figures 1(A) and (B), in order to furnish the estimates for BE in various national influents it was assumed that, for most countries, the route-of-administration mix (i.e., the relative fractions of abusers that choose various routes-of-administration) with which the entire cocaine using population abused the drug was similar to the mix reported by cocaine abusers in the respective nation's treatment programs. However, an alternative assumption that could have been made was that only chronic abusers use the route-of-administration mix reported by the abusing population in treatment, while all recreational users nasally insufflate cocaine. With such an assumption, Figures S.1 and S.2 would have resulted instead of Figures 1(A) and 1(B). The discrepancy that the revised assumption induces in the predicted influent concentrations of BE is summarized in Figure S.3. This figure suggests that the revised assumption would only alter the European nationally-averaged influent concentrations of BE by -4% to +8%. The effect on the USA estimate is more significant at 18%.

Overall, Figures S.1 to S.3 suggest, regardless of which ever assumption is made about the route-of-administration mix, the conclusion about the detectability of BE various national influents remains the same as does the comparison of generated estimates to measured data (see Section 3.1.3 main text).

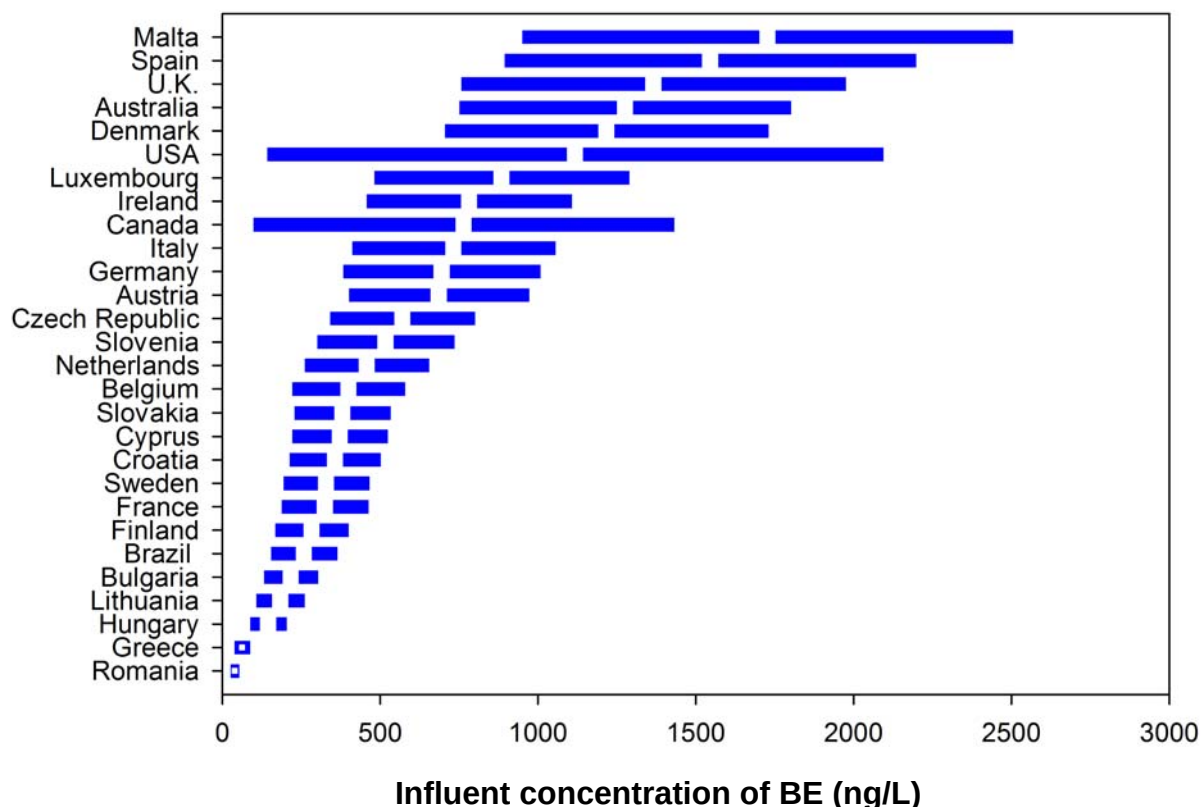


Fig. S.1 Theoretically-derived national estimates (■) of BE concentrations in the influents of various countries. Concentrations were established in a similar manner as described in Appendix G for Figure 1(A), with the only difference being that for Figure S.1 it is assumed that only chronic abusers use

the drug with the treatment route-of-administration mix while all recreational users nasally insufflate the cocaine.

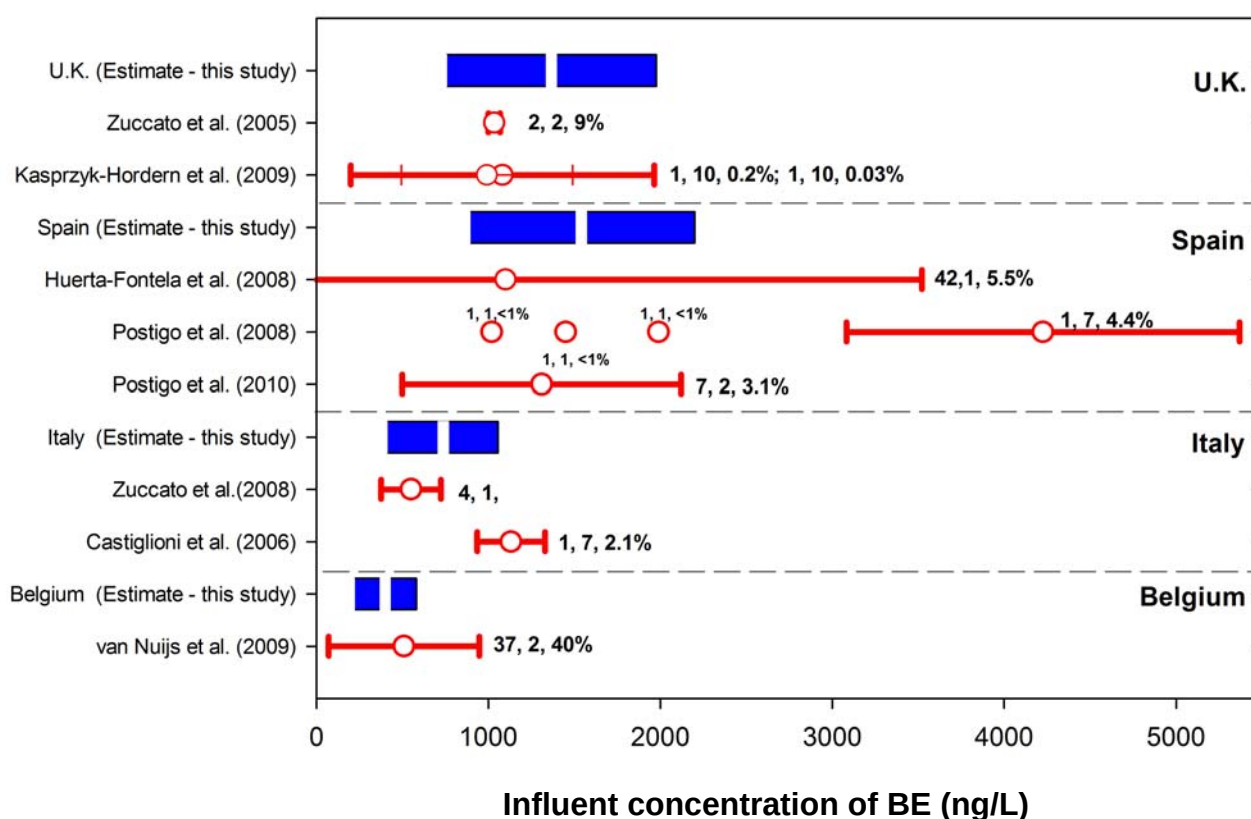
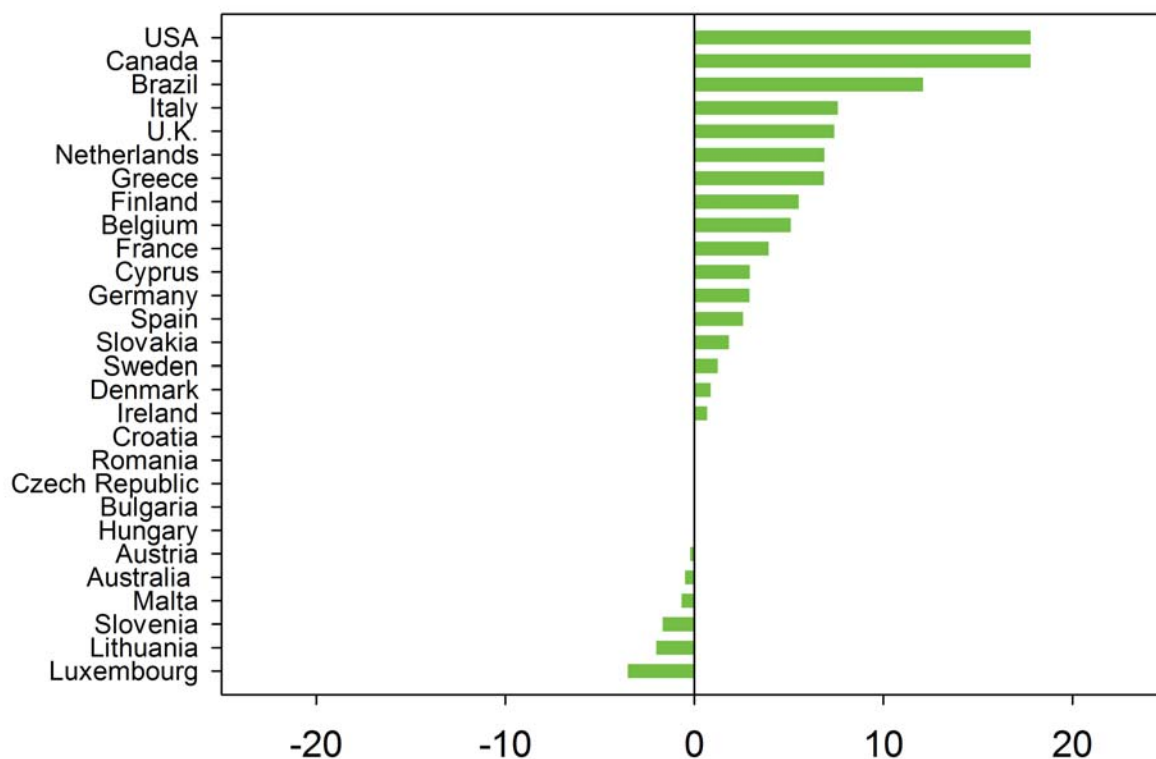


Figure S.2 Comparison of theoretically-derived (■ ■) nationally-averaged influent concentrations of BE (Figure S.1) to those reported in sub-national monitoring studies (○—○). For monitored data, hollow circles represent means reported by each study while plotted error bars represent standard deviations of the reported values. The numerical values next to the monitored data represent, in order, spatial extent, temporal extent and percentage national coverage. Spatial extent is represented by the number of STPs monitored in the investigation; temporal extent is represented by the number of days each STP was monitored, and national coverage is the percentage of the national population that was contributing wastewater to the STPs monitored by a given study.



Discrepancy in nationally-averaged theoretically-derived influent concentrations of BE (%)

Figure S.3 Discrepancy induced in the theoretically-derived nationally-averaged concentrations of BE in various national influents by the two assumptions about the route-of-administration mix used by a nation's cocaine abusing population. Estimated as follows: Percent discrepancy = $((\text{Estimates from Figure S.1} - \text{Estimates from Fig 1(A)}) / (\text{Estimates from Figure 1(A)}) \times 100\%)$.

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Appendices for Chapter 7

Supplementary Information for Chapter 7

Sewer epidemiology mass balances for assessing the illicit use of methamphetamine, amphetamine and tetrahydrocannabinol

Appendix A

Estimating the fraction of an SEM expected to be absorbed onto influent suspended solids

Appendix B

General source models for the S(+) and R(-) enantiomers of MAMP

Appendix C

Establishing the mass and the enantiomeric nature of illicit MAMP consumed by selected populations

Appendix D

Consumption of licit formulations that are metabolized to MAMP and/or AMP in selected populations

Appendix E

Data sources and procedures used to establish substance flows of MAMP

Appendix F

Predicted licit loads of MAMP in 18 national populations

Appendix G

Establishing the mass and the enantiomeric nature of illicit AMP consumed by selected populations

Appendix H

General source models for the S(+) and R(-) enantiomers of AMP

Appendix I

Data sources and procedures used to establish substance flows of AMP

Appendix J

Predicted licit loads of AMP in 17 national populations

Appendix K

Analyzing the importance of LDAMP as a source of AMP to sewer

Appendix L

Speciation of THC-COOH

Appendix M

Suitability of smoked MAMP disposition data of Cook et al. (1993) from a sewer epidemiology perspective

Abbreviations used in all appendices: AMP, amphetamine; DDD, defined daily dose; NSDUH, National Survey on Drug Use and Health; MAMP, methamphetamine; OH-AMP, hydroxyamphetamine; OH-MAMP, hydroxymethamphetamine; SEEB, sewer epidemiology extrapolation mass balance; SEM, sewer epidemiology metabolite; TEDs-A, Treatment Episode Data Set; THC, tetrahydrocannabinol; 11OH-THC, 11-hydroxy-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-tetrahydrocannabinol

Appendix A: Estimating the fraction of an SEM expected to be absorbed onto influent suspended solids

The fraction of a candidate SEM that would be expected to be absorbed onto influent suspended solids can be estimated using the equilibrium partitioning model of Deo and Halden (2010). Mathematically, their model can be expressed as follows:

$$x_{s-s} = 1 - \frac{1}{1 + x_{oc} \cdot D_{oc-s} \cdot C_{ss}} \quad (\text{A.1})$$

where: x_{oc} is the fraction of influent suspended solids that is organic carbon, for which a typical value for municipal suspended solids is 0.43 (Braga et al., 2005); D_{oc-s} is the organic carbon–water distribution coefficient (L/kg) at relevant pH values, which can be predicted using ACD Labs’ property prediction software (2010); and C_{ss} is the average concentration of suspended solids in the influent of a wastewater treatment plant, for which a typical value in municipal wastewater is 175×10^{-6} kg/L (Qasim, 1999).

D_{oc-s} and, hence, x_{s-s} were evaluated at pH values of 7.5 and 2.0. An evaluation at pH 7.5 (i.e., which corresponds to the mean pH of wastewaters (Qasim, 1999)) represents the case where the influent samples have been filtered before they are preserved through acidification. An evaluation at pH 2.0 represents the case where the influents are preserved through acidification by adjusting the pH to this level before the suspended solids are filtered off (Deo and Halden, 2010).

Estimated x_{s-s} values for all candidate SEM’s are summarized in Table A.1.

Table A.1 Estimated x_{s-s} values for candidate SEMs for the various illicit drugs of interest.

Illicit Drug	Candidate SEMs	D_{OC-S} (L/kg) ^(a)		x_{s-s} (%) ^(b)	
		pH 2.0	pH 7.5	pH 2.0	pH 7.5
AMP	AMP	1.0	1.9	< 0.01	< 0.01
	HO-AMP	1.0	1.0	< 0.01	< 0.01
MAMP	MAMP	1.0	1.4	< 0.01	< 0.01
	HO-MAMP	1.0	1.0	< 0.01	< 0.01
THC	THC	125,000	124,000	90.4	90.3
	11OH-THC	19,600	19,350	59.6	59.3
	THC-COOH	17,100	147	56.3	1.3

(a) ACD Labs (2010); (b) Estimated using Eq. (A.1).

Appendix B: General source models for the S(+) and R(-) enantiomers of MAMP

General source models for the S(+) and R(-) enantiomers of MAMP were developed (see Fig. B.1) by considering the various licit and illicit sources for the two enantiomers, the excretion profiling of MAMP precursors (see Table 2), and the excretion profiling of MAMP (see Table 1).

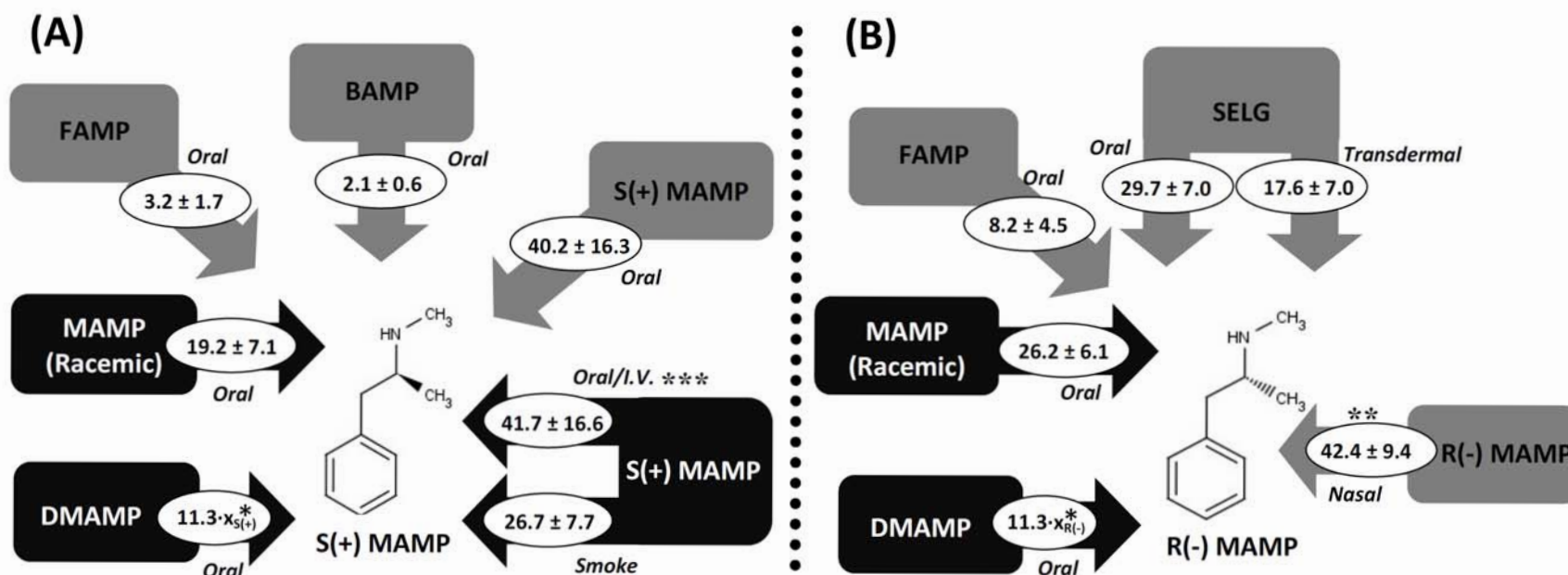


Fig. B.1 General source model for (A) the S(+) enantiomer of MAMP and (B) the R(-) enantiomer of MAMP. All excreted fractions expressed as a percentage of administered dose, unless otherwise indicated, were obtained from the compiled data presented in Tables 1 and 2. All licit and illicit sources are shown in gray and black, respectively. **Precursor abbreviations:** benzamphetamine (BAMP); dimethylamphetamine (DMAMP); famprofazone (FAMP); methylamphetamine (MAMP); selegiline (SELG).

(*) The enantiomeric disposition of DMAMP has not been reported in literature to date; $x_{S(+)}$ and $x_{R(-)}$ are the fractions of MAMP that are excreted as the S(+) and R(-) enantiomers, respectively; (**) Due to the lack of actual experimental data for the disposition of nasally-administered R(-) MAMP, an approximate value was estimated by multiplying the reported bioavailability of nasally-administered MAMP of 79% (Harris et al., 2003) by the fraction of intravenously-administered R(-) MAMP that is excreted unchanged (see Table 1); (***) Derived from pooling Oral and I.V. data for S(+) MAMP as compiled in Table 1.

Appendix C: Establishing the mass and the enantiomeric nature of illicit methamphetamine (MAMP) consumed/demanded by selected populations

Details are presented below to describe how the amount of illicit MAMP (i.e., $\sum N_{MAMP,q}$ values) used within three national markets were estimated for the year 2006.

C.1 United States of America

The National Survey on Drug Use & Health (NSDUH) suggests that there were 1.89 million users of MAMP in the United States in 2006, (SAMHSA, 2009a). A typical granular level at which the U.S.A. household surveys collect data is “last-month” users as opposed to “last-year” users (SAMHSA, 2009a). Such data can be used to define light users of MAMP as those who have used the drug in the last-year but not in the last-month and heavy users as those who have used MAMP in the last-month (Kilmer and Pacula, 2009). Using such an interpretation, data reported in the NSDUH (SAMHSA, 2009a) can be used to estimate that in 2006 there were 731,000 and 1,159,000, heavy and light users of MAMP, respectively, within the American population. Further, our analysis of the NSDUH data suggest that, on average, heavy users administered MAMP on 122.2 days of the year, while, recreational users of MAMP used the drug on 43.8 days of the year (SAMHDA, 2006a). In addition, on each day-of-use; heavy users are estimated to use 0.40 g of street-purity MAMP, while light users can be estimated to administer on average 0.25 g of street-purity MAMP on their day-of-use (Kilmer and Pacula, 2009). The average purity of seized MAMP in 2006 was 51% (NDIC, 2008). Further, illicitly-produced MAMP is in the form of its hydrochloride salt (HCl), hence the quantities must be corrected for the molecular weight of the associated salt by multiplying by 0.803. Lastly, Kilmer and Pacula (2009) suggested that, as the best approximation, 33% of MAMP users can be assumed to under-report their use of the drug. Using the above listed information one can estimate the mass demanded by light users of MAMP in 2006 to be:

$$N_{d,light} = \frac{\text{Number of light users} \times \text{days of use/yr} - \text{light users} \times \text{quantity used per day} - \text{light users} \times \text{purity} \times \text{salt adjustment}}{\text{Adjustment for under-reporting} \times \text{U.S.A. population} \times 365 \text{ days/yr}}$$

$$N_{d,light} = \frac{1,159,000 \times 43.8 \times 0.25 \times 0.51 \times 0.803}{(1 - 0.33) \times 298 \times 10^6 \times (365)} = 71.3 \text{ } \mu\text{g of pure MAMP/cap} \cdot \text{d}$$

Similarly, the mass of MAMP demand by heavy users can be estimated as follows:

$$N_{d,heavy} = \frac{\text{Number of heavy users} \times \text{days of use/yr} - \text{heavy users} \times \text{quantity used per day} - \text{heavy users} \times \text{purity} \times \text{salt adjustment}}{\text{Adjustment for under-reporting} \times \text{U.S.A. population} \times 365 \text{ days/yr}}$$

$$N_{d,heavy} = \frac{731,000 \times 122.2 \times 0.40 \times 0.51 \times 0.803}{(1 - 0.33) \times 298 \times 10^6 \times (365)} = 200.8 \mu\text{g of pure MAMP/cap} \cdot \text{d}$$

From the summation of the contributions from the two groups of users, it is estimated that, on average, American methamphetamine users demanded 272 μg of pure MAMP/cap·d ($\sum N_{MAMP,q}$) in 2006. In addition, in 2006 most illicit MAMP available in the United States was manufactured from (+) pseudoephedrine (Hunt et al., 2006; Scott et al., 2006), hence it was expected to have been primarily in the form of the S(+) enantiomer (Hunt et al., 2006). Indeed, the analysis of STRIDE data for the year 2006 (DEA, 2011) reveals that 96.2% of the mass of MAMP seized, and subsequently analyzed for enantiomeric composition, within the U.S.A. was of the S(+) form.

C.2 Czech Republic

As with the U.S.A., the MAMP-abusing population within the Czech Republic can be broadly classified into heavy and light users. Specifically, the data sources within that country make a distinction between problem users and recreational users of MAMP (Vopravil, 2005). The Czech National Monitoring Centre for Drugs and Drug Addiction estimated that there were approximately 19,700 problem users of MAMP in 2006 (Mravčík et al., 2008). Further, it is estimated that such users in the Czech Republic annually consume on a per capita basis 184 grams of street purity MAMP (Petroš et al., 2005; Vopravil, 2005). Taken together, Czech problem users of MAMP can be estimated to have consumed 3625 kg of street-purity MAMP in 2006. For the purposes of the analysis presented here, the consumption of MAMP by recreational users was approximated as 167 kg, which is an estimate furnished by the Czech Statistical Office for the consumption of such users for the year 2003 (Vopravil, 2005). Such an extrapolation is expected to be largely inconsequential in the overall analysis because recreational users of MAMP have been estimated to consume less than 5% of the total mass of MAMP used within the Czech Republic (Vopravil, 2005). Altogether, for the year 2006 the mass of illicit MAMP consumed by Czech users of the drug at street level purity can be estimated to be 3792 kg/yr. The mean purity of MAMP available on Czech streets typically varies between 60-80% (Zabransky, 2011); the mean of this range was used here. Further, illicitly-produced MAMP is in the form of its HCl salt (Zabransky, 2011), hence the quantity must be corrected for the molecular weight of the associated salt by multiplying by

0.803. Using such data, one can approximate that during 2006, 2131 kg of pure MAMP was used by Czech users. This annual value can be further expressed on a daily per capita basis to estimate $\sum N_{MAMP,q}$ as 572 $\mu\text{g}/\text{cap}\cdot\text{d}$ (i.e., 2.131×10^{12} (grams/yr) $\times 1/365(\text{yr}/\text{d}) \times 1/10.2 \times 10^6(1/\text{cap})$). Further, it has been suggested that illicit MAMP available in the Czech Republic is of the S(+) enantiomeric form (Jirovsky et al., 1998; Zabransky, 2011).

C.3 Scotland

There was very little evidence to suggest that methamphetamine was being used in significant quantities in Scotland in 2006 (Scottish Government, 2008). Such an assertion is further corroborated by the fact that no MAMP was seized within Scotland during the years 2004 to 2006 (Scottish Executive, 2007).

Appendix D: Consumption of licit formulations that are metabolized to MAMP and/or AMP in selected populations

The consumption and availability of relevant licit sources that are metabolized to MAMP and/or AMP for selected national populations are summarized in Table D.1.

Table D.1 Per capita daily consumption of licit formulations that are metabolized to MAMP and/or AMP circa 2006.

Country	Clinical consumption of precursors (µg/cap-d)								
	Metabolized to MAMP and AMP					Metabolized to AMP			
	BAMP	S(+) MAMP	SELG (O) ^{(a), (b)}	SELG (TD) ^(c)	R(-) MAMP	S(+) AMP	R/S (3:1) AMP	LDAMP	R(-) AMP
U.S.A.	8.61	0.14	0.77	0.08	6.18	40.6	32.2	0 ^(d)	≈ 0 ^(e)
Czech Republic	- ^(h)	-	6.41	-	-	-	-	-	-
Scotland	-	-	0.87 ^(f)	-	-	1.05 ^{(f), (g)}	-	-	-

(a) Since orally-administered selegiline is typically prescribed as its HCl salt the tabulated consumption levels of oral selegiline have been corrected for the salt content; (b) Orally-administered selegiline; (c) Transdermally-applied selegiline; (d) In 2006, LDAMP was yet not approved for sale in the U.S.A. (US FDA, 2010); (e) Only 14 grams of R(-) AMP were used in the entire U.S.A. during the year 2006 (DEA, 2008), which when expressed on daily per capita basis amounts to a negligible contribution of 0.0001 µg/cap-d; (f) The data source (NHS-Scotland, 2007) used to estimate the consumption of these formulation does not include the fraction that is used within hospitals - however, Danish (DKMA, 2010), Finish (FIMEA, 2009) and American (DEA, 2008) data suggest that only minor levels of these formulations are used in hospitals; (g) Since orally-administered S(+) AMP is typical prescribed as its sulfate salt, the tabulated consumption levels of oral S(+) AMP have been corrected for the salt content; (h) “-” these formulations are not used within the respective countries (US FDA, 2010; NHS-Scotland, 2007; State Institute for Drug Control, 2006). Further, FAMP, AMP R/S (1:1), CLOB, FENE and FENP are not used within any of the three countries listed above (US FDA, 2010; NHS-Scotland, 2007; State Institute for Drug Control, 2006).

Consumption data sources: USA (INCB, 2007; IMS Health, National Sales Perspectives™, 2006; DEA, 2008); Czech Republic (State Institute for Drug Control, 2006); Scotland (NHS-Scotland, 2007).

Appendix E: Data sources and procedures used to establish substance flows of MAMP

Estimates were performed using Eq. (1) (see main text), which is reproduced here to aid in the discussion below:

$$J_{T,MAMP} = J_{L,MAMP} + J_{I,MAMP} + J_{G,MAMP} \quad (E.1)$$

At present very little evidence exists to suggest that MAMP is generated *in situ* due to the degradation of other sewer-borne contaminants; hence $J_{G,MAMP} \approx 0$.

E.1 Licit contributions ($J_{L,MAMP}$)

$J_{L,MAMP}$ can be expanded using Eq. (5) to yield:

$$J_{L,MAMP} = J_{L,MAMP-m} + J_{L,MAMP-c} + J_{L,MAMP-end} \quad (E.2)$$

Since MAMP is not endogenously produced $J_{L,MAMP-end} = 0$.

$J_{L,MAMP-c}$ and $J_{L,MAMP-m}$ can themselves be expanded using Eqs. (2) and (3), respectively:

$$J_{L,MAMP-c} = \sum_{p=1}^P L_{MAMP,p} \cdot \left((1 - Y_{n,MAMP}) \left(\sum_{e=1}^E (U_{p,e,MAMP} + F_{p,e,MAMP}) \cdot x_e \right) + Y_{n,MAMP} \cdot Y_{f,MAMP} \right) \cdot (\text{EXP}(-k_{d,MAMP} \cdot t_s)) \quad (E.3)$$

$$J_{L,MAMP-m} = \left(\sum_{b=1}^B L_b \cdot \left((1 - Y_{n,b}) \cdot \left(\sum_{i=1}^I (U_{b,i,MAMP} + F_{b,i,MAMP}) \cdot x_i \right) \right) \right) \cdot \frac{Mw_{MAMP}}{Mw_b} \cdot \frac{Mo_{MAMP}}{Mo_b} \cdot (\text{EXP}(-k_{d,MAMP} \cdot t_s)) \quad (E.4)$$

Degradation studies conducted by Bisceglia (2010) suggest that for all practical purposes $k_{d,MAMP}$ can be approximated as zero.

The values for all other variables of Eqs. (E.3) and (E.4) are summarized in Table E.1.

E.2 Illicit contributions ($J_{I,MAMP}$)

$J_{I,MAMP}$ can be expanded using Eq. (8) to yield:

$$J_{I,MAMP} = J_{I,d} + J_{I,o} \quad (E.5)$$

In turn, each of the respective contributions of Eq. (E.5) can be expanded using Eqs. (6) and (7):

$$J_{I,d} = \left(\sum_{q=1}^Q N_{MAMP,q} \cdot \left(\sum_{h=1}^H (U_{q,h,MAMP} + F_{q,h,MAMP}) \cdot x_{h,q} \right) \cdot \frac{Mw_s}{Mw_d} \cdot \frac{Mo_s}{Mo_d} \right) \cdot \left(\text{EXP}(-k_{d,MAMP} \cdot t_s) \right) \quad (\text{E.6})$$

$$J_{I,o} = \left(\sum_{o=1}^O N_o \cdot \left(\sum_{a=1}^A (U_{a,s} + F_{a,s}) \cdot x_a \right) \cdot \frac{Mw_s}{Mw_o} \cdot \frac{Mo_s}{Mo_o} \right) \cdot \left(\text{EXP}(-k_{d,MAMP} \cdot t_s) \right) \quad (\text{E.7})$$

Since DMAMP is not used in the three countries of interest, $J_{I,o}$ can be approximated as zero for all three national populations.

The contributions due to the respective national population's demand for MAMP ($J_{I,d}$) was estimated using Eq. (E.6).

The respective $\sum N_{MAMP,q}$ values were estimated as shown in Appendix C.

When considering route-of-administration preferences among MAMP users, the analysis presented in section 3.1.2 (see main text) suggests that a distinction only needs to be made between smokers and non-smokers of the drug. Of the three countries selected for substance flow analyses, the smoking of MAMP is only reported in the U.S.A. (Csemy and Chomynova, 2009; SAMHSA, 2008).

Typically, route-of-administration trends for the entire MAMP-abusing population are not available. However, a dataset which is readily available and hence can be used to gain insights into the route-of-administration preferences within a population of interest are the trends reported for those who are in treatment for the use of the drug. Overall, the Treatment Episode Data Set (TEDs-A) (SAMHDA, 2006b) suggests that 66.5% of admissions for MAMP use to American treatment programs reported smoking to be their preferred route of administration. When considered collectively route-of-administration trends from such a dataset are likely to be over-representative of those who use the drug chronically. However, if TEDs-A data for the year 2006 are reanalyzed by controlling for the reported frequency of use, one can gain further insight into route-of-administration trends of the two types of users of MAMP (i.e. light and heavy), as shown in Table E.2.

Table E.1 Licit sources of methamphetamine to sewers – ($J_{L,MAMP}$)

		Various licit sources of MAMP to sewers				Units	Notes
Variables		BAMP	SELG	S(+) MAMP	R(-) MAMP		
J _{L,MAMP-m}	L _b (USA)	8.61	0.85			μg/cap·d	(a)
	L _b (Czech R.)	-	6.41				
	L _b (Scotland)	-	0.87				
	Mw _{MAMP} /MW _b	0.62	0.80			g/mole	(b)
	Mo _{MAMP} /Mo _b	1	1				
	I	1	2				(c)
	i	Oral	Oral, T.D.				
	x _{oral}	1	0.91(USA), 1(Czech R., Scotland)				(d)
	x _{T.D.}	-	0.09 (USA), 0 (Czech R., Scotland)				
	Y _{n,b}	-	-				(e)
	U _{b,i,MAMP} + F _{b,i,MAMP} (S (+))	2.1	-			%	(f)
U _{b,i,MAMP} + F _{b,i,MAMP} (R (-))	-	29.7 (Oral), 17.6 (T.D.)	%	(f)			
J _{L,MAMP-c}	L _{MAMP} (USA)			0.14	6.18	μg/cap·d	(a)
	L _{MAMP} (Czech R.)			-	-		
	L _{MAMP} (Scotland)			-	-		
	Y _{n,MAMP}			-	-		(e)
	Y _{f,MAMP}			-	-		(e)
	E			1	1		
	e			Oral	Nasal		
	U _{p,e,MAMP} + F _{p,e,MAMP} (S (+))			40.2	-	%	(g)
	U _{p,e,MAMP} + F _{p,e,MAMP} (R (-))			-	42.4	%	(g)

Footnotes

(a) From Table D.1; (b) The metabolic stoichiometry describing the generation of MAMP upon administering each of the precursors was confirmed to be equal to one by considering the respective structures of MAMP and their precursors; (c) T.D. = transdermal; (d) Transdermal SELG is not used in the Czech Republic or Scotland (NHS-Scotland, 2004-2011; State Institute for Drug Control, 2003-2009); (e) Approximated as zero since the goal here was to estimate the highest loads of MAMP possible from such licit sources; (f) From Table 2; (g) From Table 1 and Fig. B.1.

Table E.2 Admissions that prefer smoking MAMP (%) classified by frequency of use and source of referral. Estimated from an analysis of TEDs-A data for 2006 (SAMHDA, 2006b).

Frequency of use	0 /past month	1-3 /past month	1-2 /past week	3-6 /past week	Daily	All
Source of referral						
Coreced ^(a)	67.3	71.4	73.9	70.7	60.4	68
Non-coreced ^(b)	66.4	68.2	69.7	66.4	57.5	64.8

(a) Those who are coerced into treatment due to referrals from the criminal justice system; (b) Those who enter treatment voluntarily, either by themselves or through the referral of health/social care providers.

Overall, the analyses presented in Table E.2 suggest that, irrespective of the frequency of use or the source of referral, smoking of MAMP is the single most important route-of-administration among those admitted for the use of MAMP. In light of data presented in Table E.2 and the average number of days of use/year estimated earlier (in section C.1), it is assumed here that 69% and 65% of light and heavy users of MAMP, respectively, prefer smoking this drug. Such assumptions can be used along with values for $\sum N_{MAMP,q}$ and $U_{h,MAMP} + F_{h,MAMP}$ estimated in Appendix C and Table 1 (see main text), respectively, to estimate the substance flow of MAMP that are expected to be realized nationally due to use of MAMP by Americans.

Lastly, it is important to recognize that chronic users, despite amounting to 39% of the whole MAMP abusing population, consume 74% of the mass of MAMP used nationally within the U.S.A. (see section C.1). Given this and the fact that, inevitably it is the mass load of the SEM which is measured downstream in influents of sewage treatment plants, the routes-of-administration used by chronic users are expected to have the dominant influence on the mass load found in the sewers. Hence, small discrepancies between the actual and the assumed route-of-administration trends for recreational users of MAMP are expected to be largely inconsequential with respect to the net flow estimates of illicit MAMP.

Appendix F: Predicted licit loads of MAMP in 18 national populations

From a sewer epidemiology perspective, there exists particular interest in establishing the importance of MAMP sewer loads expected to arise from licit sources. To study this, licit contributions to the sewer loads of MAMP were estimated for 18 countries (see Fig. F.1). The analysis suggests that in 17 of the 18 countries considered, SELG is expected to be the only licit source of MAMP to the respective national sewers. Further, in these countries a contribution no greater than 2 $\mu\text{g}/\text{cap}\cdot\text{d}$ (all in the form of R(-) MAMP) was expected to arise from this licit source. The only exception to the aforementioned trends was the situation in U.S.A. where, in addition to the contribution from the population's use of SELG, licit loads of MAMP were also expected to be released to sewers due to the American population's medicinal use of BAMP, S(+) MAMP, and R(-) MAMP. Overall, in the U.S.A. the licit contributions to the net sewer loads of MAMP were expected to amount to 3.1 $\mu\text{g}/\text{cap}\cdot\text{d}$. Lastly, it is worth noting that the national per capita consumption of SELG, a source of MAMP expected to be present in most populations, appears to be declining in most national populations (see Fig. F.2). Overall, the analysis suggests that licit contributions to the net sewer loads of MAMP will only be relevant in those national and/or sub-national populations where minor levels of illicit MAMP are used.

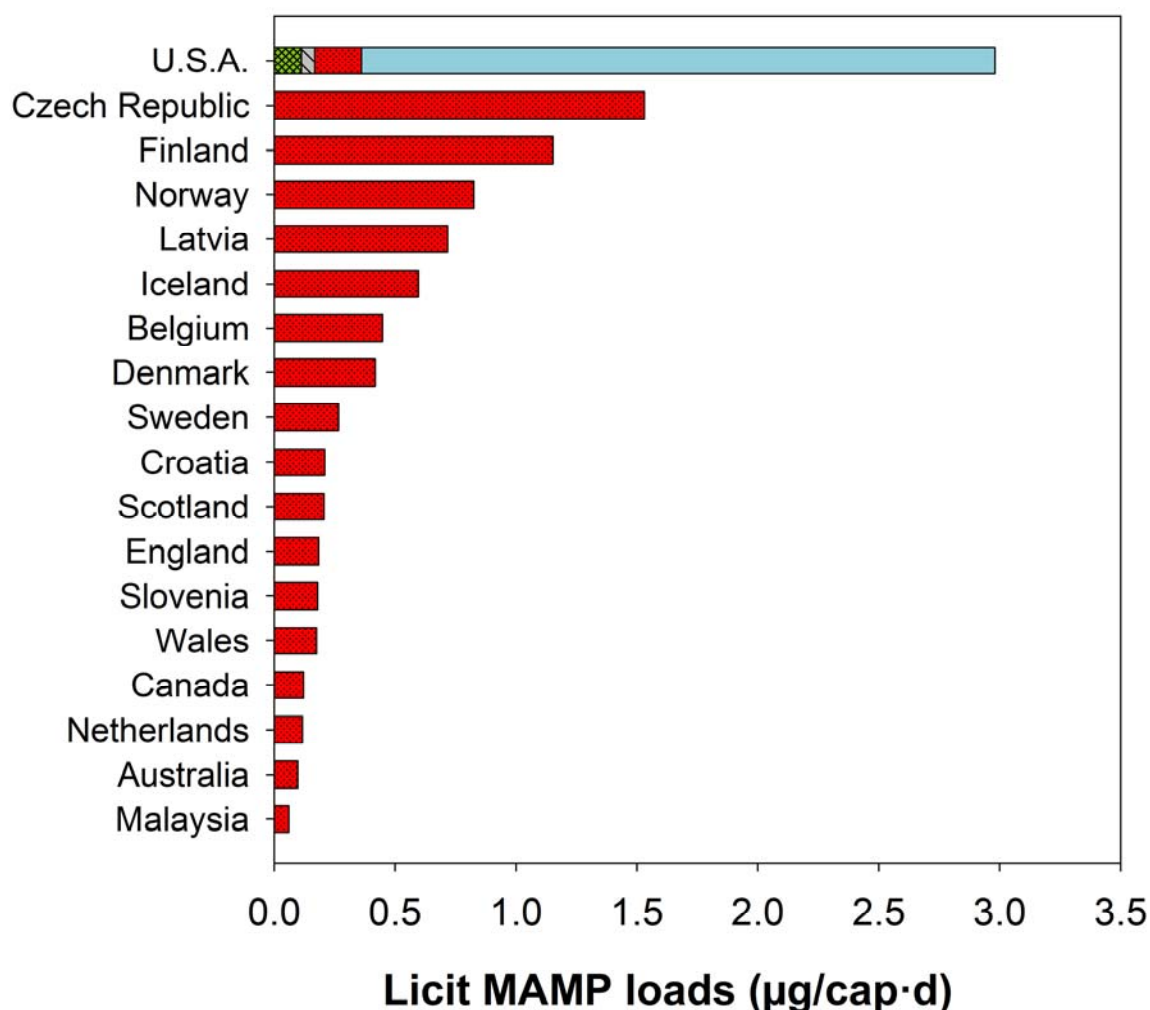


Fig. F.1 Daily per capita sewer load of MAMP due to the consumption of various licit sources in selected nations. Licit sources: (■) BAMP, (▨) Licit S(+) MAMP, (■) SELG and (■) Licit R(-) MAMP.

All contributions were calculated using either using Eq. (2) or (3) using similar procedures and assumptions as those listed in Appendix E for the licit flows of MAMP. Consumption data sources (all for the year 2006, except for Iceland, for which only quantities used in 2007 were available): Australia (DUSC, 2009); Belgium (Pharmanet, 2007); Canada (IMS Brogan (Canadian Compuscript Audit), 2006a; IMS Brogan (Canadian Drug Store and Hospital Purchases Audit), 2006b); Croatia (Agency for Medicinal Products and Medical Devices, 2006); Czech Republic (State Institute for Drug Control, 2006); Denmark (DKMA, 2010), England (NHS-England, 2007); Finland (FIMEA, 2009); Iceland (IMA, 2010); Latvia (State Agency of Medicines-Latvia, 2008); Malaysia (Ministry of Health Malaysia, 2009); Netherlands (GIP, 2010); Norway (NIPH, 2010); Scotland (NHS-Scotland, 2007); Slovenia (IVZ RS, 2009); Sweden (Apoteket AB, 2009); U.S.A. (DEA, 2008; IMS Health (National Sales Perspectives™), 2006; INCB, 2007); Wales (Wales-Statistical Directorate, 2007). Some of the consumption sources listed above did not account for the mass of SELG that is sold in hospitals; however, Danish (DKMA, 2010) and Finish (FIMEA, 2009) data both suggest that only minor levels of SELG are prescribed in hospitals.

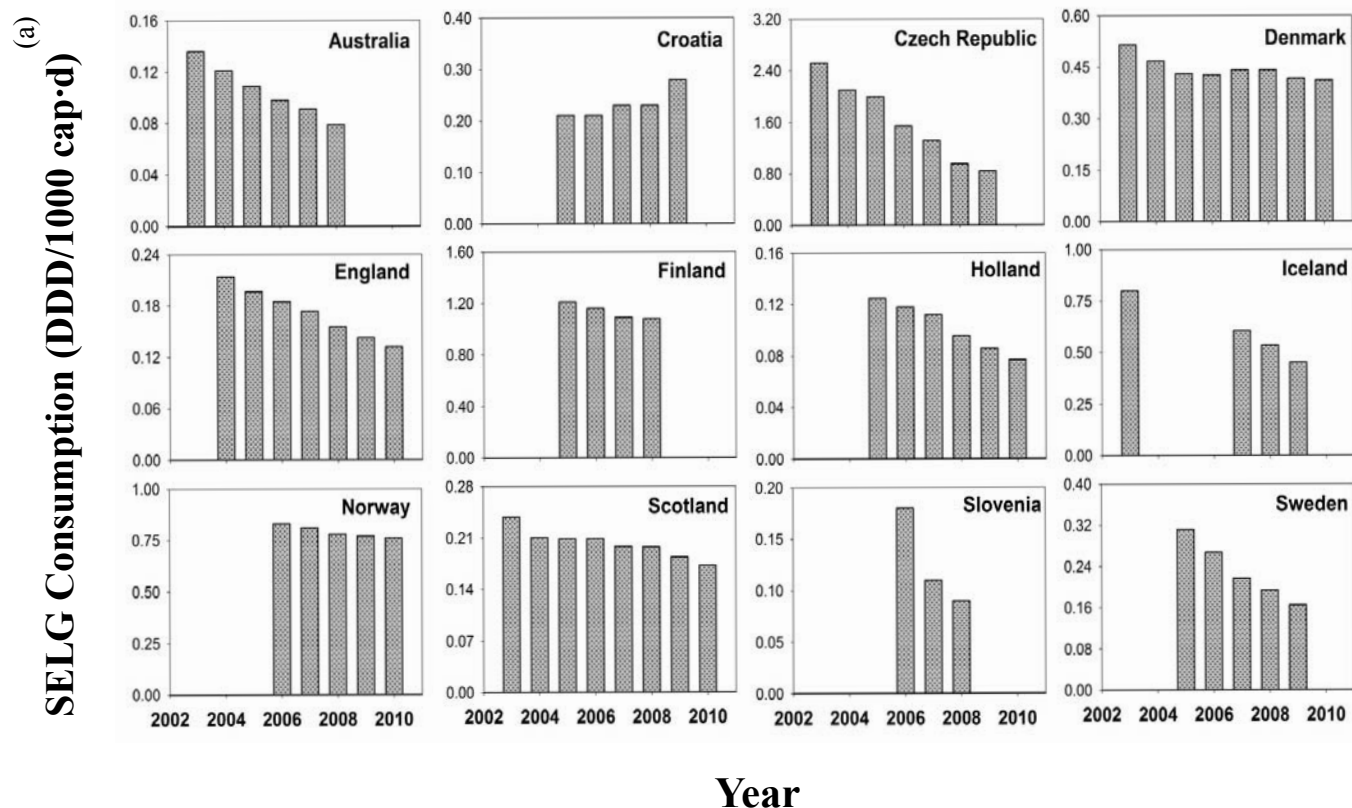


Fig. F.2 Temporal consumption patterns of SELG in various national populations.

Consumption data sources: Australia (DUSC, 2004, 2007, 2009); Croatia (Agency for Medicinal Products and Medical Devices, 2005-2009); Czech Republic (State Institute for Drug Control, 2003-2009); Denmark (DKMA, 2010-2011); England (NHS-England, 2005-2011); Finland (FIMEA, 2009); Iceland (IMA, 2004, 2010); Netherlands (GIP, 2010); Norway (NIPH, 2010, 2011); Scotland (NHS-Scotland, 2004-2011); Slovenia (IVZ RS, 2009); Sweden (Apoteket AB, 2008-2010). Some of the sources for consumption data listed above do not account for the mass of SELG that is sold in hospitals; however, Danish (DKMA, 2010), Finnish (FIMEA, 2009) and French (Afssaps, 2010) data, all suggest that only minor levels of SELG are prescribed in hospitals.

(a) DDD (defined daily dose) = 5 mg of SELG (WHO, 2010).

Appendix G: Establishing the mass and the enantiomeric nature of illicit AMP consumed by selected populations.

G.1 United States of America

Although of comparatively negligible importance to the prevalence of illicit MAMP use, the illicit use of AMP is still reported in the U.S.A. (SAMHSA, 2009b). It is generally suggested this occurs through the diversion of the various licitly-dispensed clinical formulations of AMP (Gonzales et al., 2010; SAMHSA, 2009b). Hence, the overall indications are such that the use of illicitly-produced AMP within the United States is of minor, if not negligible, importance.

G.2 Czech Republic

The use of illicit amphetamine within the Czech Republic is expected to be of minor importance. This assertion is partially corroborated by the available Czech seizure data for AMP (EMCDDA, 2010), as summarized in Table G.1. Such data suggest that even though it seems that some mass of amphetamine is available and hence illicitly used within the Czech Republic, overall the levels used are expected to be of minor importance.

Table G.1 Seizures of amphetamine made in the Czech Republic during the years 2002-2008.

Year	2002	2003	2004	2005	2006	2007	2008
Number of amphetamine seizures	3	15	9	7	9	2	1
Quantities of amphetamine seizures (kg)	0.4	0.09	0.05	0.04	6	0.03	0.002

G.3 Scotland

Casey and coworkers (2009) estimated that 19,358 kg of street-purity amphetamine was used within Scotland in 2006. Further, circa 2006 (specifically the data was for the year 2008), the purity of seized AMP samples has been reported to be around 3.8% (EMCDDA, 2010). Using aforementioned information, one can estimate that in 2006, 735 kilograms of pure amphetamine were used within Scotland. This annual value can be further expressed on a daily per capita basis to estimate $\sum N_{AMP,q}$ as $395 \mu\text{g}/\text{cap}\cdot\text{d}$ (i.e., $0.735 \times 10^{12} (\text{grams}/\text{yr}) \times 1/365(\text{yr}/\text{d}) \times 1/5.1 \times$

10^6 (1/cap)). Further, this mass is expected to be a racemic in its enantiomeric nature (George and Braithwaite, 2000; George, 2003; Tetlow and Merrill, 1996).

Appendix H: General source models for the S(+) and R(-) enantiomers of AMP

General source models for the S(+) and R(-) enantiomers of AMP were developed (see Fig. H.1) by considering the various licit and illicit sources for the two enantiomers, the excretion profiling of AMP precursors (see Table 2), and the excretion profiling of AMP (see Table 3).

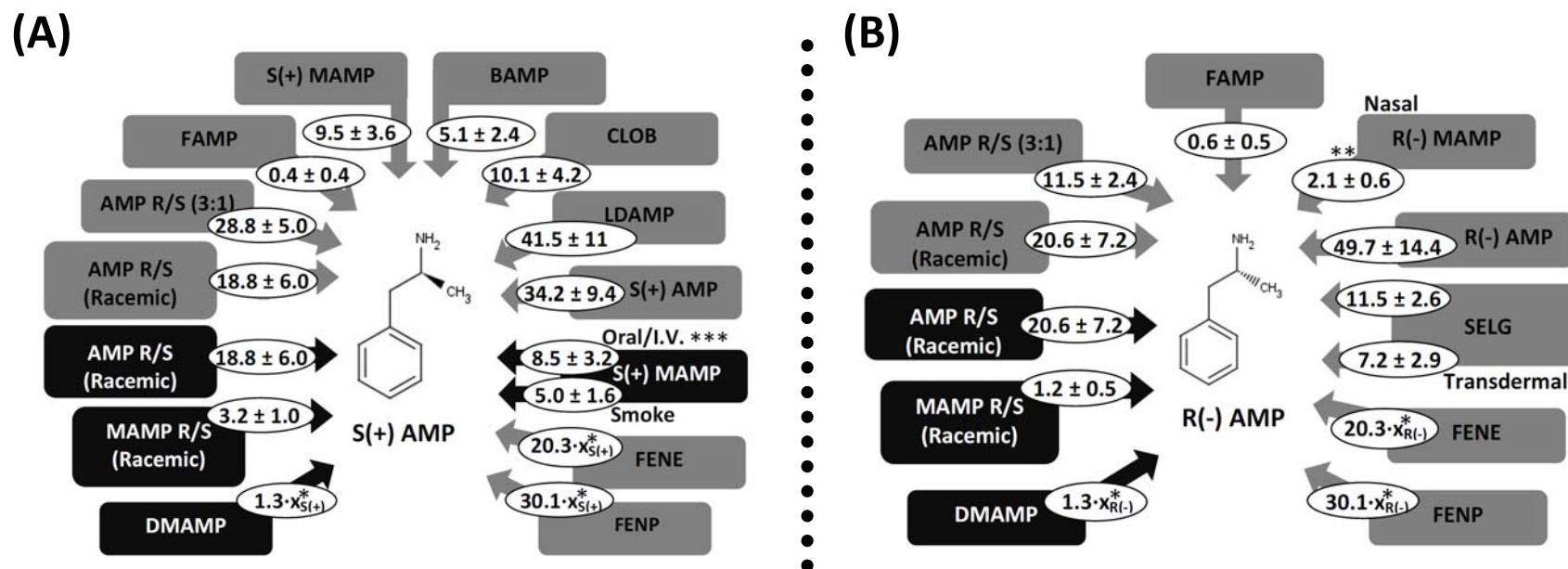


Fig. H.1 General source model for (A) the S(+) enantiomer and (B) the R(-) enantiomer of AMP. All excreted fractions expressed as a percentage of administered dose, unless otherwise indicated, were obtained from the compiled data presented in Tables 1, 2 and 3. All licit and illicit sources are shown in gray and black, respectively. Unless otherwise indicated, all excreted fractions are for orally-administered formulations of the respective sources. **Precursor abbreviations:** BAMP, benzphetamine; CLOB, clobenzorex; DMAMP, dimethylamphetamine; FAMP, famprofazone; FENE, fenethylline; FENP, fenproporex; LDAMP, lis-dexamfetamine; MAMP, methamphetamine; SELG, selegiline.

(*) Enantiomeric disposition of these formulations has not been reported in literature to date; $x_{S(+)}$ and $x_{R(-)}$ are the fractions of AMP that are excreted as the S(+) and R(-) enantiomers, respectively; (**) Due to the lack of actual experimental data for the disposition of nasally-administered R(-), MAMP an approximate value was estimated by multiplying the reported bioavailability of nasally-administered MAMP of 79% (Harris et al., 2003) with the fraction of intravenously-administered MAMP that is excreted as R(-) AMP (see Table 1); ; (***) Derived from pooling Oral and I.V. data for S(+) MAMP as compiled in Table 1.

Appendix I: Data sources and procedures used to establish substance flows of AMP

Estimates were performed using Eq. (1), which is recalled here to aid in the discussion below:

$$J_{T,AMP} = J_{L,AMP} + J_{I,AMP} + J_{G,AMP} \quad (I.1)$$

At present little concrete evidence exists to suggest that AMP is generated *in situ* due to the degradation of other sewer-borne contaminants, hence $J_{G,AMP} \approx 0$.

I.1 Licit contributions ($J_{L,AMP}$)

The contribution from $J_{L,AMP}$ can be expanded using Eq. (5) to yield:

$$J_{L,AMP} = J_{L,AMP-m} + J_{L,AMP-c} + J_{L,AMP-end} \quad (I.2)$$

AMP is not endogenously produced by humans; hence, $J_{L,AMP-end} = 0$.

The contributions $J_{L,AMP-c}$ and $J_{L,AMP-m}$ can themselves be expanded using Eqs. (2) and (3), respectively:

$$J_{L,AMP-c} = \left(\sum_{p=1}^P L_{AMPp} \cdot \left((1 - Y_{n,AMP}) \left(\sum_{e=1}^E (U_{p,e,AMP} + F_{p,e,AMP}) \cdot X_e \right) + Y_{n,AMP} \cdot Y_{f,AMP} \right) \right) \cdot \left(\text{EXP}(-k_{d,AMP} \cdot t_s) \right) \quad (I.3)$$

$$J_{L,AMP-m} = \left(\sum_{b=1}^B L_b \cdot \left((1 - Y_{nb}) \cdot \left(\sum_{i=1}^I (U_{b,i,AMP} + F_{b,i,AMP}) \cdot X_i \right) \right) \cdot \frac{Mw_{AMP}}{Mw_b} \cdot \frac{Mo_{AMP}}{Mo_b} \right) \cdot \left(\text{EXP}(-k_{d,AMP} \cdot t_s) \right) \quad (I.4)$$

Due to conflicting data available thus far for the degradation of AMP (see main text), for the analysis presented here it was assumed that no degradation of AMP sewer loads takes place. However, it is important to note that, regardless of whether the sewer loads of AMP degrade or not, when performing a substance flow analysis, the relative contributions of the various sources to the net sewer load of AMP are expected to remain the same.

The values for all other variables of Eqs. (I.3) and (I.4) are summarized in Table I.1.

Table I.1 Licit sources of amphetamine to sewers ($J_{L,AMP}$)

		Various licit sources of AMP to sewers						Units	Notes		
Variables		BAMP	SELG	S(+) MAMP	R(-) MAMP	S(+) AMP	R/S(3:1) AMP	R(-) AMP			
J _{L,AMP-m}	L _b (U.S.A.)	8.61	0.85	0.14	6.18						
	L _b (Czech R.)	-	6.41	-	-					µg/cap·d	(a)
	L _b (Scotland)	-	0.87	-	-						
	Mw _{AMP} /Mw _b	0.56	0.73	0.91	0.91					g/mole	
	Mo _{AMP} /Mo _b	1	1	1	1					mole/mole	(b)
	I	1	2	1	1						
	i	Oral	Oral, T.D.	Oral	Nasal						(c)
	x _{oral}	1	0.91 (USA); 1 (Czech R., Scotland)	1	-						(d)
	x _{nasal}	-	-	-	1						
	x _{T.D.}	-	0.09 (USA); 0 (Czech R., Scotland)	-	-						(d)
	Y _{NB}	-	-	-	-						(e)
U _{b,i,s} + F _{b,i,s} (S (+))	5.1	-	9.5	-					%	(f)	
U _{b,i,s} + F _{b,i,s} (R (-))	-	11.5 (Oral), 7.2 (T.D.)	-	2.1					%	(f)	

		Various licit sources of AMP to sewers						Units	Notes
Variables		BAMP	SELG	S(+) MAMP	R(-) MAMP	S(+) AMP	R/S(3:1) AMP	R(-) AMP	
J_{L,AMP-e}	L _{AMP} (U.S.A.)					40.6	32.2	≈ 0	
	L _{AMP} (Czech R.)					-	-	-	µg/cap·d (a)
	L _{AMP} (Scotland)					1.05	-	-	
	Y _{n,AMP}					-	-	-	(e)
	Y _{f,AMP}					-	-	-	(e)
	E					1	1	1	
	e					Oral	Oral	Oral	
	U _{AMP,e,AMP} + F _{AMP,e,AMP} (S (+))					34.2	28.8	-	% (g)
	U _{AMP,e,AMP} + F _{AMP,e,AMP} (R (-))					-	11.5	49.7	% (g)

(a) From Table D.1; (b) The metabolic stoichiometry describing the generation of AMP upon administering each of the precursors was confirmed to be equal to one by considering the respective structures of AMP and their precursors; (c) T.D. = transdermal; (d) Transdermal SELG is not used in the Czech Republic or Scotland (NHS-Scotland, 2004-2011; State Institute for Drug Control, 2003-2009); (e) Approximated as zero since the goal here was to estimate the highest loads of AMP possible from such licit sources; (f) From Tables 1 and 2 and Fig. H.1; (g) From Table 3 and Fig. H.1.

I.2 Illicit contributions ($J_{I,AMP}$)

$J_{I,AMP}$ can be expanded using Eq. (8) to yield:

$$J_{I,AMP} = J_{I,d} + J_{I,o} \quad (I.5)$$

In turn, each of the respective contributions of Eq. (I.5) can be expanded using Eqs. (6) and (7), as follows:

$$J_{I,d} = \left(\sum_{q=1}^q N_{AMP,q} \cdot \left(\sum_{h=1}^H (U_{h,AMP} + F_{h,AMP}) \cdot x_{h,q} \right) \cdot \frac{Mw_s}{Mw_d} \cdot \frac{Mo_s}{Mo_d} \right) \cdot (EXP(-k_{d,AMP} \cdot t_s)) \quad (I.6)$$

$$J_{I,o} = \left(\sum_{o=1}^O N_o \cdot \left(\sum_{a=1}^A (U_{a,s} + F_{a,s}) \cdot x_a \right) \cdot \frac{Mw_s}{Mw_o} \cdot \frac{Mo_s}{Mo_o} \right) \cdot (EXP(-k_{d,AMP} \cdot t_s)) \quad (I.7)$$

As discussed before, for both of these contributions $k_{d,AMP}$ was assumed to be equal to zero.

When enumerating contributions due to the illicit use of drugs other than the use of AMP itself, the only contribution that needs to be accounted for is the one arising from the population's use of MAMP. The respective national N_o values were established previously in Appendix C. The best assumptions that can be made for x_a values were discussed in Appendix E, while the appropriate excreted fractions (i.e., $U_{a,s} + F_{a,s}$) were obtained from the compilation presented in Table 1.

For the contributions arising from the population's use of AMP itself, $\sum N_{AMP,q}$ values were established for the respective national populations in Appendix G. As discussed in the main text, to our knowledge, only disposition of orally-administered AMP has been reported in the literature thus-far. Hence, the disposition of AMP for other relevant routes of use such as nasal insufflation and intravenous (I.V.) injection, appear to have largely remained unexplored under uncontrolled urinary conditions. However, the excretion profiling of MAMP, which is metabolized *in-vivo* to AMP, suggests that any bio-availability effects of I.V. or nasally administering AMP are expected to be largely masked by the expected inter-individual variations in the metabolic disposition of AMP (see Table 1). Therefore, excreted fractions available for orally administered AMP are used here as surrogates for all relevant routes of abusing AMP.

Appendix J: Predicted licit loads of AMP in 17 national populations

Since clinical formulations of AMP and/or its precursor SELG are expected to yield licit sewer loads of AMP for a number of populations, it is of interest from a sewer epidemiology perspective to better grasp the importance of such contributions. Such an analysis is summarized in Fig. J.1 for 17 countries, where it can be seen that in 16 of 17 countries analyzed, clinical formulations of AMP and SELG are expected to be the only licit sources of AMP to sewers. The lone exception to this is the situation in United States, where a number of minor to negligible contributions due to the population's licit consumption of S(+) MAMP, BAMP, R(-) MAMP, R(-) AMP are also expected (see also Fig. 2). The analysis summarized in Fig. J.1 suggests that in most populations a sewer load of less than 1 $\mu\text{g}/\text{cap}\cdot\text{d}$ would be expected to arise from all licit sources of AMP with the notable exception to this being the consumption patterns of clinical AMP formulations within U.S.A., Canada and Australia. In these populations, substantial contributions to the sewer loads of AMP would be expected to arise from such licit sources. However, it worth noting that in the U.S.A. and Australia, since the use of illicitly-produced AMP has largely been replaced by the use of MAMP, very little interest may exist in using influent loads of AMP to estimate the level of use of illicitly-produced AMP. Nevertheless, in such populations, there might be some interest in using influent loads of AMP to monitor consumption and, hence, the diversion patterns of relevant AMP formulations in an upstream population. For this to be done with confidence, the levels of MAMP use in the upstream population of interest would have to be low. Overall, the analysis suggests that in populations where the use of illicitly-produced AMP is currently of relevance (i.e., a number of European populations) the contribution of licit sources of AMP to sewers are expected to be largely insignificant (i.e., less than 1 $\mu\text{g}/\text{cap}\cdot\text{d}$).

The temporal consumption patterns of various licit formulations of AMP are summarized in Fig. J.2 for a number of national populations. The compiled data suggest that in a number of European populations, even though overall levels of use are low, the daily per capita consumption of licit AMP formulations is increasing. In Australia, England and Scotland, the temporal trends suggest that the levels consumed of such formulations is either declining slightly

or remaining fairly stable. The absolute levels of licit AMP consumed within a given year in the U.S.A. are exceptionally high compared to those reported for other countries and appears to be increasing steadily.

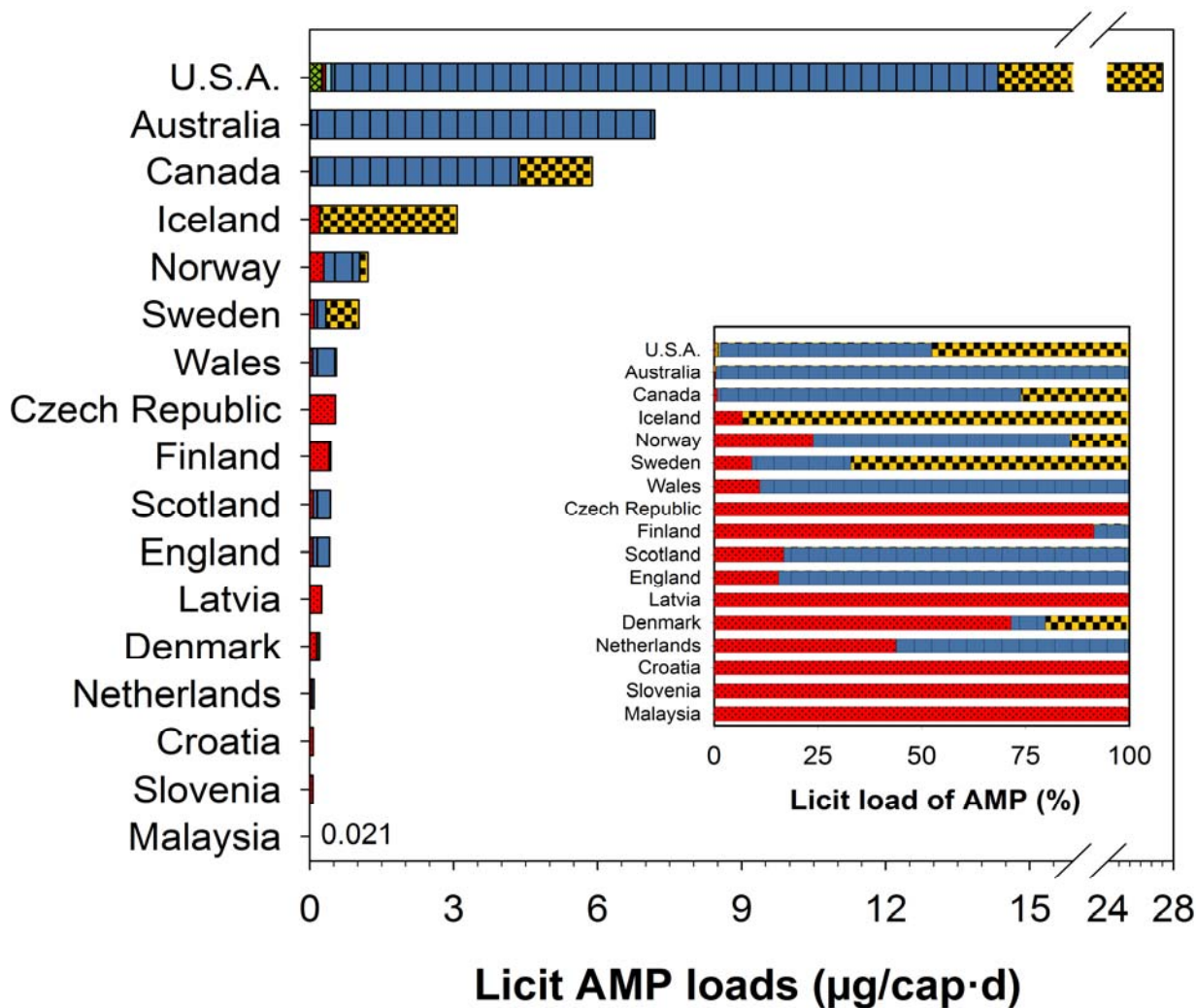


Fig. J.1 Daily per capita sewer load of AMP due to various licit sources in a number of selected national populations. Licit sources: (■) BAMP, (▨) Licit S(+) MAMP, (■) SELG, (▨) Licit R(-) MAMP, (■) Licit S(+) AMP, (■) Licit R/S(3:1) AMP.

All contributions were calculated using either using Eq. (2) or (3) using similar procedures and assumptions as those listed in Appendix I for the licit flows of AMP. Consumption data sources (all for the year 2006, except for Iceland where, all consumption data was for the year 2007 and for Finland where only the consumption of S(+) AMP was for the year 2007): Australia (DUSC, 2009); Canada (IMS Brogan (Canadian Compuscript Audit), 2006a; IMS Brogan (Canadian Drug Store and Hospital Purchases Audit), 2006b); Croatia (Agency for Medicinal Products and Medical Devices, 2006); Czech Republic (State Institute for Drug Control, 2006); Denmark (DKMA, 2010); England (NHS-England, 2007); Finland (FIMEA, 2009; KELA, 2011); Iceland (IMA, 2008); Latvia (State Agency of Medicines-Latvia, 2008); Malaysia (Ministry of Health Malaysia, 2009); Netherlands (GIP, 2010); Norway (NIPH, 2010); Scotland (NHS-Scotland, 2007); Slovenia (IVZ RS, 2009); Sweden (Apoteket AB, 2009); U.S.A. (DEA, 2008; IMS Health (National Sales Perspectives™), 2006; INCB, 2007); Wales (Wales-Statistical Directorate, 2007). Some of the consumption sources listed above did not account for the mass of SELG or AMP that is sold in

hospitals; however, Danish (DKMA, 2010), Finish (FIMEA, 2009) and American (DEA, 2010) data suggest that only minor levels of AMP and SELG are prescribed in hospitals.

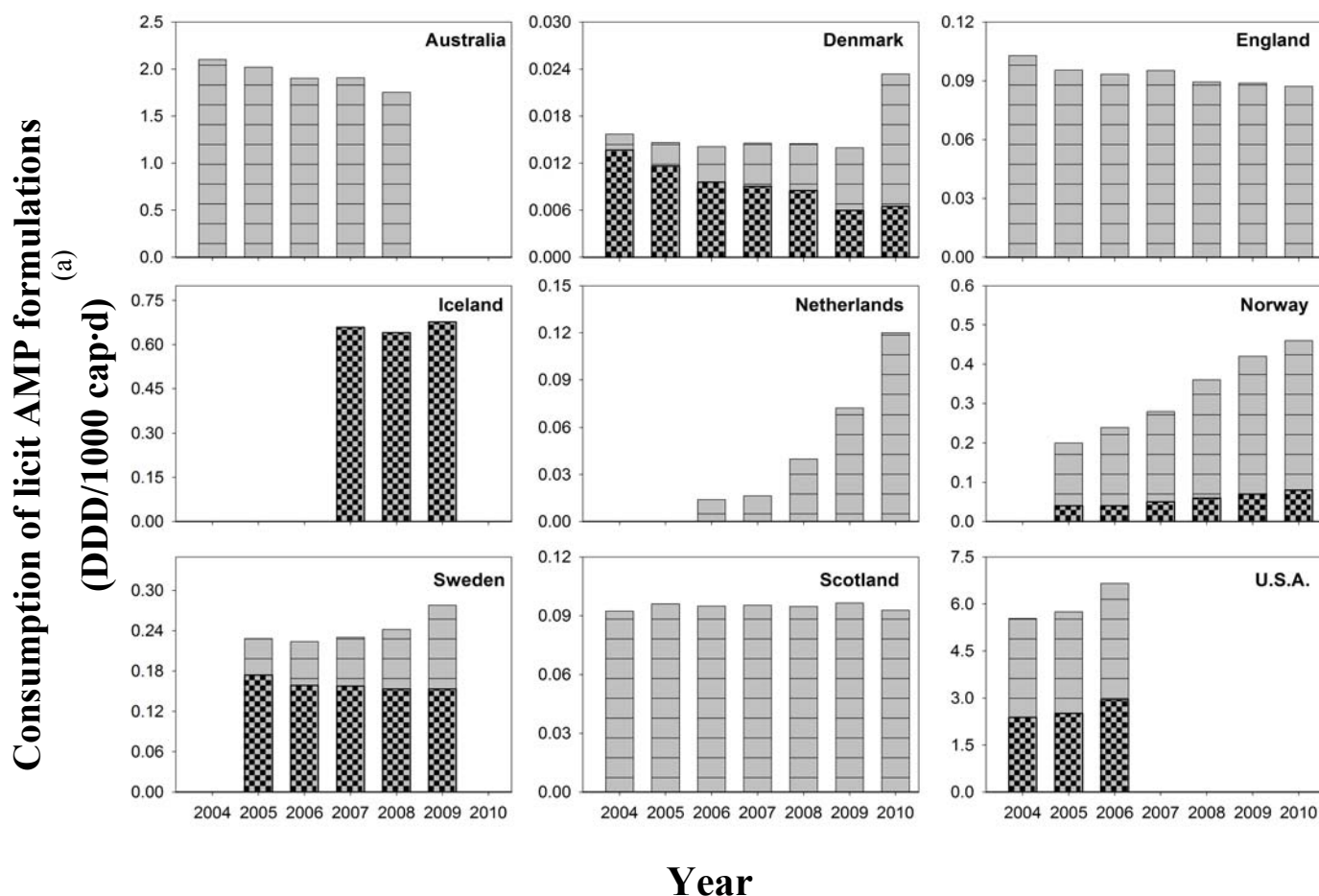


Fig. J.2 Temporal consumption patterns of various licit formulations of AMP in a number of national populations.

Individual contributions: Enantiomeric mixtures of AMP (checkered) and S(+)-AMP (solid grey).

Consumption data sources: Australia (DUSC, 2009, 2007); Denmark (DKMA, 2010-2011), England (NHS-England, 2005-2011); Iceland (IMA, 2008); Netherlands (GIP, 2010); Norway (NIPH, 2010, 2011); Scotland (NHS-Scotland, 2004-2011); Sweden (Apoteket AB, 2008-2010); U.S.A (DEA, 2005-2008). Some of the sources for consumption sources listed above do not account for the mass of licit AMP that is sold in hospitals; however, Danish (DKMA, 2010) and American (DEA, 2008) data both suggest that only minor levels of licit AMP formulations are prescribed in hospitals.

(a) DDD (defined daily dose) = 15 mg of AMP (WHO, 2010).

Appendix K: Analyzing the importance of LDAMP as a source of AMP to sewers

In the one-year period preceding April 2011, the sales of LDAMP amounted to \$US 1.1 billion (Zacks Investment Research, 2011). Such sales figures were used in combination with the pricing of various strengths of LDAMP (UpToDate, 2011), the fraction of LDAMP that is excreted as S(+) AMP (Krishnan et al., 2008), and the molecular weight correction for the amphetamine base content of LDAMP, to estimate that, circa 2011, levels of between 6 – 10 $\mu\text{g}/\text{cap}\cdot\text{d}$ of S(+) AMP were expected to be released to American sewers due to the population's consumption of LDAMP. At present, the use of this formulation remains fairly limited in Europe. For example, in 2010 only 10.3 grams of this formulation were used within the community in England (NHS-England, 2011). However, the use of this formulation is expected to substantially expand in Europe. For example, Schlender (2007) predicted that consumption levels of 26 and 37 $\mu\text{g}/\text{cap}\cdot\text{d}$ are expected to be realized in England and Germany, respectively, four years after its approval for use. Such consumption levels can be estimated to yield sewer loads of 3.2 and 4.6 $\mu\text{g}/\text{cap}\cdot\text{d}$ of S(+) AMP to English and German sewers, respectively. Overall, the current consumption levels in the U.S.A. and the predicted levels in Germany and England suggest that LDAMP could in certain instances be a significant licit source of S(+) AMP to sewers - particularly if the use of LDAMP expands significantly beyond the currently observed or predicted levels.

Appendix L: Speciation of THC-COOH

Speciation of THC-COOH is plotted in Fig. L.1. The trends suggest that for the typical pH of 7.5 for fecal matter and the surrounding wastewater (Qasim, 1999; Tietz, 1995), THC-COOH is expected to be exclusively found as the carboxylate anion, THC-COO^- .

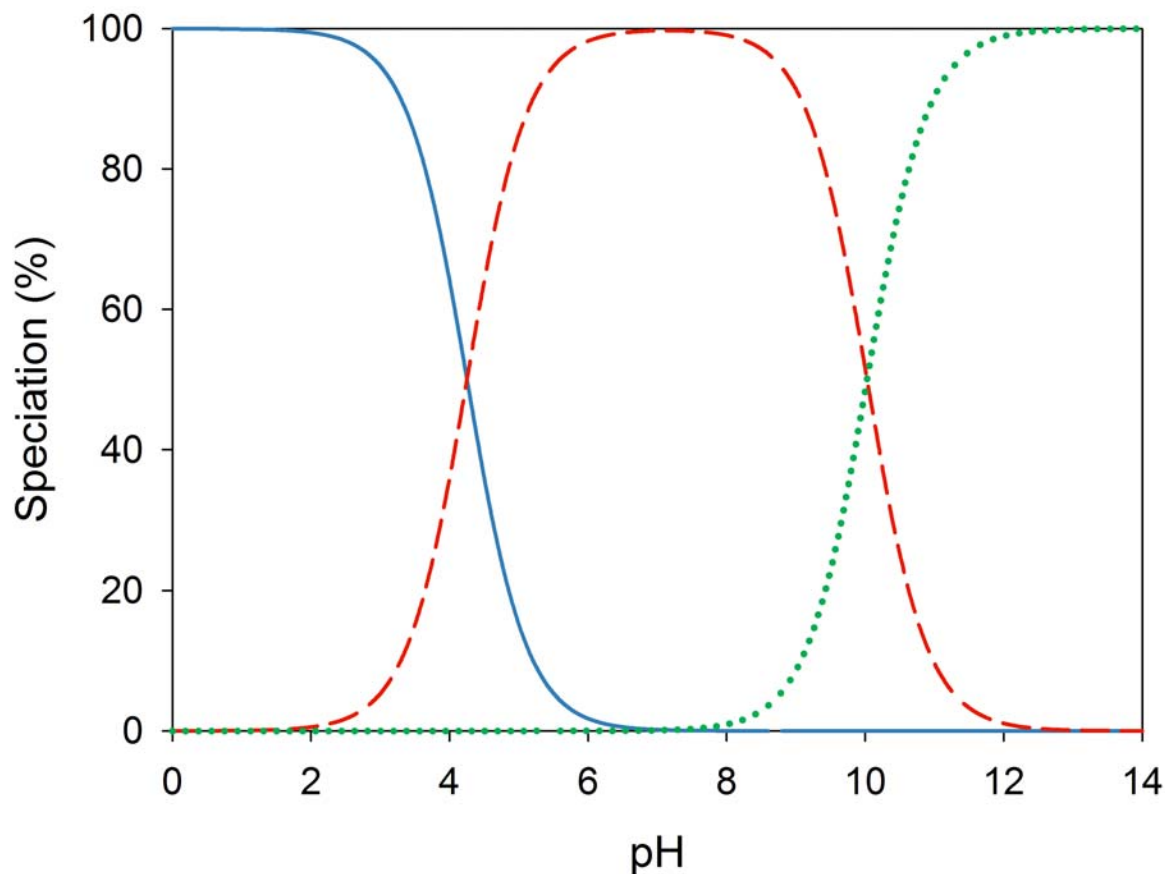


Fig. L.1 Speciation of THC-COOH. Predicted using Henderson–Hasselbalch’s equation with pK_a values for THC-COOH estimated using MarvinView (ChemAxon, 2010). Symbols: (—) Neutral THC-COOH; (- -) Ionic THC-COO⁻; (.....) Ionic THC-COO²⁻.

Appendix M: Suitability of smoked MAMP disposition data of Cook et al. (1993) from a sewer epidemiology perspective

The smoking protocol is described by the authors as follows “... pipe was then heated as above to 300-305°C in an aluminum block. The subjects were instructed to inhale the vapors produced completely and to hold them in their lungs for 15 sec. This process was repeated at 1-min intervals until no drug or vapors were visibly present in the pipe...”. Further, in a related publication by the same group (Perez-Reyes, et al., 1991), the following additional details about the smoking device and the mode of use are given: “Because the pipe was capped, no vapors escaped to the atmosphere..... To provide even heating, the pipe's bowl was placed in an aluminum block pre-heated to 305°C. Simulated inhalation experiments demonstrated this temperature to be optimal for the rapid vaporization of methamphetamine HCl with negligible pyrolytic degradation.” Overall the authors themselves asserted the following about the manner in which they choose to administer MAMP to their subjects (Cook et al., 1993): “The temperature and mode of smoking of methamphetamine hydrochloride were chosen in order to deliver the drug effectively, but with as little decomposition as possible.” Given these descriptions of the smoking device and the mode of use, the data-set of Cook et al. (1993) deviates significantly from real-life use in terms of the extended inhalation durations employed, the use of an aluminum block to optimally vaporize MAMP at an accurately controlled temperature, and the capping of the smoking device.

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