Occupational solvent exposure and mental disorders

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Abstract

A case-referent study was designed to investigate the relationship between occupational solvent exposure and mental disorders. New cases of mental disorder (males, 40 to 69 years old), were individually matched for age and date of admission to hospital patients and neighbors. An occupational history was obtained from 91.7% of the sample (1143 subjects, or 381 'trios'), during a telephone interview or by mail.

No increased risk of mental disorders was found among subjects exposed to moderate levels of solvents, but the risk was elevated - though not to a statistically significant degree - at exposure to high levels When diagnoses were divided into psychotic (ICD-9 codes 290-299) and non-psychotic (ICD-9 codes 300-316), the latter group presented an increased risk with exposure to high levels of solvents (odds ratio=2.43, 90% C I =1 16-5.08) No systematic exposure-response relationship was demonstrated, although there was a suggestion of increased risk of mental disorders among subjects exposed to high levels for 5 to 9 years.

Various aspects of referent selection - with a specific comparison of hospital and population referents - were also examined as a methodological issue of case-referent studies.

Résumé

Le lien entre l'exposition professionnelle aux solvants et les maladies mentales a été exploré au moyen d'une étude de type cas-témoins. De nouveaux cas de maladies mentales (chez des hommes âgés de 40 à 69 ans) ont été appariés individuellement, pour l'âge et la date d'admission, à des témoins hospitaliers et du voisinage. On a obtenu l'histoire de travail de 91,7% de l'échantillon (1143 sujets, ou 381 'trios'), lors d'une entrevue téléphonique ou par la poste.

Il n'y avait pas de risque accru de maladie mentale chez les sujets exposés à des niveaux modérés de solvants, mais le risque était plus élevé, sans toutefois l'être significativement, avec une exposition à de hauts niveaux. La séparation des diagnostics en psychotiques (codes 290-299, CIM-9) et non-psychotiques (codes 300-316, CIM-9), a révélé un risque accru chez ce dernier groupe avec une exposition à de hauts niveaux de solvants (rapport de cotes ('odds ratio')=2,43, I.C. à 90%=1,16-5,08). Aucun lien systématique exposition-réponse n'a été démontré, bien qu'il y ait une suggestion de risque accru parmi les sujets exposés à de hauts niveaux pendant 5 à 9 ans.

Divers aspects de la sélection des témoins (avec une comparaison spécifique entre témoins hospitaliers et du voisinage) ont aussi été examinés en tant que problèmes méthodologiques des études de type cas-témoins.

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Statement of originality

My study formed part of a research program on the health effects of solvent exposure designed jointly by Dr. J. Corbett McDonald, Dr. Nicola Cherry and myself. The research described in this thesis was my primary responsibility, though discussed with others and modified as necessary. I designed and conducted the pilot study, designed the questionnaires, supervised the field work and was responsible for all exposure assessments. The data analysis, interpretation and authorship of the thesis were entirely my own. No comparable study of the effects of solvent exposure in the etiology of mental illness has been made previously and the results make a unique contribution to knowledge in this subject.

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I. Introduction

Organic solvents have been used for several centuries. Their volatility and liposolubility explain the rapid spread of their use - as degreasers, dry cleaning agents, refrigerants, paint and varnish removers, anesthetics, in the synthesis of paints, varnishes, lacquers, adhesives, plastics, in the formulation of pesticides, cleaning products, etc. [IARC 1979; Acres Consulting Services 1981]. That same popularity causes them to be an omnipresent hazard, all around the world.

The narcotic effects of organic solvents on the central nervous system was recognized by their use in the early stages of anesthesiology [Fülöp-Miller 1938]. Animal studies, in addition to human ones, also confirmed deleterious effects on the peripheral nervous system (namely an axonal polyneuropathy) of a few specific solvents - n-hexane, methyl n-butyl ketone, carbon disulfide, impure trichloroethylene (containing dichloroacetylene) and toluene (through glue sniffing) [Spencer and Schaumburg 1985].

In the last two decades however, the concern focused on neurobehavioral effects of solvents. It has since been demonstrated repeatedly - by case reports, experimental studies on volunteers and cross-sectional studies - that many organic solvents used in the workplace had definite short term toxic effects on the central nervous system On the other hand, the Scandinavian countries recognize the existence of a 'psycho-organic syndrome' linked to occupational solvent exposure, and compensate workers with such a diagnosis, when they are found to have been exposed.

The first epidemiological study to demonstrate a link between solvent exposure and early retirement because of psychiatric illness was made in Sweden [Axelson *et al.* 1976] and demonstrated a relative risk of 1.8 of early retirement for psychiatric reasons. Two Danish studies followed - a case-referent and a retrospective cohort - with similar conclusions and relative risks ranging from 1 7 to 3.5 [Olsen and Sabroe 1980; Mikkelsen 1980]. These three studies dealt with similar populations - workers in the construction industry who retired early because of mental illness - and relied on job titles to classify exposure It was important to test these results in another country, using another indicator of mental disorder and assessing exposure more quantitatively.

While exploring the various design aspects of case-referent studies, a methodological issue became evident: the respective merits of more than one referent group, namely hospital and population referents here. That issue was tackled by selecting a series of neighborhood referents and then comparing them to the main referent group chosen among hospital patients.

The case-referent study presented in this thesis, also called Study A, was set up and undertaken in conjunction with a second study, hereafter called Study B; each study was designed to answer one of two major research questions stated in a larger project funded by the Institut de recherche en santé et en sécurité du travail du Québec (IRSST), from April 1984 to March 1988.

These two questions were:

i) are men admitted to hospital for the first time because of a mental disorder more likely to have been occupationally exposed to solvents than comparable referents (question addressed in Study A); and

ii) are psychiatric patients with a diagnosis of organic mental disorder more likely to have been exposed to organic solvents than comparable patients with other psychiatric diagnoses (question addressed in Study B).

Five hospitals from the Montreal area participated in this study, whereas thirteen more hospitals throughout the Province collaborated for Study B. The final report on the whole research project, entitled "The risk of serious psychiatric illness attributable to occupational solvent exposure", has been submitted to the IRSST in July 1988 [Cherry and McDonald 1988]; part of the results have also been presented at the Sixth International Symposium on Epidemiology and Occupational Health held in Stockholm in August 1988 [Cherry *et al.* 1988]

This thesis is divided in eight chapters apart from the introduction. After a rapid review of the literature on organic solvents and mental disorders, Chapter II will focus on the neurobehavioral effects of solvents. The research protocol and the pilot study that preceded the study proper will be presented in Chapter III; they will be followed by a description of the associated studies done to assess the reliability and, to a certain extent, the validity, of the solvent exposure assessment procedure used in both this thesis project and Study B. Chapter V will describe various characteristics of the study population, and the results of the main analyses of the study will be shown in the next chapter. As one of the most important methodological aspect of case-referent studies is referent selection, it will be addressed separately in Chapter VII. Lastly, Chapters VIII and IX will discuss the study findings and the design characteristics and give a general conclusion.

II. Review of the literature

A. INTRODUCTION

Organic solvents are ubiquitous in products used daily: from gasoline to typewriter correction fluids, from shoe polish to nail polish remover, from perfumes to cough syrups, etc. [Ontario Ministry of Industry and Tourism 1978: 4-8].

Our century has seen an exponential development and use of organic solvents with, unfortunately, a few bad surprises about their adverse health effects on the exposed workers; liver necrosis and fatty degeneration among workers using tetrachloroethane in the aircraft industry during World War I are sad examples of an 'after the fact' discovery [Zimmerman 1978 315]

There has been, particularly since the early 1970's, an increasing concern about neurobehavioral effects of organic solvents. In 1979, Arlien-Søborg and his colleagues coined the expression 'chronic painters' syndrome' to describe a set of symptoms present among workers with long-term high level exposures to organic solvents [Arlien-Søborg *et al.* 1979] Such a syndrome may have been foreshadowed in 1705 by Bernardino Ramazzini who stated, in the first known book on occupational diseases, *De Morbis Artificum* (Diseases of Workers), the following:

> "Painters too are attacked by various ailments such as palsy of the limbs, cachexy, blackened teeth, unhealthy complexions, melancholia, and loss of the sense of smell." [Ramazzini 1940. 67]

It is impossible, in this example, to disentangle the effects of solvents from those of the heavy metals used in the pigments to produce the paints, but the same comment may apply to the Scandinavian chronic painters' syndrome

The following review of the literature is divided into three parts. The first gives an overview of the classification, metabolism and toxicology (neurotoxicology in particular) of organic solvents and is presented without critical appraisal. The second briefly describes the classification of mental disorders and some etiological theories. The third part focuses in more detail on the neurobehavioral effects of organic solvents in both animals and man.

B. ORGANIC SOLVENTS

1) Classification

A solvent is a substance "...by means of which a solid may be brought to a liquid state" [Durrans, 1971: 3] and water is the most prevalent solvent on earth. The term

'organic' characterizes solvents, the chemical structure of which contains carbon atoms; most such solvents have the ability to dissolve lipid-like substances.

Organic solvents can be arranged into 10 groups according to their chemical composition. Table II-1 lists these with some examples of their most frequent uses [Durrans 1971].

It is difficult to estimate the quantitative extent of occupational exposure to solvents in Canada, but the proportions of exposed workers are probably comparable to that of the United States. The National Occupational Hazard Survey conducted in the United States between 1972 and 1974 estimated that about 9.8 million workers were potentially exposed to organic solvents [NIOSH 1977a]. Additional estimates from the National Institute for Occupational Safety and Health (NIOSH) mentioned 600 000 workers exposed solely to naphthas [NIOSH 1977b], and over 2 million workers to benzene [NIOSH 1977c].

According to a consultant's evaluation of the Canadian market for chlorinated hydrocarbons in 1979, 12 600 tons of methylene chloride were imported; a few examples of the quantities produced in Canada are listed below [Acres Consulting Services 1981]:

-Trichloroethylene: 15 500 tons (in Québec)
-Tetrachloroethylene: 18 500 tons
-Ethylene dichloride: 18 500 tons
-1,1,1-Trichloroethane: 18 500 tons
-Benzene: 626 000 tons
-Styrene: 340 000 tons
-Toluene: 430 000 tons
-Xylenes: 349 000 tons.

The amount of trichloroethylene produced yearly in Sweden (a country with a somewhat larger population than Québec) was 12 100 tons in roughly the same years [Swedish Work Environment Fund 1980: 107]. In 1984, the United States produced approximately 49 million tons of industrial solvents altogether [NIOSH 1987].

2) Metabolism

The factors governing solvent uptake and metabolism are related to i) the solvent itself (physico-chemical characteristics, blood/air and blood/fat partition coefficients, impurities, formulation factors); ii) exposure (duration, concentration, frequency, route of entry); finally, iii) the exposed person (sex, age, adiposity, genetic variability in clearance rates, nutritional status, etc.) [Andrews and Snyder 1986: 636-637].

Table II-1. Classification and use of organic solvents

Chemical group	Examples	Industrial use
Aliphatic & cyclic hydrocarbons	Hexane, pentane,heptane, cyclohexane	Fabrication of glues, paints, varnishes, cements, soaps, lacquers, polishes, in leather processing, etc
Aromatic hydrocarbons	Benzene, toluene, xylene, styrene, cumene	Fabrication of paints, varnishes, synthetic fibers, in printing, etc.
Halogenated hydrocarbons	Trichloroethylene, tetrachloroethylene, methylene chloride	Fabrication of plastics, pesticides; in dry cleaning, metal degreasing, etc.
Nitrocompounds	Nitroethane, nitropropane, nitromethane	Fabrication of chemical products
Alcohols	Methanol, ethanol, propanol	Fabrication of lacquers, plastics, industrial coatings, etc
Ketones	Acetone, methyl butyl ketone (MBK), MIBK, MEK	Synthesis of various chemicals; for cleaning purposes, etc.
Ethers	Diethyl ether, diisopropyl ether	Dewaxing of lubricating oils; synthesis of various chemicals
Esters	Ethyl acetate, butyl acetate, propionic acid	Fabrication of plastics, lacquers, etc.
Glycols	Ethylene glycol, cellosolves	Fabrication of pharmaceutical substances
Others	Carbon disulfide Refined petroleum solvents kerosene, naphtha, white spirits, mineral spirits, etc.	Fabrication of viscose rayon Fabrication of paints, lacquers, varnishes, cement diluent; in asphalt coatings, etc

[Adapted from Durrans 1971]

The volatility and liposolubility of most organic solvents explain the following characteristics [Andrews and Snyder 1986: 636-637]:

- inhalation is a major route of exposure, followed by skin absorption;
- solvents are readily transferred from the lungs into the blood and to lipid rich organs;
- many of them cause narcosis (the central nervous system is rich in lipids).

Respiratory uptake of solvents varies mainly according to the ratio of their respective air and blood solubilities, and to pulmonary ventilation, blood circulation and amount of body fat [Veulemans *et al.* 1982; Åstrand 1985]. Solvents are then distributed to tissues and organs, largest amounts going to the tissues containing the most blood vessels, and accumulate in tissues which are rich in lipids (hence the susceptibility of the nervous system which is well irrigated by blood vessels and contains a high proportion of lipids) [Cohr 1986].

As with most toxic substances, liver is the main organ of biotransformation for solvents. Most solvents undergo some form of oxidation (or epoxidation for aromatic solvents) mediated by mixed function oxidases which depend on cytochrome P-450; some of them are also reduced (Phase I reactions). Certain solvents also go through the Phase II reactions, being conjugated with endogenous substances that will confer to the solvent or its metabolite an increased water solubility, facilitating further biodegradation. Some metabolic activity of microsomal enzymes has also been measured in other organs (intestinal mucosa, gonads, kidneys, lungs, skin) and could be important in the scavenging processes [Riihimäki 1986].

Most solvents are partly excreted unchanged via the lungs and in very small amounts in urine and other biological secretions (sweat, saliva, etc), the most important excretion pathway is however that of metabolites in the urine and the other biological fluids [Riihimäki 1986].

3) Toxicology

a) Aliphatic and cyclic hydrocarbons

Apart from a depressing effect on the central nervous system, and except for n-hexane, alkanes and cycloalkanes have not been reported to produce any particular toxic effects. The former is one of the few recognized solvent neurotoxicants to cause peripheral sensorimotor and motor polyneuropathy [Toftgård and Gustafsson 1980].

b) Aromatic hydrocarbons

Acute high exposures to these solvents produce narcotic symptoms [Bruckner and Peterson 1977]. Workers exposed to styrene have been found to suffer from psychomotor disturbances [Lindström *et al.* 1976] and slowed reaction time [Cherry *et*

al. 1980]; xylene was also reported to slow reaction time and impair body balance and manual coordination in volunteers [Savolainen *et al.* 1979; Savolainen *et al.* 1980a].

Cardiac sensitization and hepatorenal damage have been reported in inhalent abusers, probably due to the toluene portion of the inhaled material [Bruckner and Peterson 1977]. However toluene exposure in the workplace did not affect liver function in a group of 59 men, according to Waldron *et al.* [1982].

Hematopoietic toxicity (taking the form of bone marrow depression) has been linked to benzene exposure for some time [Browning 1953: 15-16]. There is epidemiologic evidence that benzene is leukemogenic, but other studies did not confirm this [IARC 1982; Rushton and Alderson 1981]; nonetheless, NIOSH recommended in 1976 that benzene be considered leukemogenic for regulatory purposes [NIOSH 1976]. Chromosomal abnormalities have been found repetitively in man following benzene exposure, but not in animals [Picciano 1979].

Exposure to aromatic solvents and the occurrence of adverse effects on pregnancy and the foetus have been studied on several occasions with inconsistent results. Some studies, mainly case-referent in design, have found associations with congenital defects [Holmberg 1979; Holmberg *et al.* 1982; McDonald *et al.* 1987] while others did not [Harkonen and Holmberg 1982; Olsen 1983; Harkonen *et al.* 1984]. McDonald *et al.* [1987] attributed most of the increased risk to toluene exposure.

c) Halogenated hydrocarbons

Chlorinated solvents are the most used hydrocarbons of the halogenated class of solvents. They have marked narcotic properties [Finkel 1983: 226-227], and many of them have been used as general anesthetics, for example chloroform, ethylene dichloride, trichloroethylene, etc. [Fulòp-Miller 1938].

Many halogenated hydrocarbons produce hepatotoxic effects ranging from a slight fatty accumulation to liver necrosis; carbon tetrachloride served as a classic study model of a syndrome consisting of centrolobular necrosis and fatty degeneration of the liver, often accompanied by renal damage [Zimmerman 1982: 5].

A few epidemiological studies reported associations between exposure to chlorinated hydrocarbons and liver cancer; however no information was available on hepatitis or liver cirrhosis as potential risk factors in these studies [Blair *et al.* 1979; Stemhagen *et al.* 1983]. Some degree of mutagenicity, teratogenicity and foetotoxicity has been demonstrated, but not consistently, with chlorinated hydrocarbons [IARC 1979; Bartsch *et al.* 1979; Elovaara *et al.* 1979; Nelson *et al.* 1980].

d) Nitrocompounds

Apart from having irritative effects on the mucosae, most nitrocompounds produce methemoglobinaemia through oxidation of hemoglobin [Browning 1953: 373-376; Finkel 1983: 256]. They can also give rise to liver damage [Hine *et al.* 1978], and are considered potentially carcinogenic for humans, based on animal studies [OSHA/NIOSH 1980].

e) Alcohols and glycols

Most of these solvents have a low vapor pressure [Durrans 1971: 111-135, 166-178], and thus inhalation is not an important route of absorption, except in hot environments where vapors or mists can be produced [Andrews and Snyder 1986: 654]. Skin absorption is also quite low and unlikely to be very important.

Wilcosky and Tyroler [1983] reported a significant association between occupational exposure to ethanol and phenol, and ischemic heart disease mortality among rubber industry workers. They concluded that the two alcohols were plausible occupational atherogens, since ethanol can increase mortality from heart disease, and phenol was shown, in animal studies, to cause myocardial degeneration.

A few reports were published on neurotoxicity, reproductive toxicity and teratogenic effects of some glycol ethers on animal models [Savolainen 1980, Nelson *et al.* 1984].

f) Ketones

Methyl n-butyl ketone (MBK) is recognized as a potent neurotoxicant and responsible for polyneuropathies in occupational settings [Mendell *et al.* 1974]. Most probably this is due to a metabolite, 2,5-hexanedione, which is common to n-hexane's metabolic pathway [Cavanagh 1985].

g) Ethers and esters

The narcotic properties of ethers were first used in the development of anesthetics [Fulop-Miller 1938]. However as they are irritant to the mucosa, their use is quite limited.

Dioxane, or diethylene ether, appears to be a potent toxicant for liver and kidneys, with some rodent studies revealing hepatocarcinogenicity, mutagenicity and teratogenicity [NIOSH 1977d].

Aliphatic esters also have narcotic properties and are mucosal irritants [Toftgård and Gustafsson 1980].

h) Others

Carbon disulfide (CS_2) is a well known neurotoxicant, and responsible for a series of adverse health effects ranging from ischaemic heart disease to liver damage, toxic

polyneuritis and neurobehavioral disorders [Wilcosky and Tyroler 1983; Sweetnam *et al.* 1987]. As early as 1899, Laudenheimer [Finkel 1983: 263] reported the presence of psychiatric symptoms in solvent intoxicated subjects, ending in dementia for some patients. In 1938, Gordy and Trumper presented a review of literature on the effects of CS_2 before reporting on their own clinical observations [Gordy and Trumper 1938]. Vigliani [1950; 1954] made clinical observations on workers poisoned by CS_2 during the war. A follow-up of some of these workers revealed 43 cases of chronic vascular encephalopathy in men aged 37 to 68 years old, and who had had an average of 21 years of exposure to carbon disulfide in viscose rayon factories; the author concluded that "... prolonged exposure to CS_2 can lead to a favourable situation for producing atherosclerosis" [Vigliani 1954]. Hänninen [1971] made the important observation that signs of depressive mood, slight motor disturbances and intellectual impairment were more frequent among workers exposed to CS_2 but without clinical poisoning than among non-exposed workers. Mancuso and Locke found increases in suicide rates among American viscose workers using a cohort design [1972]. A follow-up study of viscose workers confirmed the presence of a permanent axonal neuropathy [Corsi *et al.* 1983]. A case-referent study from Sweden [Ohlson and Hogstedt 1981] could not confirm an association between carbon disulfide and Parkinson's disease.

Refined petroleum solvents constitute a group with toxic properties which vary according to their composition. Apart from dermatitis and mucosal irritation, commonly observed, these solvent mixtures can affect the peripheral nervous system (PNS) because of n-hexane, the hematological system because of benzene, etc. [NIOSH 1977c].

4) Neurotoxicity

Neurotoxicity is a prominent feature of the adverse health effects of organic solvents, most of which produce loss of consciousness when inhaled in sufficient quantity [Axelson *et al.* 1980: 237]. As mentioned earlier, several solvents were used as general anesthetics: ether, chloroform, ethylene, ethylene dichloride, acetylene, cyclopropane, trichloroethylene, ethyl n-propyl ether, cyclopropyl methyl ether, propylene, etc. [Fulòp-Miller 1938; Keys 1963].

The exact mechanisms by which solvents affect the central nervous system are still somewhat conjectural. Disturbance of the cells lipid layer may result in changes in membrane permeability; there are also indications of effects on neurotransmittor concentration - through inhibition of dopamine ß-hydroxylase by carbon disulfide, for example - at the synaptic level, and of blood hormone levels [Swedish Work Environment Fund 1980: 72-76; Cavanagh 1985]. At the peripheral nervous system level, some solvents produce a syndrome of axonal swellings due to accumulations of

neurofilaments and of an attenuation of the myelin over the swellings; these neurofilament aggregations would be caused by solvent metabolites (e.g. 2,5-hexanedione) reacting with the neurofilament proteins [Cavanagh 1985].

Five organic solvents are proved human neurotoxicants: carbon disulfide, n-hexane and methyl n-butyl ketone (with or without methyl ethyl ketone), toluene (substance abuse only) and impure trichloroethylene (dichloroacetylene as a composition or metabolic product) [Spencer and Schaumburg 1985]. All of these have also been linked with neurotoxicity in animals [Bus 1986].

Several studies have provided substantial evidence of adverse effects of CS_2 exposure on both central and peripheral nervous systems [Hänninen 1971; Mancuso and Locke 1972; Knave *et al.* 1974; Seppäläinen and Tolonen 1974; Wilcosky *et al.* 1984].

n-Hexane and methyl n-butyl ketone have been proven, by human and animal studies, to cause the same type of peripheral neuropathy as carbon disulfide (central-peripheral distal axonopathy) following a similar metabolism; however, no consistent symptoms at the central level are associated with these two solvents [Spencer *et al.* 1980; Altenkirch *et al.* 1982; Cavanagh 1985].

Toluene abuse - mostly as glue sniffing - has been linked to a progressive syndrome of brain damage accompanied by brainstem and/or cerebellar atrophy; the onset of the syndrome takes place after one to twenty years of exposure to several parts per million of toluene [Spencer and Schaumburg 1985]. These findings have not been substantiated by studies on toluene exposed workers, but exposure in the workplace was usually around 100 to 300 parts per million [Elofsson *et al.* 1980; Iregren 1982; Struwe and Wennberg 1983].

Trichloroethylene (TRI) intoxication produces sensory loss and motor weakness in cranial nerves, particularly in the distribution of the trigeminal nerve [Spencer and Schaumburg 1985]; the biological mechanism is unknown, but could be linked to a viral infection [Cavanagh 1985]. In the 1950's, cross-sectional studies of workers exposed for a long time to a low level of TRI found signs of neurological and neuropsychiatric effects [Grandjean *et al.* 1955; Bardodej and Vyskocil 1956].

Studies on laboratory animals have also identified a few other solvents that can be considered as potential neurotoxicants in man, e.g. nitrobenzene, ethyl n-butyl ketone, styrene, and ethyltoluene [Bus 1986].

Still other solvents are suspected of eliciting adverse effects on the central and/or peripheral nervous systems, but the lack of consistent results between animal and human studies, and also between similar human studies, leaves the question in doubt.

5) Combined exposures

a) Mixed exposures

Excess mortality from esophagus and stomach malignancies has been reported among painters in the United States [Viadana *et al.* 1976]. Wilcosky and his colleagues [1984] found, among a cohort of rubber industry workers, a significant association between lymphosarcoma (9 cases) and exposure to CS_2, CCl_4, hexane and xylene, and also between lymphatic leukemia (10 cases) and CS_2, CCl_4, acetone and ethyl acetate exposure. An association was found between exposure to organic solvents and Hodgkin's disease in two Swedish case-control studies [Olsson and Brandt 1980; Hardell *et al.* 1981]; the second study also found an increased risk of non-Hodgkin malignant lymphoma.

Car painters, who are exposed to a variety of solvents including toluene, xylene, butyl acetate, white spirit, methyl isobutyl ketone, isopropanol, ethyl acetate, acetone and ethanol [Kurppa and Husman 1982], have been found to suffer from vestibular dysfunction [Arlien-Søborg *et al.* 1981]; active workers had normal liver enzyme activities [Kurppa and Husman 1982]. One paper [Milling Pedersen *et al.* 1980] reported significantly elevated levels of serum creatinine kinase (an indicator of damaged muscular tissue) among solvent intoxicated patients.

Scandinavian studies on exposure to mixed solvents and pregnancy outcome among laboratory workers used mainly information from interviews with the mothers. Strandberg *et al.* [1978] found an increased risk of miscarriage among hospital laboratory workers, but the study population was small and the increase was of borderline significance ($p \simeq 0.05$, one-tailed); Hansson *et al.* [1980] showed increased proportions of miscarriage, of perinatal death and of major malformations in chemical laboratory workers. These findings were not fully substantiated by Axelsson *et al.* [1984] who did not find differences in perinatal deaths or malformations, but an increased rate of miscarriage when shift work was done during pregnancy.

A review of 14 studies on exposure to anesthetic gases, most of which are solvents, indicated an increased risk of spontaneous abortion among exposed females (but not among wives of exposed males), and no definite evidence of increased congenital abnormality rates [Tannenbaum and Goldberg 1985]. Olsen and Rachootin did not find any effect of parental solvent exposure on birthweight [1983]. A large study made in Montreal [McDonald and McDonald 1986] showed a significant excess of stillbirths without defect among female leatherworkers, and the authors concluded this could likely be due to solvents used in glues. Two case-referent studies found an excess of parental exposure to organic solvents (defined by job titles) among children dying from cancer

before the age of five [Fabia and Thuy 1974], or brain tumors before the age of ten [Peters *et al.* 1981].

b) Interactions

Logically, any substance modifying the activity of enzymes affecting the metabolism of solvents will affect their biotransformation. Cigarette smoking, alcohol and drug consumption have all this potential [WHO Expert Committee 1981: 32].

Toluene has been reported to slow the metabolism of other aromatic hydrocarbons [Ikeda *et al.* 1972] and to potentiate the toxicity of perchloroethylene in the rat [Withey and Hall 1975]. Animal experiments showed a potentiation of haloalkane-induced hepatotoxicity when administration of ketones and ketogenic agents precede the exposure to halogenated alkanes [Abdel-Rahman *et al.* 1976; Hewitt *et al.* 1980]. Exposure of rats to m-xylene also disturbed their microsomal enzymatic activity [Elovaara 1982]. Severe liver necrosis was reported in three workers exposed simultaneously to carbon disulfide, isopropanol, toluene and acrylonitrile; the authors attributed the damage to an interactive effect of the chemicals [Døssing and Ranek 1984].

The mechanisms of interaction between alcohol and solvents are numerous. Ethanol's vasodilator effect and increased capillary permeation accelerates solvent distribution; it increases hepatotoxicity associated with chlorinated solvents [Haguenoer *et al.* 1982; Hills and Venable 1982]; and may blur the neuropathic and neuropsychological pictures of solvent exposure [Juntunen 1982]. Alcohol often inhibits microsomal metabolism enhancing the blood levels of unchanged solvents [Riihimäki *et al.* 1982; Waldron *et al.* 1983].

Potentiation of carbon tetrachloride toxicity was observed among workers of an isopropyl alcohol packaging plant in the United States [Folland *et al.* 1976]. Ingestion of alcohol simultaneously with exposure to trichloroethylene slowed down considerably solvent metabolism in a study on volunteers [Muller *et al.* 1975]. Ethanol seems to worsen the visuo-motor performance of persons exposed to trichloroethylene [Ferguson and Vernon 1970], and the body balance (it increases body sway) of persons exposed to xylene [Savolainen *et al.* 1980b].

The important question of interactions deserves much more research.

C. MENTAL DISORDERS

1) Classification

The first International Classification of Mental Disorders was issued in 1889, comprising eleven groups, and mental disorders were included for the first time in the WHO International Classification of Diseases (ICD) in 1948 for its 6th revision.

Despite the international standing of the ICD classification system, Scandinavians and Americans still use their own systems.

Two broad classification schemes are generally used in North America: the WHO ICD-9 (9th revision), Chapter V-Mental Disorders, and the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) produced by the American Psychiatric Association. The ICD-9 is used by the hospitals' nosologists, and the DSM-III by psychiatrists to describe their diagnoses.

Kraepelin's (1855-1926) work on mental disorders led to a three-faceted classification: organic psychoses, endogenous psychoses without known structural pathology, and deviations of personality and reactive states [Mayer-Gross *et al.* 1960: 15]. Psychotic conditions imply disorders in which impairment reaches a degree where it interferes "grossly with insight, ability to meet some ordinary demands of life or to maintain adequate contact with reality" [WHO 1977: 177].

From an etiological point of view, mental disorders can be classified in two broad categories, organic and non-organic (or functional), the former characterized by histopathological lesions in certain parts of the brain, whereas little or no pathological lesion is found in the latter [Mayer-Gross *et al.* 1960: 419].

Both ICD-9 and DSM-III differentiate organic mental disorders from other disease categories. ICD-9 pools under 'Organic psychotic conditions': 'Senile and presenile organic psychotic conditions' (290), 'Alcoholic psychoses' (291), 'Drug psychoses' (292), 'Transient organic psychotic conditions' (293), and 'Other organic psychotic conditions (chronic)' (294) [WHO 1977: 177-182]; the DSM-III also adds to its 'Organic mental disorders' category intoxications by alcohol and drugs and syndromes resulting from brain damage, which are classified in the ICD-9 under 'Neurotic disorders, personality disorders and other non-psychotic mental disorders' (codes 303, 304, 305 and 310) [Spitzer *et al.* 1981: 372-373]. Annex 1 lists the principal disease categories and sub-categories used in this thesis (ICD-9).

2) Etiological theories

Psychiatric textbooks generally classify causes of mental disorders chronologically into predisposing, precipitating and perpetuating factors [Gelder *et al.* 1983: 84-85]. Predisposing causes have to do with the mental and physical make-up of a person at birth (or his constitution) and modifications as years go by; this concept implies that an individual may be predisposed to mental disorder, although he may never develop one. Precipitating factors convey the notion of inducing the disorder in a predisposed subject. Perpetuating factors finally prolong the course of a disease.

According to Gelder *et al.* [1983: 87], etiological theories in psychiatry follow two general patterns: reductionist models that look back at simpler earlier stages in an individual (thus 'pinpointing' a few more or less discrete causes), and non-reductionist models, that look outward to further complicated and wider issues (for example attributing the disease to family circumstances). Organic mental disorders are then to be explained by reductionist models and non-organic (functional) disorders by either reductionist or non-reductionist models.

Schizophrenia and affective disorders are the only two that gather some form of consensus on their association with genetic factors [Gelder *et al.* 1983: 203-204, 246-249; Gruenberg 1980: 1347; Weissman and Klerman 1978]. Many mental disorders have been attributed to poisons and other harmful extraneous substances; Gruenberg [1980: 1330-1334] presents two tables prepared by the American Public Health Association where 20 infectious agents and more than 70 poisons are imputed as causing mental disorders. About 32 of these are related to occupational exposure: mainly heavy metals (lead, mercury, manganese, cadmium), organic solvents (benzol, carbon disulfide) and drugs. Indeed, Kraepelin and Lange mentioned in their classical textbook organic mental deterioration and transient delirious psychoses associated with carbon disulfide in 1927 [Mayer-Gross *et al.* 1960. 340-343]. However, these assertions were largely based on uncontrolled case reports [Mayer-Gross *et al.* 1960. 341-343, 621-657].

Finally, some forms of dementia have been linked to viruses, namely Creutzfeldt-Jakob disease, Kraepelin's disease and Parkinson-dementia complex of Guam [Haase 1971; Roth 1980; Crapper-McLachlan and deBoni 1980].

If organic solvents hold a place in the etiology of mental disorders, they could do so in various ways. They could predispose to mental disorders through deleterious effects on the CNS - poor nerve conduction, hormonal disturbances, alterations of respiration and protein synthesis [Joint WHO/Nordic Council of Ministers Working Group 1985]. They could also trigger the onset of symptoms in a predisposed or genetically susceptible individual - deleterious effects on the CNS causing the predisposed person to feel sick and depressed.

3) Factors associated with mental disorders

In accordance with the multifactorial etiology of mental disorders, many psychosocial factors have been identified and associated with increased rates of mental disorders: social class, life stress, social mobility, urban anomia, migration, segregation, sick role behavior, personality and childhood experiences [Weissman and Klerman 1978].

Increases in mental illness rates among immigrants appear to be linked to age at immigration, length of stay in the adoption country, country of origin, reasons for immigration, social isolation, hardiness of the immigrants' personality, and many other factors very difficult to correct for in analyzing rates [Kuo 1976; Kuo and Tsai 1986]. Cultural values and attitudes also appear to influence the symptomatology of mental disorders, and consequently their treatment [Murphy 1974].

D. NEUROBEHAVIORAL EFFECTS OF SOLVENTS

1) Animal studies

As pointed out by Tilson *et al.* [1979], two methodological problems in behavioral toxicology affect the use of animal models in studying neurobehavioral effects of solvents. First there is "...the insidious onset of effects..." and, second, "...the subjective nature of the complaints that are associated with earlier stages of toxicosis."

The methods used to assess neurobehavioral effects in animals commonly consist of cage-side observations of clinical signs and reflexes [Bus 1986; Evans *et al.* 1981]. Alpers and Lewy [1940] reported behavioral effects (excitation, aggression, apprehension, apathy) and neurotoxic effects (tremor, ataxia, muscle flaccidity and spasticity) of exposure to CS_2 in dogs evaluated by observation. Assessment of learned behaviours is now used more frequently, and reports can be found on exposure of rats, mice, pigs, dogs, pigeons, gerbils, baboons and squirrel monkeys to dichloromethane, carbon disulfide, toluene, trichloroethylene, methyl ethyl ketone, methyl isobutyl ketone, and other solvents [Winneke 1981; Wood 1981; Benignus 1981; Annau 1981; Geller *et al* 1979].

The results are often inconsistent and confusing; according to Annau [1981], because of an array of factors, these include the use of different techniques, the lack of statistical power in many studies and the absence of solvent concentration measurements during exposure The use of widely different animal species also reduces consistency. Another major problem in assessing so-called chronic effects is the use of high concentrations from which the prominent narcotic effects blur those less immediate [Colotla *et al.* 1979, Colotla *et al.* 1980; Winneke 1981].

Despite these reservations and the fact that studying truly neuropsychiatric effects of solvents in animal models is almost impossible, these studies can be helpful in describing the effects of low level and repeated exposures [Bus 1986]. Thus, Taylor and Evans [1985] produced in the monkey impairment of cognitive function by toluene using repeated exposures ranging from 100 to 4500 ppm (over 6 weeks, twice a week). Haglid *et al.* [1985] exposed Mongolian gerbils to trichloroethylene (60 ppm),

tetrachloroethylene (60 ppm), methylene chloride (350 ppm) and ethanol (11.7g/kg/day) for 3 months, let the animals recuperate for 4 months, and found increased levels of protein in the astroglial cells of the brain - an indication of brain damage.

Nevertheless, there remains the need for the development of more sensitive tests of impaired performance in animals [Wood *et al.* 1983].

2) Human studies

a) Solvent abuse

Adverse health effects of solvent abuse - excess intake of alcohol or misuse of glues and other volatile substances - although not directly applicable to occupational exposures, are informative in that they reflect a 'worst situation': abusers are often malnourished and in poor general health, and they voluntarily expose themselves to huge quantities of solvents. Reports on psychological deficits in abusers merit attention because, if there were no problem, it would be unlikely that workers exposed to much lower levels would suffer any [Cherry *et al.* 1982]. Alcoholism and glue sniffing are presented as two examples of solvent abuse causing neurobehavioral adverse health effects.

1. Alcoholism

Ethanol, the alcohol in beer, wines and spirits, is an organic solvent industrially used in the fabrication of resins [Durrans 1971: 113]. Although ethanol enters the body by mouth, it is absorbed unchanged into the blood from the stomach, and so shares a common metabolism with inhaled alcohols [Shoemaker 1981]. Studies of alcoholics therefore provide a valid substitute for persons occupationally exposed to alcohols

Ingested ethanol undergoes oxidation to acetaldehyde, and then to acetate, in the liver; if this metabolism is altered, by the competing presence of other solvents for example, acetaldehyde levels increase [Haguenoer *et al* 1982; Hills and Venable 1982]. This accumulation is responsible for the 'Antabuse' effect seen after ingestion of disulfiram; this flushing effect has also been observed among workers exposed to high levels of CS_2 and to trichloroethylene [Haguenoer *et al* 1982, Hills and Venable 1982] Alcohols seem to exert their toxicity mainly by decreasing the viscosity of biological membranes, resulting in alterations of interactions between neurones in the central nervous system, probably by modification of the sodium balance [McCreery and Hunt 1978].

Several neuropsychological studies indicated some evidence of cognitive loss among long term alcoholics. Parker and co-workers [1974] noted poor conceptual function in a small group of alcoholics (sober for 3 weeks before tests) compared to non-alcoholics

alcoholics and reported impairment in active adaptation and abstract thinking. In the United States, Brandt *et al.* [1983] demonstrated memory and visuoperceptual disorders among detoxified alcoholics when compared to matched non-alcoholics, and observed improvement after prolonged abstinence of performance on tasks requiring short-term retention of verbal and non-verbal information. A study among 1367 working men and women in the Detroit region showed that cognitive function was inversely correlated with the amount of alcohol consumed per drinking occasion [Parker *et al.* 1983].

Ron *et al.* [1980] described radiological abnormalities extending to both the cortex and ventricules (a picture termed 'brain shrinkage') among male alcoholics as compared to non-alcoholic referents.

A particularly severe form of brain damage, Korsakow's psychosis, has long been recognized among alcoholics: this disease is characterized by loss of recent memory, confabulation, shallowness of affect and polyneuropathy [Luby 1981]. This syndrome appears to result from the concomitant effects of long term excessive alcohol intake, malnourishment and thiamin deficiency [Berkow and Talbott 1977: 1522].

A few etiological studies probed the hypothesis that long term excessive alcohol intake accelerated aging of the brain that is held responsible for the neuropsychological deficits observed in alcoholics. Blusewicz and his colleagues [1977] investigated the performance of 'young normals' (average age 31 years), 'young alcoholics' (mean age of 33 years) and 'elderly normals' (average age 71 years) on several neuropsychological tests; among the alcoholic group, they observed a general decline in performance on short-term memory and abstract reasoning tests. This decline was less important than that of the elderly group, but significantly different from that of the young normal group. Using a cross-sectional design, Ryan and Butters [1980] administered a series of cognitive tests on small groups (20 subjects each) of younger (34-49 years old) and older (50-59 years old) detoxified alcoholics and non-alcoholics, matched for education and Wechsler Adult Intelligence Scale (WAIS) vocabulary scores. They reported impairments of all measures of learning and memory, in the alcoholic groups; the impairments were compatible with both a premature-aging hypothesis, and an hypothesis of cognitive deterioration, additive to that seen with normal aging, but independent of it.

New trends of research in that direction now include evoked potential (EP) techniques that record electrical brain activity following the delivery of a discrete stimulus Porjesz and Begleiter [1982] argue that despite some electrophysiological similarities between aging and alcoholism, the cause of aberrations may be quite different. In support of this view, they present the results of a study on event-related

different. In support of this view, they present the results of a study on event-related potentials where they observed voltage aberrations in alcoholics and latency dysfunctions in elderly subjects.

Finally, Overall and others [1978] examined the performance of patients with several psychiatric diagnoses, including alcoholism and organic brain syndrome, on WAIS subtests; after controlling for some factors influencing the WAIS scores, they observed that the alcoholics performed quite similarly to patients with organic brain damage.

From these studies, the existence of cognitive deficits among subjects with a lengthy history of heavy alcohol intake can hardly be disputed. These deficits are common to solvent workers exposed for a long time [Arlien-Søborg *et al* 1979; Juntunen *et al.* 1980; Seppäläinen *et al.* 1980; Struwe *et al.* 1983; Linz *et al.* 1986], and to patients suffering from degenerative brain disorders presenting as dementia [Roth 1981].

2. Solvent sniffing

The term solvent abuse implies sniffing solvent-containing substances such as adhesives, various cleaning substances, petrol, aerosols, paraffin, butane, lighter fluid, furniture polish, etc. [Chaudron 1978; Anderson *et al.* 1982]; these substances contain toluene, and some of them, hexanes and heptanes, ethyl acetate, acetone, methyl ethyl ketone, methylene chloride, 1,1,1-trichloroethane, etc. [Akerman 1982; Clark and Tinston 1982]. Health effects of this practice vary according to the type of solvent involved and include aplastic anaemia, acute hepatic and renal damage, peripheral neuropathy, encephalopathy and optic atrophy, etc. [Tenenbein *et al* 1984, Sourindrhin 1985]. These parallel the severe chronic toxic encephalopathy found in toluene abusers [Lazar *et al.* 1983]. Brain damage progresses after one to twenty years of repeated exposures to very high concentrations of the solvent. The first signs resemble those found in solvent workers: anxiety, irritability, mood swings, forgetfulness, impairment of cognitive function, emotional instability, etc. [Spencer and Schaumburg 1985]. However, the human evidence linking solvent abuse to encephalopathy is based only on case reports; no epidemiological studies have so far been reported [Knox and Nelson 1966; King *et al.* 1981; Lazar *et al.* 1983].

b) Occupational exposure

Very many studies have been published, mostly since the early 1970's, on the neuropsychiatric effects of solvents; most deal with acute and subacute effects, and few with long term effects.

1. Acute and subacute effects

Evidence on acute and subacute effects of solvent exposure on humans depend mainly on case reports, experimental laboratories studies, and epidemiological studies (chiefly cross-sectional and a few cohort studies).

Case reports can be considered an early warning signal. In her well known book on the toxicity of solvents, Browning [1953] cites numerous case reports for every chemical class of solvent. The common features of acute and subacute neurobehavioral effects include giddiness, headache, staggering gait, anxiety, euphoria and excitation, with narcosis at high concentrations. These effects have been described in case reports for many years (for example Browning [1953] cites a report on xylene by Rosenblath in 1902).

Laboratory studies can investigate solvent metabolism and determine the threshold of concentrations producing neurobehavioral effects. Experimental exposure of human volunteers was practiced extensively in the 1970's and early 1980's. A review of 35 studies using behavioral performance tests to assess solvent toxicity underlines their principal findings [Gamberale 1985]. The exposure conditions varied across the studies (from one to eight hour-exposures, solvents used alone or in combinations with drug or alcohol ingestion, with and without exercise, pure single solvents or mixtures of commercial grade). Most of the investigated solvents produced decrements in performance at relatively low concentrations (i.e. at concentrations below permissible limits). This was true for chlorinated solvents (methylene chloride, trichloroethylene, 1,1,1-trichloroethane), aromatic solvents (toluene, styrene and xylene) and also for white spirits.

A review of all the epidemiological studies on acute and subacute effects of organic solvents is not relevant to this thesis which is oriented toward chronic effects of long term exposure. Annex 2 presents several epidemiological studies (all cross-sectional except for that of Anshelm Olson *et al.* [1981] which was a cohort study), some of which aimed at investigating the effects of long term exposure. As these studies could not determine whether the effects were permanent, they are listed in the annex as acute and subacute. Their prominent features are narcotic symptoms (drowsiness, dizziness), and mood changes with irritability, tiredness, etc. Slower reaction times are often encountered in exposed workers, but most authors cannot disclose subacute effects imputable to actual solvent concentrations in the body and the effects that are not transient. Neurasthenic symptoms (fatigue, nervousness, lack of manual dexterity) are also frequently reported, but again personality changes are not consistent.

The major question in the cross-sectional studies concerns the comparability of the groups in performance of various tests prior to exposure.

2. Long term effects

Case studies have provided a picture of the full syndrome of solvent poisoning and give some indication of its reversibility; that syndrome has been termed 'psychoorganic syndrome' in Finland and Sweden, and 'presenile dementia' in Denmark and Norway [Gamberale 1985], but an international consensus has been reached to call it 'chronic toxic encephalopathy of mild or severe degree' [Baker and Fine 1986] The clinical picture consists of: fatigue, headache, dizziness, anxiety, depressive complaints and personality changes, with defective memory, concentration and learning capacity [Arlien-Søborg *et al.* 1979; Juntunen *et al.* 1980, Seppäläinen *et al.* 1980; Struwe *et al.* 1983; Linz *et al.* 1986]. A Swedish study of 128 cases of psychoorganic syndrome revealed a minimum exposure duration of nine years, with 'incipient' syndromes after a minimum of 3 years of exposure [Flodin *et al* 1984].

Scandinavian follow-up studies of intoxicated workers did not show much reversibility of damage, except possibly some improvement of subjective symptoms (headache, dizziness, etc.) [Bruhn *et al.* 1981, Juntunen *et al.* 1982]. The patients did not die rapidly as do patients suffering from Alzheimer's dementia [Arlien-Søborg *et al.* 1982]. The psychological prognosis seemed to be better for younger men, with a better recovery of intellectual functions [Lindström *et al.* 1982].

A Danish follow-up study of 21 painters who stopped work because of encephalopathy showed that 11 of them - the younger subjects with the least impairment of intellectual functions and the least exposure - had found another job 5 years later [Gregersen *et al.* 1987].

Thus clinical studies shed some light on a condition that appears to be encountered in solvent-poisoned workers, but as they are uncontrolled they do little to clarify an etiological relationship between occupational organic solvent exposure and neuropsychiatric disorders. This is especially so given the non specificity of the disease entity and the widespread exposure to solvents.

Thus we are left with six studies with which to evaluate long term effects of solvent exposure: five of those are case-referent in design [Axelson *et al.* 1976; Olsen and Sabroe 1980; Lindström *et al.* 1984; Rasmussen *et al.* 1985; O'Flynn *et al.* 1987], and the sixth longitudinal [Mikkelsen 1980].

The first epidemiological study on long term neuropsychiatric effects of organic solvents was conducted in Sweden [Axelson *et al.* 1976]. The subjects were skilled workers in various construction trades, selected from a regional pension fund register

(in the province of Örebro), between 1969 and 1972. Cases were defined as men between 35 and 64 years old when considered for a disability pension because of mental disorder or certain somatic disorders (such as 'atrophia cerebri', 'vertigo and encephalopathia', 'nervositas' and 'cephalalgia'). The diagnoses of primary debility, schizophrenia, manic-depressive psychosis, and mental disorders of obvious somatic origin (e.g. dementia due to brain trauma) were excluded. Alcoholism was included but treated separately. The referent subjects were disability pensioners from the same register "completely free of any kind of mental disorder or social experience which might indicate mental disorder"; no more details are given about the referent selection process, and we must assume that they were probably stratum-matched to the cases.

Solvent exposure was defined in terms of the number of years spent as a painter, varnisher or carpet layer, the minimum being 6 months; this was later divided, for statistical purposes, into less than or equal to 30 years and more than 30 years. Of the potential confounders identified by the authors, account only was taken of age. Occupational histories were extracted from the Pension Fund Register's files. The solvents thought characteristic of these occupations were turpentine and a mixture of aliphatic and aromatic hydrocarbons within the C_6-C_{10} range.

On a total of 151 cases and 248 referents, 35 subjects in each group had been in one of the three 'exposed' jobs, yielding a relative risk of 1.8 of receiving a disability pension for a mental or related somatic disorder. There was some indication of an exposure-response relationship: an exposure of 30 years or less gave a risk ratio of 1.3 and an exposure of more than 30 years, a risk ratio of 2.3.

A further analysis of the same data looked into separate diagnostic categories and found a 'crude rate ratio' of 2.5 for senile and presenile dementia, and one of 2.0 for 'nervositas' [Axelson 1982]; however the number of subjects in each of these diagnostic categories was rather small (7 cases and 17 referents with senile and presenile dementia, 7 cases and 21 referents with 'nervositas').

Two studies made in Denmark appeared in 1980. Olsen and Sabroe [1980] conducted what could be called a case-referent study within a cohort, all the subjects being members of the Carpenter/Cabinet Makers' Trade Union who received disability or old-age pensions between January 1971 and December 1975. The cases were selected for disability or early retirement with diagnoses of 'psychoses, neuroses, changes of character, oligophrenia, mental retardation and diseases of the nervous system or sense organs' either as the main diagnosis in early retirees, or as a main or secondary diagnosis in those with disability. The referents, also chosen among new pensioners but with diagnoses of physical disorders, were matched with the cases for the type of pension

received and for age (closest age-match). In both series, the diagnoses were ascertained from the hospital records.

Information on occupational exposures, alcohol consumption and medical history was gathered from a self-administered questionnaire mailed to all study subjects, and was complemented from trade union's files. High solvent exposure was defined as employment in lacquering or glueing ('indoor' and 'outdoor') for at least 4000 hours; being a cabinet-maker also defined exposure in a sub-analysis of the data. To correct for potential confounders, the study subjects were categorized according to their age, their alcohol consumption and previous head injury with unconsciousness. The solvents concerned in this study were those found in lacquers, glues and paints, without further identification of their chemical nature.

The authors identified 171 pairs from the disability pensioners and 35 pairs from the early retirees. Among the first group, 124 of the 141 traced cases and 135 of the 146 traced referents filled the questionnaire. Among the second group (old-age pensioners), of the 28 traced cases and 27 traced referents, 24 cases and 24 referents returned the questionnaire. Analyses were made separately for the two types of pensioners, for various diagnostic groups and for indoor and outdoor exposures. A statistically significant increase in relative risk (RR) was found among disability pensioners (RR=2.80 for indoor exposure and 2.12 for any exposure); among cabinet-makers the relative risk was raised (RR=1.79) for disability pensioners doing surface treatment. Further analyses, focusing on particular diagnostic categories among the disability pensioners, revealed, for those exposed indoor for more than 4000 hours, a significant increased risk of dementia (RR=2.00) and of non-psychotic psychiatric diagnoses (RR=3.11). Cabinet-makers were likewise found to have an elevated risk of non-psychotic psychiatric disorders, whether or not they were doing wood surface treatment (RR=2.24, and 2.29 with surface treatment).

The second Danish paper is the only reported longitudinal study on neurobehavioral long term effects of organic solvents to date [Mikkelsen 1980]. This historical cohort study looked at the incidence of disability pensioning and death, between January 1971 and December 1975, among a cohort of 2601 male painters and 1790 male bricklayers from the Copenhagen area. The cohorts were established using records from three local trade unions and comprised all men born before 1941 who were members of these unions in January 1971.

The outcomes were ascertained from the disability pension files under the label 'pension diagnoses'. As the author was specifically interested in presenile dementia and as the pension diagnoses were grouped heterogenously, the psychiatric diagnoses were

reclassified to extract 'presenile dementia with and without cause-indication' from the other groups, namely 'psychoses', 'diseases of the nervous system (excl. epilepsy)' and 'neuroses, personality disorders, etc.'. As a blind reclassification was not possible, and to lessen observer bias, the case diagnoses were required to include the terms 'dementia or some close equivalent' among psychotic diagnoses, and 'cerebral atrophy or some close equivalent' among diseases of the nervous system. Only age was controlled as a potential confounder. The types of solvents used were not detailed except a specific reference to white spirit

A total of 143 painters and 75 bricklayers had been awarded a disability pension during the 5 years of the study, and death certificates were obtained for the 291 painters and 169 bricklayers who died during the same period. All the analyses were made by comparing the painters first to the bricklayers, and then to the general male population of Copenhagen. The author found an increased relative risk of disability pensioning, among painters compared to bricklayers and to the Copenhagen male population, due to 'psychoses' (RR=2.1 and 1.9 respectively) and to 'neuroses, personality disorders, etc.' (RR=2.8 and 1.7 respectively). A further analysis on presenile dementia showed an increased relative risk for painters, again compared to both types of referents, especially for presenile dementia without cause-indication (RR=3.3 to 3.6 depending on whether only chief diagnoses or chief and subsidiary diagnoses were considered). The relative risk of death from the circulatory system for painters compared to bricklayers, 1.3, was of borderline significance (95% CI=1.0-1.8).

In Finland, Lindström *et al.* [1984] conducted a case-referent study very similar to that of Axelson and colleagues [1976]. The study subjects were selected from construction workers who first became, between the ages of 30 and 64 years, recipients of a disability pension, during the period 1978 to 1980, as registered at the Finnish Employment Pension Fund. Cases were those receiving a pension from a psychiatric diagnosis or specified somatic disorder ('psychosomatic disease', 'cerebral atrophy', 'vertigo or encephalopathy' and 'nervositas'), excluding primary debility, schizophrenia and mental disorders with obvious extraneous causes (e.g. encephalitis, traumatic disorders, etc) As in the Swedish study [Axelson *et al.* 1976], alcoholism was included and analyzed separately. Referents were construction workers who had received a disability pension for non-neuropsychiatric reasons; they were pair-matched with the cases on the time of pensioning and age at that time (within 2 years).

Exposure to solvents was defined by jobtitle, painters and carpetlayers being considered as the only ones exposed, and all others treated as unexposed. For some

analyses, the exposure duration was divided into less than 16 years and more than or equal to 16 years in the exposed jobs. Age at time of pensioning was taken into account as a potential confounder (by the matching procedure). Information on the occupations held by the pensioners was extracted from the Employment Pension Fund Register. Here again no particular organic solvent was identified by the authors as being representative of the painters and carpetlayers' exposure.

Of the total of 374 pairs thus constituted, 10% of cases and 6% of referents had been exposed. A statistically significant increase in the odds ratio estimate was found only for the group of 'neurosis, persona pathologica, psychosomatic disease' and 'nervositas' (OR=5.5). A dose-response relationship could not really be investigated because of the small number of exposed subjects.

A third Danish study was published in 1985 [Rasmussen *et al.* 1985]. Using a case-referent design, the investigators studied senile dementia and encephalopathia among male applicants for nursing home and other social support facilities between 1981 and 1983. The study subjects comprised all males under 81 years of age admitted to a local geriatric ward in Odense for an assessment of their need of supportive facilities. The diagnoses (main one and up to eight secondary diagnoses) used to define the cases and referents were made during hospitalization at the geriatric ward. The case group diagnoses included 'senile and presenile dementia', 'alcoholic psychosis', 'psychosis (from atherosclerotic or cerebrovascular disturbances)', 'cerebral and cerebellar atrophy', 'cerebrovascular disease', 'hypertensive encephalopathia', 'ischemic cerebral atherosclerosis' and 'other cerebrovascular diseases'. The referent group was selected from the remaining subjects who were awarded supportive facilities, but for other reasons. Both onset of a chronic disease or presence of a 'serious handicap' before the age of 50 caused the exclusion of a study subject.

Two sources of data were used: the medical records (for diagnosis, established supportive facilities, social status, physical fitness, previous head traumas, clinical symptoms of atherosclerosis and jobtitles) and mail questionnaires or telephone interviews (for the longest-held occupation, employment for more than five years in 7 solvent-exposed jobs, and alcohol consumption). Whenever it was impossible to complete a questionnaire because of a refusal or lack of an informant for a deceased subject, the jobtitle reported in the medical record was used as a substitute; this happened in 27 cases and 30 referents. Solvent exposure was assessed by two methods: i) by using the job-exposure matrix of Ravnskov and colleagues [1983] to classify the longest-held job as 'never', 'rarely', 'often' or 'always' exposed to organic solvents, and

ii) classifying as 'exposed' any subject who had worked more than 5 years in one of the seven specific occupations and as 'unexposed' all the others.

Of the 767 men aged less than 81 years of age at time of hospital admission, 229 were eligible as cases. Thirty-six percent of the mailed questionnaires were returned and telephone interviews were used for the rest of the study population. The authors did not find any significant increase in the rate ratios of suffering from 'late encephalopathia' among solvent-exposed individuals, except for a rate ratio of 1.7 of 'borderline significance' (*sic*) when comparing the 'often' and 'always' exposed to the 'never' and 'rarely' exposed (based on the longest-held jobtitle classified according to the job-exposure matrix). Correcting for income, education, vocational training, occupational status before pensioning and need for social support did not change much the estimates of odds ratios. Finally, a further analysis by diagnostic categories again contrasting 'often' and 'always' exposed to 'rarely' and 'never' exposed, did not produce statistically significant results, although there was a trend toward higher rate ratios for psychotic diseases, cerebrovascular diseases and senile dementia.

The most recent study to have been published on long-term neuropsychiatric effects was also a case-referent study, using solely death certificates as the source of data [O'Flynn *et al.* 1987]. The authors had begun to set up a study of Alzheimer's disease but abandoned that project because of too few eligible subjects. In the course of this work, they had obtained copies of all death certificates bearing 'dementia' (when the man was less than 65 years old at his death), 'presenile dementia' or 'Alzheimer's disease' as a cause of death for all the men who died in England and Wales between 1970 and 1979 inclusively. The 557 cases thus defined were matched for age (±2 years) to a male referent drawn at random amongst the rest of death certificates.

General demographic data as well as the subject's most recent full time paid job were extracted from the death certificate. The jobtitles were then classified into one of 3 categories ('no exposure', 'possible exposure' and 'probable exposure') in relation to solvents and to lead.

In a total of 557 pairs, 30 cases and 22 referents had a 'possible' exposure to solvents, while 13 cases and 17 referents had a 'probable' exposure. No increase in the relative risk of death with presenile dementia was apparent for either exposure to organic solvents or lead. The authors recognized that data from death certificates are far from the most complete and accurate source of information on both diagnoses and main life time occupation.

E. SUMMARY

Organic solvents are ubiquitous and their importance undisputed in the industrialized world. Their physico-chemical properties are responsible for their affinity for lipid-rich organs. Organic solvents encompass several types of chemicals: aliphatic and cyclic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, nitrocompounds, alcohols, ketones, ethers, esters, glycols and other solvents like carbon disulfide and petroleum solvents.

Most organic solvents are mucosal irritants and have a depressive effect on the central nervous system. Some of them have been found to produce neurotoxic effects (n-hexane, MBK, carbon disulfide, impure trichloroethylene, toluene), hematotoxicity (benzene, nitrocompounds), and hepatorenal toxicity (halogenated hydrocarbons). Adverse effects in pregnancy and the foetus (teratogenicity, foetotoxicity) and on the cardiovascular system (cardiac sensitization, ischaemic heart disease), and cancerogenicity have been demonstrated but the evidence here is less consistent.

Long term exposure to high levels of organic solvents is associated with neurobehavioral problems; this has been substantiated by both animal and human studies. Acute and subacute effects comprise depression of the central nervous system (with narcotic symptoms), slowing of reaction time, neurasthenia and mood alterations

A more or less irreversible syndrome of organic brain damage has been described in Scandinavia among solvent-exposed persons in uncontrolled clinical studies. The extent to which these findings can be solely attributed to organic solvent exposure is limited.

To date, only five published papers (all from Scandinavia) presented studies with designs that address the etiological link between organic solvents and mental disorders. A sixth published study, from the United Kingdom, was not so designed. Its findings are less clear Four of the five Scandinavian studies selected as the outcome for investigating a disability pension award on psychiatric grounds, the fifth used hospital diagnoses in a geriatric ward. The subject selection (members of a union or men over 64 years old applying for supportive facilities) and exposure definition by jobtitle limited the conclusions that can be drawn from these studies.

The three first reports [Axelson *et al* 1976; Mikkelsen 1980; Olsen and Sabroe 1980] all found an increased risk of being prematurely pensioned for a neuropsychiatric disorder. These studies included in the case definition diseases of the nervous system or sense organs), while the two later reports [Lindstrom *et al.* 1984, Rasmussen *et al.* 1985] did not find that increased risk When the data were analyzed by diagnostic categories, inconsistent results were found: dementia was increased in 3/5 studies, an increased risk of neurosis, persona pathologica and other non-psychotic

psychiatric problems in 3/5, an increased risk of all psychoses in 1/5, and finally an increased risk of 'nervousness' in 1/5. Three of the Scandinavian studies did not look at exposure-response relationships, a fourth had insufficient numbers of solvent-exposed subjects to do so [Lindström *et al.* 1984]. The fifth study [Axelson *et al.* 1976] found evidence of a stronger relation above than below 30 years of exposure.

In summary, although there is some evidence linking exposure to organic solvents and neuropsychiatric disease, numerous gaps in knowledge persist.

No study of the long-term solvent exposure and mental disorder has been published from outside Scandinavia (except the British study mentioned earlier).

It is not known whether the relationship still holds when we consider a different outcome than early pensioning due to a mental disorder (e.g. a first hospitalization in psychiatry).

A systematic dose-response relationship still has to be demonstrated.

The chronological steps leading to the neuropsychiatric disorder are not delineated. Do solvents act by damaging the brain soon after the first exposure, but with the mental disorder appearing only after a given latent period? Or do they trigger the onset of the mental disorder among predisposed subjects? Or is it a mixture of both scenarios?

It is still not clear whether solvent-exposed workers will be found more often within particular psychiatric diagnostic categories or if the effects of solvents are so unspecific that any psychiatric diagnosis has a more or less equal chance to be represented.

The pattern of exposure leading to incapacitating mental disorder also needs to be clarified. Is a heavy exposure for a short period of time more important than a lower exposure for a very long time? Or is it only a heavy, long-term, exposure that can lead to a neuropsychiatric disorder?

These are some important questions that can be addressed, at least partially, by an epidemiological study. The research project on which is based this thesis was designed to tackle some of these yet unanswered questions.

III. Research protocol

A. INTRODUCTION

Based on the Scandinavian studies and on studies of a few particular solvents, there is a high suspicion of a link between exposure to organic solvents and the development of neuropsychiatric disorders. However many areas of uncertainty remain:

- the Scandinavian studies, which first brought the attention on organic solvents as possibly increasing the risk of neuropsychiatric disorder, have not been reproduced elsewhere;
- the relationship between solvents and mental disorders has been mainly investigated by looking at early pensioning: the situation with other outcomes is still unclear;
- most of the case-referent studies entailed only a few exposed jobs - such as carpetlayers, cabinet makers, painters, etc. - mostly in the construction industry;
- some evidence of a systematic exposure-response relationship exists but remains to be confirmed;
- the chronological stages between the first solvent exposure and the onset of neuropsychiatric disorders are uncertain;
- doubts persist on specific diagnostic categories being more at risk within the classification of mental disorders;
- studies published to date barely discuss the patterns of exposure to the organic solvents leading to mental disorder (low exposures for a long time or very high exposures for one or several short periods of time, etc.).

These aspects of the relationship between occupational solvent exposure and mental disorders were addressed in the present study.

B. AIM, OBJECTIVES AND OVERALL DESIGN

The general objective was to investigate the presence of an association between mental disorders and a history of occupational exposure to organic solvents.

Several specific questions were addressed:

- Do men admitted for the first time in psychiatry between the ages of 40 and 69 have a higher frequency of previous occupational exposure?
- Is it possible to identify certain diagnostic categories that are more strongly associated ?

- Can the nature of exposure be related to mental disorder in terms of type of solvents involved, existence of an exposure-response relationship, identification of a latency period, etc.?

Lastly, the adequacy of hospital referents compared to neighborhood referents was investigated as a methodological question; it is addressed in a separate chapter.

A retrospective case-referent design was chosen. Cases were selected from men admitted, during a four-year period, to two psychiatric hospitals and the psychiatry department of one large general hospital in the Montreal area. These men were individually matched with a patient admitted for non-psychiatric reasons.

The subjects were to be interviewed by telephone - using a structured questionnaire - to obtain their work history. Solvent exposure was assessed blindly by the author for each job reported and lifetime occupational exposures were compared within each case/hospital referent pair.

C. FEASIBILITY STUDY

The pilot study had three objectives: i) test the questionnaire comprehensibility, ii) assess the feasibility of interviewing ex-psychiatric patients or one of their close relatives by telephone, and lastly iii) see whether occupational information was available from medical records.

1) Description

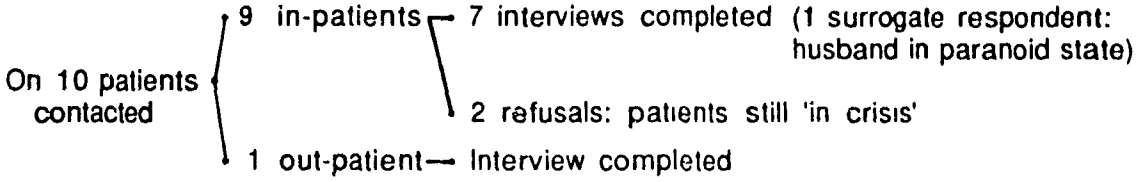
The questionnaire was tested by using face-to-face interviews with male patients hospitalized in a psychiatric ward or treated at the out-patient psychiatry clinic of a large general hospital. The subjects were selected with the collaboration of the head nurse of each ward so that they would be between 30 and 65 years of age. Diagnoses of schizophrenia and mental retardation were excluded because of the 'chronicity' attached to them. I explained the study to the patient and asked if he would agree to answer a questionnaire during a face-to-face interview. When the head nurse considered that a patient was not able to give a sound interview, the subject's relative was contacted. The interview was postponed if requested by the subject but if he refused to cooperate, no further contact was made Any patient considered to be in a crisis by the head nurse was excluded.

The second phase of the feasibility study addressed the other two objectives. Hospital admission records of men between the ages of 30 and 65, during the years 1976 to 1982, were made available to us by the Medical records department. Each record was reviewed and basic information extracted such as patient's address and telephone number, any mention of jobs, marital status, final and associated diagnoses and dates of

readmission. I telephoned the selected subjects, read to them a standard introductory statement and proceeded with the interview if they agreed. As for the first phase of the pilot study, the interview was postponed upon request by the subject, and if the latter was unable to answer a questionnaire by telephone, the interview was conducted with a close relative.

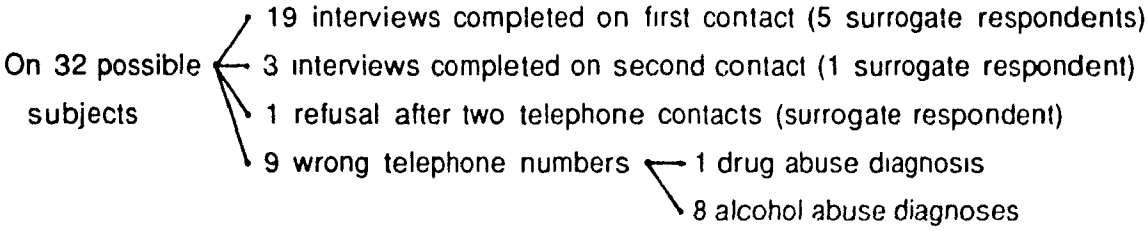
2) Results

The results of the face-to-face interviews were as follows:



The interviews lasted on average 35 minutes (15 to 65 minutes) The patients were aged between 42 and 66 years (with an average of 55.8 years), and their provisional major diagnosis covered various categories from personality disorders to manic-depressive illness and organic brain syndrome.

The results of the telephone interviews were the following:



It took on average 18 minutes to complete the questionnaire by telephone (from 10 to 30 minutes). The interviewed men were between 46 and 76 years old (average of 60.0 years), and their psychiatric diagnoses were varied, with an overrepresentation of alcoholism. The participation rate was good, 22 of the 23 traced subjects (or relatives) agreed to be interviewed (96%) As locating subjects who had moved since their last hospital admission was not an objective, only minimal efforts were invested to trace them (i e. consultation of the Montreal area telephone directory) The reasons for surrogate interviews were the following: 3 study subjects were in a chronic care facility and were not interviewable, 2 had died, one was at home but unable to use the telephone and one was in a paranoid state and afraid to talk on the telephone. The surrogate interviews, although somewhat less precise, all gave information on most of

the working history of the study subjects. Lastly, some information on occupations was present in 28 out of the 32 hospital records reviewed for the telephone pilot study.

3) Conclusions

As a result of the pilot study, the questionnaire (Annex 3) was shortened and many questions were modified to make them more easy to understand. Sensitive questions that were not essential were removed - e.g. if the subject was living alone or with someone else; so were questions that were too detailed - e.g. questions on the number of hours per week exposed to each chemical, or type of personal protection used in each job. Several questions were cut out of the questionnaire because they were not important and unnecessarily lengthened the interview. The pilot study also helped to clarify which interviewer's remarks might be usefully collected.

The 'Hospital extraction sheet' (Annex 4) was modified to take advantage of additional pertinent information collected routinely in the medical records.

Following the study, the 'Identification sheet' (Annex 5), to be given to the interviewer, was improved; this sheet was a record of all the contacts that were attempted in order to reach the subject or his family.

The contact procedure was also slightly changed; it was decided that an introductory letter (Annex 6), explaining the study, would be essential to encourage participation.

It was thus possible to obtain occupational histories from psychiatric ex-patients, although not always blindly, because a certain amount of disorganization of the thought processes of some of them became evident during the interview. Information acquired from a surrogate respondent, though less complete, was detailed enough to permit exposure assessment. Lastly, the medical records were inconsistent as a source of occupational information. The hospital admission form usually contained the job held at the time of hospitalization, for insurance purposes. For non-psychiatric admissions, no other information was available unless it was directly pertinent to return to normal activities after the health disorder (e.g. if a patient did heavy physical work and was hospitalized for a myocardial infarction). The psychiatric record systematically contained at least some information on the occupational history of the patient as it is a standard component of the psychiatric interview.

D. STUDY PROCEDURES

1) Subject selection

Cases were selected from the two large psychiatric hospitals in the Montreal area in order to gather a sufficiently high number of subjects to attain a satisfactory power. Over 3000 men had been admitted within a five-year period at these two hospitals. It

was estimated that about 1200 of them would be first admissions: the first admission rate was inferred from the numbers of first admissions over those of total admissions for all psychiatric diagnoses in the Province of Quebec during 1978 - last year for which the figures were available for first admissions [Statistique Canada 1982]. Psychiatric admissions at a referent hospital offering psychiatric care were also included in the study.

The hospital referents were chosen from general hospitals geographically closest to the two psychiatric hospitals in order to account for consultation patterns in the same socio-economic area. The computerized hospital lists of discharges provided the required information for matching the referents with the cases. Whenever possible, the hospital referent living the closest to the case's area of residence was selected.

a) Case series

The cases were identified from hospital admission lists for the period between April 1st 1981 and March 31st 1985. The inclusion criteria were a first admission in psychiatry between the ages of 40 and 69 and for 5 nights or more.

The psychiatric diagnoses at discharge were coded according to the International Classification of Disorders (9th revision), Chapter V-Mental disorders: codes 290 to 316 inclusively, excluding codes 299 (Psychoses with origin specific to childhood) and 317 to 319 (Mental retardation of varying severity). Annex 1 contains a list of the psychiatric diagnoses included in the study.

Only residents of the Province of Quebec at the time of admission, who were still living either in the Province or in one of the adjacent provinces at the beginning of the study, in April 1985, were selected.

According to Schlesselman [1982: 161-162], a sample size of 392 pairs for a matched analysis using a one-tailed α of 0.05 and a β of 0.20 was sufficient to be able to detect a relative risk of 2.

b) Referent series

The hospital referents had been admitted to the nearest general hospital and were individually matched to the cases on the time of admission (same administrative year) and age on admission ($\pm$2 years). Because of the unavailability of computerized lists for the last year of inclusion in the study, referents for the cases hospitalized between April 1984 and March 1985 had to be selected from the preceding year.

All non-psychiatric diagnoses were accepted with a few exceptions. Cirrhosis of the liver, because of its possible association with high alcohol intake, was excluded. Admissions for elective surgery or because of injuries following an accident were not eligible because of the absence of corresponding conditions for psychiatric patients. A

history of previous admission in psychiatry was obviously an exclusion criterion. The referents' admission did not have to be the first one for that condition. A few eligible hospital patients were selected for each case, and the one whose place of residence was the closest to that of the corresponding case, was finally chosen as the referent.

As for the cases, the hospital referents were Quebec residents at the time of their admission, and were still living in the Province or an adjacent one at the start of the study in April 1985.

2) Data collection

a) Procedure

After identification of the cases from the psychiatric hospitals registers, the individual charts were reviewed to insure that they fitted the eligibility criteria and some information was extracted from the records onto a hospital extraction sheet shown as Annex 4. Hospital referents were then individually matched to the cases.

1. Standard interview

An introductory letter was sent on the same date to the members of each pair; it explained the study and mentioned that someone from our team would call them within a few days for an interview on their work history. The letter also emphasized the voluntary nature of the interview (see Annex 6). The interviewers were given an identification sheet, with names and addresses of the person(s) to be contacted, as well as the identification number of the duo (see Annex 5). They were asked to complete the questionnaire as thoroughly as possible, keeping the wording as stated. They were also instructed to obtain a complete work history if possible, and to focus on the job history if the respondent became hesitant to finish the interview. The interviewers were not permitted to probe for any particular exposure. Although they were aware of the nature of the study and which subjects constituted a pair, they were blind as to their study status.

A telephone call was made one week after posting the letter. If the subject was ready to give an interview, the interviewer proceeded with the study questionnaire (Annex 3). Sometimes the interview was postponed, to suit the subject. If the subject was not capable of answering the questionnaire over the telephone (because of hearing or speaking problems, poor understanding of French or English, confusion, etc.), the questionnaire was administered to the subject with the help of a relative. If the subject was incapable of contributing to the interview or if he had deceased, the wife and children were asked to give a surrogate interview, followed by brothers and sisters or parents, and then any other relative or friend. If the subject was in hospital at the time

the interviewer called, she(he) inquired when the subject was expected to return home. A telephone call was then made a few weeks after the expected date home.

2. Uncooperative subjects

A subject who gave a straight refusal over the telephone or by return mail, or who was never ready to give the interview after several attempts, was considered 'uncooperative'. A short letter was sent to him a few months later mentioning that although he had not been ready to answer our questionnaire the first time, it was really important for us to know about his main jobs (see Annex 7). To compensate for any inconvenience or expense, a $10.00 money order was sent to him upon receipt of his reply. If the subject agreed to give us additional information, a short questionnaire (Annex 8) was sent to him along with his money order. Approximately two weeks later, a reminder postcard was sent; upon no reply from the subject after about a month, no further attempt was made.

3. Tracing procedures

When the telephone numbers for the subject and his relative(s) were wrong, we consulted the telephone directory and then the Lovell's Criss-Cross reference directory (giving telephone numbers according to civic address). When no new information was available from the directories, the hospital chart was checked again for a more recent address or telephone number. If these attempts failed, a tracing bureau was asked to locate the subjects or their family and to provide us with telephone numbers and addresses.

Given a more recent address, the whole interview procedure started over again. When a new telephone number was found, the interviewer verified whether the subject had received our letter; if he had, the interview procedure started over from that point. When we obtained only a new address (confidential number or no telephone in the house), we sent a special letter explaining the study and asking the subject to contact us to arrange for an interview. If at the end the search done by the tracing bureau was negative, no further tracing attempt was made.

b) Available data

The information was thus collected in two ways: with the hospital extraction sheet and with the questionnaire.

The hospital extraction sheet (Annex 4) recorded data from the medical records on date of birth, last known address, dates of admission and discharge from the hospital, final and secondary diagnoses; last job at the time of admission, work history and comments on alcohol intake, when available; subsequent admissions following the key

admission and name of a resource person for tracing purposes. This information was coded and entered unchanged on computer.

The second and most important source of information was the interview questionnaire (Annex 3). It was divided into six sections, under the headings of:

1) 'General information' (information on date of birth, place of birth, language spoken at home, father's occupation during childhood, level of education);

2) 'Occupational history' (type of company, job title, job description, years in each job, reasons for stopping work for periods of 6 months or more, last year at work, reported exposure to certain chemicals at work);

3) 'Hobbies' (hobbies involving the use of solvents);

4) 'Personal habits' (cigarette smoking, alcohol consumption in some detail);

5) 'Medical history' (episodes of meningitis, convulsions, head injury, stroke, any admission since the age of 21); and lastly

6) 'Interviewer's remarks' (relationship with the subject of persons who gave the information, degree of cooperation from respondent, language used and reliability of interview, comments, study status of the subject according to the interviewer, initials of the interviewer).

The questionnaire data were of two kinds: the job history, that had to go through further coding and exposure assessment before being entered onto the computer, and all the rest of the information, that was coded and entered directly.

As previously stated, two other data collection methods were used for the subjects who were difficult to contact: a short letter and a short questionnaire. The short letter (Annex 7) consisted of two questions; one on the main jobs held since beginning to work and the other asking if the man had been exposed to some solvents in any of his jobs. The respondent was also asked if he or she would agree to be contacted again, and if so, to specify a preference by telephone or letter. The short questionnaire (Annex 8) had similar questions on one side - rather more detailed than the short letter - and was almost identical to the occupational history section of the main questionnaire on the other side. These two sources of job histories were then coded as for the main questionnaire.

If no information could be gathered because of refusal or tracing problems any occupational information in medical records or electoral lists was extracted and set out similarly to a job history, but with unknown duration of employment in those jobs.

c) Data preparation

All the occupational histories went through three preparatory steps prior to computer entry: job title coding, exposure assessment and job history editing. The

original pages of the questionnaire dealing with the job history were photocopied and numbered with a three-digit identification number without indicating case-referent status. Job titles were then coded using four digits as used by Statistics Canada during the last census [Statistics Canada 1986a]; an experienced coder who worked for several Canadian censuses undertook this task. The two other preparatory steps were somewhat more complicated and are described below.

1. Job history editing

The editing procedure had several purposes: to ensure comparability between work histories, to facilitate a computer analysis and to permit a more refined description of the exposure level.

The histories were first divided into several 'time periods' that represented homogeneous working activities. For example, someone who was a factory worker, always with the same job title at the same company, would have had one time period of work. If that man had a second job (job B) for some years while still working at the first job (job A) and then returned to the first job, his history would have consisted of four time periods: the first one with job A alone, the second and the third as respectively jobs A and B (for the same years) and then a fourth time period describing his return to job A.

All the gaps between jobs and years were filled according to each history, usually by periods of 'unknown activities'. If the questionnaire showed that the subject had been employed all his life, the gaps were replaced by periods of work in his trade When the information was particularly scant and only job titles were available, without years, the various job titles were distributed equally among the years during which the subject was assumed to have been employed. This procedure thus accounted for all the years between leaving school and retirement. If these two last dates were unknown but some job history information was available, the man was assumed to have left school when 16 years old and to have worked until the year of the interview, or 65 years of age, or the date of his 'key' admission, whichever was the most appropriate Nevertheless, if the job title indicated the necessity for further education, e.g engineer, accountant, etc , a 'probable' date was assigned to his leaving school based on the traditional training time for these occupations.

2. Exposure assessment

The solvent exposure for each reported job was assessed by me personally using a specially designed composite score based on intensity of exposure, confidence in the assigned intensity, and the estimated percentage of the work week exposed at that level.

Intensity was based on a ten-point scale derived from the one used to classify chest radiographs for pneumoconiosis [ILO 1980]. The procedure was similar to that also used to assess asbestos exposure in a study of mesothelioma [McDonald and McDonald 1980] with a four-point scale. 0 (no exposure), 1 (light exposure), 2 (moderate exposure) and 3 (heavy exposure). Two intensities of exposure were attributed: the intensity given on 'first thought' and the alternative intensity that I seriously considered, both intensities being separated by an oblique. That method, developed by Liddell [1963] to read chest radiographs, is expressed with the different logical combinations of the four-point scale (i.e. 0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3). The rating was based on personal knowledge of the jobs and also from books and other references on the subject. Conceptually, the intensity level reflects a time-weighted average of a 'typical' work week exposure; for example, a continuous 'moderate' exposure might be rated lower than a moderate exposure with occasional peaks.

My confidence in the assigned intensity was described with a three-point scale from 1 (low) and 2 (moderate) to 3 (high)

Percentage of the work week at a given level of exposure theoretically ranged from 0 to 100%, based on a 40-hour work week. In practice, 0%'s were much more frequent than 100%'s because an occupation rarely entailed an important exposure all the time.

3) Data analysis

As specified earlier, the main referent group considered here is the hospital one. Accordingly, the main analyses were done between cases and their hospital referents, whereas, comparisons were also performed between the two referent groups to identify any discrepancies between them that could restrain external extrapolation of the results (see Chapter VII. Comparison of hospital and population referents).

Classical methods of analysis for case-referent studies were used [Breslow and Day 1980; Fleiss 1981; Schlesselman 1982] after a series of unmatched descriptive statistics (frequencies for categorical data and means with standard deviations for continuous data). The subsequent analyses were all done retaining the matching to maximize the usefulness of the matching process. Contingency tables and the corresponding odds ratios were computed, crudely at first, and then controlling for potential confounders and diagnostic category. Then some mathematical modeling (conditional logistic regression) was performed to try and estimate the respective importance of some confounding factors among the study population. Lastly, the existence of a systematic exposure-response relationship was investigated by an unmatched analysis.

E. ETHICAL ASPECTS

The study protocol and the pertinent accompanying forms were sent to and approved by the corresponding ethical committees of the hospitals, the Bureau général des élections du Québec and McGill University.

The consent of the individual was obtained *de facto* when the subject or a surrogate respondent agreed to give the interview. In case of a refusal, a follow-up would be attempted only if the refusal was based on 'lack of interest' or 'lack of time'. If someone explicitly expressed their unwillingness to participate in the study even after additional discussions, no further follow-up was undertaken.

All the identifying information concerning the subjects has been stored separately from the questionnaires. No information which would permit the identification of an individual has been coded, nor has it be used in the analysis or reporting of the results.

F. SUMMARY

The feasibility study aimed to test the questionnaire, to assess the feasibility of interviewing psychiatric patients and their family, and to explore the type of occupational information available in medical records It consisted in interviewing 10 patients face-to-face to experiment with the questionnaire, and then 32 ex-patients by telephone to test the whole data collection procedure

It clearly demonstrated that the interview process was feasible with both the patient, and a family member (despite less complete information). The questionnaire was modified following the pilot study to clarify some questions and shorten it. Finally, the hospital records were confirmed to routinely gather some information on the job held at the time of admission for insurance purposes Moreover, obtaining an occupational history was a 'standard' procedure in the psychiatric interview and could perhaps, if necessary, serve as a complementary source of data

This research was aimed at investigating the presence of an association between mental disorders and occupational exposure to organic solvents. It consisted in a case-referent study comparing the job histories of men hospitalized for the first time in psychiatry between the ages of 40 and 69, to that of a set of referents issued from patients hospitalized for non-psychiatric reasons, approximately at the same time, in a nearby hospital. This research protocol has been designed to address three questions.

- Do men hospitalized for the first time in psychiatry between the ages of 40 to 69 have a higher frequency of prior occupational exposure to organic solvents?
- Is it possible to identify certain diagnostic categories that are more strongly associated with organic solvent exposure?

- Can the nature of the exposure be characterized in regard of its relationship to mental disorder (type of solvents involved, existence of a systematic exposure-response relationship, identification of a latency period, etc.)?

The job histories were obtained mainly from a structured telephone interview where the interviewer filled a questionnaire with either the study subject himself, a surrogate respondent or both when necessary. Occupational exposure was assessed by the author, according to her knowledge of the jobs and reference readings, using the extension of a four-point scale ranging from no exposure ('0') to high exposure ('3'), with low ('1') and moderate ('2') as intermediate exposure categories. The percentage of work week exposed was also estimated for each exposed job.

As the exposure assessment procedure had never been used to evaluate organic solvent exposure, it was validated by three reliability trials to compare the author's exposure assessments to those of experts in the field; the following chapter reports the results and conclusions of these trials.

IV. Reliability and validity studies

Occupational histories obtained by questionnaire inevitably lack precision and details, and so do the subsequent exposure assessments. I carried out all the solvent exposure assessments for both my research project ('Study A') and the related study focusing on organic diagnoses ('Study B'), to ensure internal and external ('between studies') comparability. The assessments were done using my experience and knowledge from reference documents and from information gained from discussion with experts

Three different studies were set up to address two objectives: i) to determine the reliability of the solvent exposure assessment procedure and ii) to identify the nature and extent of any difference in opinion that would affect the comparisons between cases and their referents.

The first of these studies, the agreement trials, will be described in more detail, whereas only partial results are available for the two others, which were set up with other objectives.

A. AGREEMENT TRIALS

1) Description

After all the occupational histories had been entered on computer, a stratified random sample was selected from a pool of all the individual jobs ever held by both studies' subjects, regardless of their status as a case or referent. The method of stratification was to take 1.5% of all jobs rated as non exposed (0/0 and 0/1 ratings), and 15% of the remaining jobs. This sampling scheme was aimed at weighting the sample towards exposed jobs for which disagreement in opinions could arise concerning solvent exposure.

For each selected job, the following information was extracted from the original questionnaire: subject identification number, type of company, job title, job description, year started, number of years the job was held and any reported exposures The information was then typed in a standard way, two jobs per page (see Annex 9 for an example), printed and organized in sets of 26 jobs A total of 20 such sets were formed for a total of 516 different jobs. These jobs served two similar trials one made in Montreal between two experienced industrial hygienists and myself, and one made in London, England, between three international experts.

Exposure assessment was made according to three criteria: intensity, confidence in our judgement and percentage of time exposed during a 40-hour work week. A standard

set of rules, similar to those which I used to attribute the initial ratings, was given to both groups of raters:

i. Exposure intensity was to be assessed on a four-point scale: '0' for 'no exposure' - at least not more than the average citizen; '1' for 'light exposure' - at a level not considered biologically important, perhaps less than 30% of the threshold limit values (TLV's); '2' for 'moderate exposure' - at levels that would need to be monitored, probably from 30 to 50% of the TLV's; and '3' for 'heavy exposure' - at a level that is undesirable, probably over 50% of the TLV's. The raters were asked if they would consider attributing an alternative intensity and if so, to report it besides the first intensity, separated by an oblique. This produced the 10-point scale presented earlier (from 0/0 to 3/3).

ii. Confidence in our judgement of the intensity was to be scored on a three-point scale: '1' for a low certainty, '2' for a moderate certainty, and '3' for a high certainty.

iii. Percentage of the work week during which the intensity applied was estimated as follows: this percentage was to range from 0% (for no exposure) to 100% (excluding lunch time and coffee breaks from the assessment), with a category of 'less than 5%' for minimal exposure.

iv. Our overall exposure assessment - intensity, confidence and percentage of time exposed - was weighted to reflect the presence of peak exposures during the work week.

a) Montreal agreement trial

The Montreal agreement trial was conducted over a 2-day period. Two experienced industrial hygienists from the Montreal area were involved: D Bégin and J. Lavoie. At a joint meeting, the two hygienists and I received the 20 sets of 26 jobtitles each to rate according to the above-mentioned set of rules. We worked in separate rooms and were not allowed to use any aids (e.g. books, catalogues, lists, etc.) to help us take our decisions.

On the second morning, the six first sets of 26 jobs were given to us for a repeat rating session to collect some data on a test-retest situation of the rating procedure.

The data gathered during this trial were entered on the computer along with the job classification code [Statistics Canada 1986a] of each described occupation and with my initial assessment.

b) London agreement trial

A similar trial was held in England a few months later. The international experts involved were an epidemiologist from Sweden, Prof. O. Axelson, an industrial hygienist from Finland, Ms. R. Riala, and an occupational physician, also trained in industrial hygiene from Great Britain, Dr H A. Waldron. The three experts were given the 12

first sets of 26 jobs used for the Montreal trial and were asked to rate them, again in separate rooms, according to the same rules.

The collected data were pooled with the data on the first 12 sets of 26 jobs from the Montreal trial, thus producing a rectangular set of data with 7 different ratings for each of the 312 jobs.

2) Analysis

The collected data have been analyzed as two data sets. the first one, from the Montreal trial, consisted in the subset of 156 occupations for which there were test-retest data available. This data set served to look at intra-rater variation The second data set consisted of the data collected in London on the first 312 occupations plus the corresponding figures from the Montreal trial.

These two data sets were analysed using the same methods and looking at the same indices. The intensity was considered both as ranging from 0/0 to 3/3 on a 10-point scale, and from 0 to 3 on a four-point scale. The raters' confidence in their ratings was also recorded. The percentage of work week exposed was incorporated in the calculation of a 'time-weighted average' by multiplying it by the intensity level (10-point scale), it will be referred to as 'weighted exposure' in the rest of this chapter

The different indices used to report the variations between and amongst raters are described below with an explanation on how they were calculated This first series of indices were applied only to the intensity levels.

- Exact agreement Although exact agreement is more meaningful when the observations are more or less equally distributed in each category, it is still frequently used and is easy to understand. Since sampling for the agreement trials was weighted towards getting exposed rather than unexposed jobs, we cannot expect an exact agreement as good as it could have been if the same sampling fraction had been applied to the entire data set. Exact agreement was calculated as the ratio of identical intensity ratings, using the 4-point scale, over the total number of jobs to be rated.

I decided not to use the Kappa statistic because of the recent controversy over its use, and because of the difficulties of properly interpreting the statistic in the case of more than two raters and more than two classification categories [Maclure and Willett 1987].

- Under- and over- estimations. One of the objectives of the agreement trials was to identify whether my ratings were systematically different from those of the experts - whereby affecting the case-referent comparisons To identify the extent and direction of these differences, any systematic under- or over- estimation of the exposures was also explored. This was done by adding up separately the number of my intensity ratings that

were lower (under-estimations) and higher (over-estimations) than that of the other raters.

- Spearman's rank correlation coefficient (r_S). An intuitive way of comparing ratings on the same jobs is to assess their degree of correlation. Spearman's rank correlation coefficient, as a non-parametric estimator of association between ranked series, was used with the 10-point (from 0/0 to 3/3) scale. Approximate 95% confidence intervals were calculated with the formula given in Kleinbaum and Kupper [1978: 80] for the Pearson's correlation coefficient (which is a reasonable approximation as Spearman's coefficient is equal to Pearson's coefficient applied to ranks [Hollander and Wolfe 1973. 191-192]). The 95% confidence interval reflects the variability of the correlation coefficient. It implies that if the rating session were repeated several times, ninety-five per cent of the intervals calculated for the correlation between each rater would contain the same coefficient r_S.

- Comparison of medians. The 10-point scale used during our agreement trials is analogous to that described by Liddell [1963] in his experiment of chest X ray readings. A similar method of reporting observer error was adopted to assess the validity of my ratings. It consisted in comparing my ratings to a reference value, that of the median of the Montreal raters (including my ratings), and also the median of the London raters for each job. After creating a contingency table similar to those computed for each set of two raters, the four previous types of indices were again calculated, using the median as the 'true' value The median ratings of the Montreal and the London raters were also compared in the same way

Differences between the weighted exposures computed from each rater's assessment of the exposure were studied using two indices: Spearman's rank correlation coefficient (r_S) (described above) and under- and over- estimations. These 'disagreement' indices were calculated by computing the number of jobs for which the weighted exposures, based on my second ratings, were lower (under-estimations) and higher (over-estimations) than the corresponding weighted exposures from the other raters The results of the analyses on the weighted exposures will not be presented in detail here.

In each data file are recorded two of my ratings. the 'initial' assessment made while having access to the entire work history for each study subject, and a second assessment made under exactly the same conditions as the 'experts', during the 'Montreal trial'. As my second rating was the more directly comparable, it was used in most of the comparisons

3) Results

a) Characteristics of the ratings

Each rater exhibited preferences for certain categories in the 10-point scale (Table IV-1). The London raters, on average, gave lower scores than the Montreal raters, and they were more homogeneous in attributing them. Rater 1 appeared more sure of his assessments in that he tended to use the middle categories of 0/0, 1/1, 2/2 and 3/3.

The certainty levels with which the raters assessed the job descriptions given to them (Table IV-2) followed a similar pattern. Rater 1 again indicated more confidence about his ratings, whereas, the others were usually only 'moderately' confident There was also more homogeneity among the certainties given by the London raters. The differences between my initial and second ratings demonstrated a slightly increased use of 'low certainty' codes the second time.

The raters again showed preference for certain percentages more often than others (Table IV-3). The Montreal raters gave higher percentages slightly more often and their scores were more heterogeneous (especially below 40%) than that of the London raters.

b) Inter-rater comparisons

1. Exact agreement and disagreement

Intensity levels. Exact agreement and both under- and over- estimation of exposure level attributed to each job are described in Table IV-4. Here, my second rating was compared to that of each of the Montreal and London experts. Under-estimation implied that I gave an intensity rating less than that of the rater in question, and over-estimation implied that I gave the higher rating. From this table, my ratings appeared to agree exactly on the exposure level of more than 50 per cent of the jobs. Most of the disagreement was due to my over-estimation of the exposure compared to the experts' evaluations.

When the same indices were computed between the median ratings of the Montreal and the London raters, a similar picture was found. Exact agreement occurred in 59.3% of the ratings, with 6.1% of under-estimation and 34 6% of over-estimation from the Montreal raters compared to the London raters. This discrepancy between both sets of raters could be related to differences in their level of experience (the Montreal raters were younger than the London raters), in their knowledge of the Quebec situation (two of the Montreal raters were industrial hygienists experienced with solvent exposure assessment), and perhaps in their individual perception of the described jobs

Table IV-1 Percentage prevalence of the intensity levels attributed by the raters (n=312)

Intensity level	Rater 1 (D.B.)	Rater 2 (F.L.)	Rater 3 (J.L.)	Rater 4 (O.A.)	Rater 5 (R.R.)	Rater 6 (H.A.W.)
0/0	17.3%	17.3%	15.7%	25.1%	22.4%	34.6%
0/1	10.9%	14.7%	10.9%	20.3%	18.3%	13.1%
1/0	17.0%	5.8%	10.0%	13.8%	4.8%	3.9%
1/1	17.9%	4.8%	6.4%	10.0%	11.5%	1.6%
1/2	3.2%	11.2%	8.7%	11.9%	17.3%	13.5%
2/1	5.8%	7.4%	19.2%	6.7%	8.6%	11.9%
2/2	23.1%	12.5%	6.4%	3.9%	5.8%	6.1%
2/3	2.6%	17.0%	16.0%	4.8%	6.1%	7.0%
3/2	0.6%	6.1%	1.9%	1.9%	2.6%	4.8%
3/3	1.6%	3.2%	4.8%	1.6%	2.6%	3.5%

Table IV-2 Percentage prevalence of the levels of certainty

(n=312)

Certainty level	Rater 1 (D.B.)	Rater 2 (F.L.)	Rater 3 (J.L.)	Rater 4 (O.A.)	Rater 5 (R.R.)	Rater 6 (H.A.W.)
1 (low)	8.3%	15.7%	13.5%	15.4%	15.1%	13.5%
2 (moderate)	22.5%	68.6%	74.0%	52.4%	50.3%	43.3%
3 (high)	69.2%	15.7%	12.5%	32.2%	34.6%	43.2%

Table IV-3 Percentage prevalence of the percentages of the work week exposed (n=312)

Percentage of work week	Rater 1 (D.B.)	Rater 2 (F.L.)	Rater 3 (J.L.)	Rater 4 (O.A.)	Rater 5 (R.R.)	Rater 6 (H.A.W.)
0-19%	83.2%	52.8%	62.2%	82.3%	71.5%	79.8%
20-39%	9.8%	25.1%	24.0%	9.35	20.8%	10.3%
40-59%	3.0%	8.2%	6.0%	3.95	6.15	0.6%
60-79%	2.7%	4.3%	0.45	2.65	1.3%	8.3%
80-100%	1.3%	9.6%	7.4%	1.9%	0.3%	1.0%

Table IV-4 Agreement between my second rating and that of the Montreal (Raters 1 and 3) and the London (Raters 4, 5 and 6) experts. 4-point scale.*

	Montreal experts		London experts		
	F.L. vs. Rater 1	F.L. vs. Rater 3	F.L. vs. Rater 4	F.L. vs. Rater 5	F.L. vs. Rater 6
Exact agreement	57.4%	52.9%	49.2%	59.6%	56.4%
n	179/312	165/312	153/311	186/312	176/312
Disagreement					
Under-estimation	14.1%	24.4%	5.5%	6.7%	9.6%
n	44/312	76/312	17/311	21/312	30/312
Over-estimation	28.5%	22.7%	45.3%	33.7%	34.0%
n	89/312	71/312	141/311	105/312	106/312

* 4-point scale: from 0 (no exposure) to 3 (high exposure)

Weighted exposures. It could be foreseen from the previous findings on intensity levels, that a large part of disagreement on the weighted exposures was caused by an over-estimation of the solvent exposure based on my ratings. The trend was less obvious with the Montreal experts (who attributed higher percentages than their London counterparts), in fact, disagreement with Rater 3 was almost equally distributed between under- and over- estimations.

2. Correlations

Intensity levels. The Spearman's rank correlation coefficients are presented in Table IV-5. Except for one correlation with a Montreal expert (r_s=0.676), the coefficients describing the correlation between my second rating and that of the experts were all above 0.78. The correlation between my initial and second rating (not presented in the table) had a coefficient r_s equal to 0.825.

The correlation coefficients of the London raters between themselves (r_s=0.751 to 0.822) were slightly higher than that of the Montreal raters between themselves (r_s=0.676 to 0.798); considering the sampling strategy where more weight was placed on obtaining exposed jobs, the correlations between the six of us were remarkably high.

Weighted exposures The coefficients ranged from 0.670 to 0.833 and were of the same order of magnitude as the correlation coefficients obtained for the intensity ratings only. For this index however, the correlation coefficients of the Montreal raters between themselves were very similar to that of the London raters between themselves.

c) Intra rater comparisons

1. Exact agreement and disagreement

Intensity levels Table IV-6 shows the extent of agreement and disagreement observed in the test-retest comparison during the Montreal trial. Here, the reference value was the first rating, consequently, an under-estimation (or an over-estimation) was a lower (or a higher) rating attributed during the retest session. My second rating agreed exactly with its retest value on more than 80% of the jobs and the disagreement was equally distributed between an under- and over- estimation of the solvent exposure. The two other Montreal raters attributed lower ratings during the retest session, giving a ratio of under-estimation to over-estimation of about 1.5.

Weighted exposures. Introducing 'percentage of the work week exposed' in the exposure indices marginally modified the conclusions drawn from the analysis of the intensity levels alone. My ratings were more consistent than those of the two other Montreal raters.

Table IV-5 Matrix of Spearman's rank correlation coefficients (r_S), with their 95% confidence interval, between all the raters for the detailed ratings*

	Rater 1 (D.B.)	Rater 2 (F.L.)	Rater 3 (J.L.)	Rater 4 (O.A.)	Rater 5 (R.R.)
Rater 2 (F.L.)	0.798 (.754-.835)	1			
Rater 3 (J.L.)	0.736 (.680-.783)	0.676 (.611-.732)	1		
Rater 4 (O.A.)	0.757 (.705-.801)	0.810 (.768-.845)	0.675 (.610-.731)	1	
Rater 5 (R.R.)	0.746 (.692- 791)	0.805 (762- 841)	0.719 (661-.769)	0.822 (782- 855)	1
Rater 6 (H.A.W.)	0.717 (.658- 767)	0.781 (.734- 821)	0.627 (555- 690)	0.770 (721.812)	0.751 (698-.796)

* Based on the10-point scale. Correlation coefficients corrected for ties, all significant at $p<0.001$. 95% C.I.'s are between parentheses. n= 312.

Table IV-6 Intra-rater agreement among the Montreal raters*

	Rater 1 (D.B.)	Rater 2 (F.L.)	Rater 3 (J.L.)
Exact agreement	84.0%	81.4%	71.8%
n	131/156	127/156	112/156
Disagreement			
Under-estimation	9.6%	9.6%	17.3%
n	15/156	15/156	27/156
Over-estimation	6.4%	9.0%	10.9%
n	10/156	14/156	17/156

* 4-point scale: from 0 (no exposure) to 3 (high exposure)

The disagreement between my test and retest ratings was again equally distributed between under- and over- estimations, whereas, the other raters gave lower values the second time. The ratio of under-estimations to over-estimations, which was around 1 5 for intensity levels alone, rose to 2.2 when percentages of time were taken into account.

2. Correlations

Intensity levels The Spearman's rank correlation coefficients computed between the test-retest ratings were quite good (r_s=0 868 to 0.955), also indicating that the procedure used to assess solvent exposure was reproducible (Table IV-7).

Similar patterns were found again with my initial and second ratings. They were less well correlated than my test-retest ratings, which were higher than for the other Montreal raters.

Weighted exposures. Correlations between the weighted exposures based on test-retest figures - ranging from 0.833 to 0.943 - indicated a pattern similar to that obtained with intensity levels alone. Rater 1 presented the best correlation coefficient of the group.

d) Validity comparisons

Consensus validity of the exposure assessment procedure was investigated by comparing my second intensity ratings to the median of the intensity ratings attributed by the Montreal raters and to that of the London raters Table IV-8 reports those figures.

My exact agreement with the median, which can be considered here as similar to a consensus agreement, was better with the Montreal median (76 6%) and the disagreement was more or less equally distributed between under- and over- estimation of the exposure.

The Spearman's correlation coefficients computed between the Montreal median and my initial rating (r_s=0.805), and my second rating (r_s=0.889) were again reasonably high. The same coefficients computed with the London median were lower, but still quite high: r_s=0.787 for my initial rating, and r_s=0 843 for my second rating.

B. JOB HISTORIES ASSESSMENT

1) Description

This was set up to verify whether discrepancies between my ratings and the London experts' ratings (considered here as a 'Gold Standard') would modify conclusions on whom of the case or his referent was the most exposed within each pair

Table IV-7 Spearman's rank correlation coefficients, with their 95% confidence intervals, between the Montreal raters test-retest detailed ratings *

	r_s
Rater 1 with himself (D.B.)	0.928 (.902-.947)
Rater 2 with herself (F.L.)	0.955 (.939- 967)
Rater 3 with himself (J.L.)	0.868 (823-.902)
F.L.'s initial rating vs. 2nd rating	0.861 (.814- 897)

* Based on the 10-point scale. Correlation coefficients corrected for ties, all significant at $p<0.001$. 95% C.I.'s are between parentheses. $n=156$.

Table IV-8 Agreement between my second rating and the Montreal median rating*

	F.L. vs. Montreal median	F.L. vs. London median
Exact agreement	76.6%	57.4%
n	239/312	179/312
Disagreement		
Under-estimation	9.6%	5.1%
n	30/312	16/312
Over-estimation	13.8%	37.5%
n	43/312	117/312

* 4-point scale: from 0 (no exposure) to 3 (high exposure)

For both studies, A and B, the pairs where at least one member had been exposed at 2/1 and above for 10 years or more (according to my initial ratings) were identified. Complete job histories for each of these pair members were typed and given their pair identification number plus a digit ('1' or '2') allocated randomly to the case and his hospital referent (see Annex 10 for an example).

A total of 96 pairs from Study A and 98 pairs from Study B were thus selected to be reviewed by each of the three London experts.

The raters were asked to decide whether one member of each pair was more exposed to solvents than the other; then to describe how confident they were about that (using '0', '+' or '++'), and finally whether any member, both of them or any of them, had an important exposure, i e. an exposure that could affect their health. An example of the coding sheet used by the experts is displayed as Annex 11.

2) Results and discussion

A crude analysis of the data revealed the following. In Study A, at least 2 out of the three experts found that the case was more exposed than the referent in 15 pairs, and that the referent was more exposed than the case in another 15 pairs. For each of these discrepant pairs, at least one expert considered this exposure to be etiologically important An odds ratio of 1 0 was computed from these discordant pairs.

In Study B, cases were more exposed than their general hospital referents in 16 pairs, versus 10 pairs where the referents were more exposed. This gave an odds ratio of 1 6, which was not, however, significant.

These results, although preliminary, were consistent with the results found in the two studies· when considering as a cut-off point an exposure to moderate levels and higher, for 10 years and more, no increased risk was found in Study A (see Chapter V. Main results), whereas one was found in Study B [Cherry and McDonald 1988].

C JOB TITLES CODING

1) Description

Many epidemiological studies resort to using job titles as a surrogate for exposure assessment To explore the usefulness of such an index of exposure, it was decided to ask the London experts to rate job titles previously rated as entailing at least a minimal solvent exposure. All the occupations ever held by all the subjects of both studies A and B were pooled and then listed with corresponding frequencies of the 10-point scale intensities initially attributed by myself The job titles for which there were more than 10 jobs reported and of which at least 10 per cent had received an exposure rating of 1/0 and above (any duration of exposure), were identified and then listed in random

order. The 131 job titles thus assembled were then described according to the Canadian Classification of Occupations [Statistics Canada 1986a], and were submitted to the London experts and to me, to be rated as for the agreement trials - using the 10-point intensity scale and the confidence 3-point scale (see Annex 12 for an example)

2) Results and discussion

Again, only preliminary results are available for this agreement study. The ratings were entered on computer as for the agreement trials mentioned earlier. Of the 131 job titles, 49 were rated as exposed to solvents by at least two of the three expert raters: 33 job titles had a median exposure of 1 ('low'), 11 job titles had a median of 2 ('moderate') and 5 job titles, a median of 3 ('high'). The five job categories that were rated as highly exposed to solvents were 'Laundering and dry cleaning occupations', 'Marine craft fabricating, assembling and repairing occupations', 'Painters, paperhangers and related occupations', 'Printing press occupations' and 'Printing and related occupations' (Canadian Classification of Occupations codes 6162, 8592, 8785, 9512 and 9519, respectively).

My ratings of the same 131 job titles attributed a 'low' exposure to 39 job titles, a 'moderate' exposure to 24 job titles, and a 'high' exposure to 16 job titles. Apart from the 5 highly exposed job categories identified by the London experts, I also considered the following ones to entail high exposures regularly if not daily:

- Chemists (code 2111)
- Advertising and illustrating artists (3314)
- Service station attendants (5145)
- Bonding and cementing occupations: Rubber, plastic and related products (8571)
- Motor vehicle mechanics and repairers (8581)
- Aircraft mechanics and repairers (8582)
- Industrial, farm and construction machinery mechanics and repairers (8584)
- Painting and decorating occupations n e c (8595)
- Deck crew, Ship (9155)
- Engineering officers, Ship (9153)
- Engine and boiler-room crew, Ship (9157)

A discussion following that rating exercise gave a partial explanation to my over-estimation of the number of highly exposed jobs. The experts tended to rate according to the job title and the typical activities associated to it, whereas I tended to consider all the possibilities of exposure that could happen with a given job title. For example the deck crew on a ship does not paint as a daily activity, but they will do it regularly. I thus gave them a rating of high exposure but a low percentage of work week exposure

D. SUMMARY

Three studies were designed to explore the stability of the solvent exposure assessment procedure and to determine the nature of differences in opinion that could affect the case-referent comparisons.

The agreement studies consisted in submitting a sample of 312 job descriptions to two panels of experts: one from Montreal and one from three European countries (Sweden, Finland and the United Kingdom). The sample was submitted to the author at the same time and under the same conditions to ensure direct comparability of the ratings. Intra-rater variation data was collected on a subset of the job descriptions.

My levels of agreement were very similar to those between the experts (not presented here), however, this could be inferred from the correlation between my ratings and those of the experts, and the correlation between the experts. My disagreement with the experts was largely at the higher exposure levels; this should not bias the results of the study. The ratings were blind as to the study status of the person whose occupational history was being assessed. However, this 'over-estimation' could induce disagreement at two adjacent levels of exposure - e.g. a 'moderate' exposure ('2' on the scale) and a 'high' exposure ('3' on the scale).

The job histories assessments consisted in submitting to the London panel 96 pairs from Study A and 98 pairs from Study B - where at least one subject was rated to have had a 'moderate' exposure for 10 years and more. The results obtained were consistent with the results of the main study for exposure at 'moderate levels and above' for 10 years and more, i.e. no increased risk for Study A, and an increased one for Study B.

The London panel and myself also coded 131 job titles that I had considered at least exposed to low solvent levels. These job titles were presented to us as described in the Canadian Classification of Occupations [Statistics Canada 1986a]. The experts identified 11 job titles moderately exposed and 5 job titles highly exposed to solvents; I rated 24 job titles as moderately exposed and 16 job titles as highly exposed (including the 5 job titles identified by the experts).

Two broad conclusions can be drawn from the reliability studies; my ratings were consistent and they tended to be higher than those of the experts for the same job descriptions or job titles. The results of the reliability and validity studies thus provide some assurance that the methods used to quantify solvent exposure in this research project were reproducible. They also show that my ratings compared well with that of both the Montreal and European experts, and that differences in opinion between them and myself should not be important as to modify the conclusions of Studies A and B.

V. Description of the study population

A. INTRODUCTION

A total of 387 men aged 40 to 69 years were identified as having been admitted for the first time with mental illness, during the period April 1981 to March 1985 Most of them came from the two psychiatric hospitals in the Montréal area (84 0%) and 62 of them from the psychiatric ward of a general hospital Six cases were subsequently found to be ineligible after the interview - 5 had been admitted in psychiatry previously and one had left the country before the interview - and were excluded, producing a final sample of 381 cases. Each case was matched with two referents - a general hospital and a neighborhood referent - giving a total of 1143 study subjects I reiterate that the main referent group for this study is the hospital one, neighborhood referents being selected only to address the methodological issue of choosing between hospital or population referents in hospital-based case-referent studies (see Chapter VII Comparison of hospital and population referents)

We obtained information directly from the subject, or a relative, for 94 2% of both referent groups and for 86 3% of the cases (Table V-1)

Some information about occupation was available - through hospital charts or electoral lists - for more than half of the subjects who did not participate in the study (untraced or uncooperative) Consequently, we had access to at least minimal occupational information for 96 7% of the total study population

A greater proportion of cases were untraced (7 6%), compared to hospital referents (2.4%) or population referents (1 3%) The percentage of untraced population referents was lower, probably because they were included in the study only if a telephone number could be found at the time of interview Slightly more cases refused to participate in the study 5 8% of cases compared to 3 4% of hospital referents and 4 5% of population referents

The following sections will describe the three study groups The questionnaire data will be presented first (demographic characteristics, occupational history, hobbies, personal habits, medical history and interview characteristics), this part concerns the subjects who completed the questionnaire The data extracted from the hospital chart will then be tabulated for the cases and the hospital referents A table at the end will summarize the information available on subjects who did not participate in the study.

Table V-1 Levels of participation

	Cases	Hospital referents	Population referents	Overall
Information from respondents				
Complete questionnaires	75.3%	84.5%	83.7%	81.2%
n	287	322	319	928
Incomplete interviews	11.0%	9.7%	10.5%	10.5%
n	42	37	40	119
Information from other sources				
Untraced				
Some information	4.5%	1.6%	0.0%	2.0%
n	17	6	0	23
No information	3.1%	0.8%	1.3%	1.7%
n	12	3	5	20
Uncooperatives				
Some information	5.0%	3.1%	1.1%	3.0%
n	19	12	4	35
No information	0.8%	0.3%	3.4%	1.5%
n	3	1	13	17
No informant available	0.3%	0.0%	0.0%	0.1%
n	1	0	0	1
Total	100.0%	100.0%	100.0%	100.0%
n	381	381	381	1143

B. DEMOGRAPHIC CHARACTERISTICS

Table V-2 presents the principal demographic characteristics of the three study groups. The population referents resembled more the cases on place of birth and - for Canadian born subjects - on mother tongue. The three groups were fairly alike on highest level of education attained; about the same proportion of each group had at least some technical training, even though a slightly higher proportion of cases had primary schooling or less.

Social class of the family during childhood of the subject was derived from the socioeconomic index for occupations in Canada originally designed by Blishen [Blishen and McRoberts 1976]. This index is based on employment income, educational status, and the prestige associated with the job; it ranges from 14 to 75, a higher score denoting a higher status. A score lower than 35 indicates a manual job. The three groups of subjects appear to have been brought up in families with very similar social class distributions.

The proportion of subjects who had died at the time of the interview was highest (27.3%) amongst the hospital referents; the high proportion of deaths amongst cases compared to population referents (6 times higher) agreed with the world-wide observation of increased death rates amongst psychiatric patients [Babigian and Odoroff 1969; Black *et al.* 1985]. About fifteen per cent died between 40 and 49 years of age, 36 percent between 50 and 59, and the remaining, above 59 years of age.

C. OCCUPATIONAL CHARACTERISTICS

A brief description of some occupational characteristics of the study population is presented in Table V-3. The subjects started work on average in 1943 and about a quarter of them held a part-time job at some point in their working life The cases' work history was 2 to 3 years shorter than that of the referents, and included 5 9 months not working without reason compared to about 2.3 months for the referents. Twice as many cases and hospital referents stopped work 6 months or more for health reasons

The cases reported more often some 'non-job' activities entailing solvent exposure (65.0% compared to 59.0% for the two other groups) These 'non-job' activities consisted, for example, in fibreglass boat-building, using pesticides on trees or weeds, processing photographs, etc. Finally, the three study groups reported exposure to lead and pesticides in similar proportions.

Table V-2 Demographic characteristics of the study population

	Cases	Hospital referents	Population referents	Overall
Place of birth				
Canada	84.3%	93.5%	82.1%	86.7%
Western Europe & Oceania	10.5%	5.0%	12.5%	9.3%
Other	5.2%	1.5%	5.4%	4.0%
n	286	322	319	927
Mother tongue (Canadian born subjects)				
French	89.6%	95.7%	87.4%	91.2%
English	5 0%	2.0%	9.6%	5.3%
Bilingual	4.2%	1.0%	1.5%	2.1%
Other	1.2%	1.3%	1.5%	1.4%
n	241	301	262	804
Educational level				
Primary school and less	16.8%	13.3%	9.1%	13.0%
Secondary school or Technical training	71.9%	74.6%	78.8%	75.2%
College or University	11 3%	12 0%	12.1%	11.8%
n	274	308	307	889
Social class				
Father in low status job	61.0%	60.1%	59.5%	60.5%
n	259	301	309	869
Deceased subjects at time of interview	11.5%	27.3%	1.9%	13.7%
n	287	322	319	928

Table V-3 Occupational characteristics of the study population

	Cases	Hospital referents	Population referents	Overall
Part time job	26.4%	25.4%	26.5%	26.1%
n	273	315	317	905
Total years worked	31.6	34.6	33.5	33.2
S.D	12 3	10 1	12 0	6.9
Total years not worked	0.49	0.18	0.20	0.29
S.D.	1.66	0 68	0.72	1.12
Stopped working 6 months or more for health reasons	32.8%	31.0%	15.1%	26.0%
n	268	316	317	901
Lead exposure	14.3%	16.8%	16.4%	15.9%
n	286	322	318	926
Pesticide exposure	5.2%	5.3%	6.0%	5.5%
n	286	322	318	926
Solvent exposure outside main job	65.0%	59.0%	58.6%	60.7%
n	280	322	318	920

D. LIFESTYLE

Around twenty per cent of the study population practiced a hobby where some solvents were used - glueing plane or car models, artist painting, etc. (Table V-4).

Smoking status was ascertained for comparison purposes with the 1978-79 Canada Health Survey. A larger proportion of cases had smoked and fewer were ex-smokers than in the two referent groups. Nevertheless, their smoking figures were close to those of the Canada Health Survey for employed men in the Province of Quebec - 56.5% of current smokers and 83 8% who ever smoked [Armstrong and Nicoll-Griffith 1987].

Alcohol intake was of special interest because of its potentially confounding effect. Seventy per cent of the subjects reported weekly drinking for some time in their life. Slightly more cases reported drinking at least 14 drinks per week during the last ten years This cut-off point, used by Statistics Canada for the last Canada Health Survey and identifying 'significant alcohol intake', showed that about 29% of our referents drank 'significantly', compared to 17% of the male Quebecers, at the time of the Survey [Canada Health Survey 1981· 23-27] This difference might be due in part to the fact that our population was not representative of the Province, being essentially urban, and that the Canada Health Survey sample includes everybody over 14 years of age, whereas ours is restricted to ages at which men drink more When an approximate lifetime index of alcohol intake was calculated (total units of beer, cider, wine and spirits drunk weekly, multiplied by the total number of years the subject reported drinking that amount), the cases consumed almost twice as much alcohol than either referent group.

E MEDICAL HISTORY

The medical history section of the questionnaire was aimed at identifying the previous occurrence of disorders associated with some form of organic psychosis. The cases were very similar to the hospital referents in their history of meningitis and convulsions; slightly more cases than hospital referents had a history of previous head injury with loss of consciousness or stroke prior to their hospitalization (Table V-5).

F. INTERVIEW CHARACTERISTICS

The proportion of surrogate interviews, slightly over 30%, was similar in the case and the hospital referent groups (Table V-6). Most of the interviews were in French and took on average 25 minutes. Half of the completed interviews were made during the day for the population referents, whereas the proportion raised to 60% for cases and hospital referents; this partly reflects the lower employment rate of disabled persons.

Table V-4 Solvent exposed hobbies and personal habits

	Cases	Hospital referents	Population referents	Overall
Solvent exposed hobby	19.9%	18.1%	18.6%	18.8%
n	277	315	317	909
Smoking status				
Non smoker	15.9%	10.9%	20.8%	15.8%
Ex-smoker	27.2%	42.4%	35.8%	35.5%
Smoker	56.9%	46.7%	43.4%	48.7%
n	283	321	318	922
Alcohol intake				
Ever drank alcohol once a week or more	71.1%	68.5%	71.6%	70.4%
n	280	317	317	922
14 drinks or more per week in last 10 years	34.3%	32.7%	26.6%	31.1%
n	277	318	316	911
Lifetime alcohol intake in units*	29130.4	19109.0	16013.2	20882.4
n	235	283	295	813

* 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine= 1 1/2 oz. of spirits.

Table V-5 Report of medical problems that occurred prior to admission

	Cases	Hospital referents	Population referents	Overall
Meningitis	1.9%	1.9%	0.6%	1.4%
n	269	313	317	899
Convulsions	3.9%	3.3%	1.7%	2.9%
n	229	273	295	797
Head injury	15.3%	12.5%	13.8%	13.8%
n	261	296	312	869
Stroke	6.9%	5.4%	0.6%	4.2%
n	274	314	317	905

Table V-6 Interview characteristics of the study population

	Cases	Hospital referents	Population referents	Overall
Respondent:				
Subject	69.0%	67.4%	94.0%	77.1%
Family	30.0%	32.0%	6.0%	22.4%
Other	1.0%	0.6%	0.0%	0.5%
Language of interview				
French	86.8%	96.9%	82.1%	88.7%
English	13.2%	3.1%	17.9%	11.3%
Average length (minutes)	26.9	23.7	24.0	24.8
S D	12 9	9 4	10 2	10 8
Day interviews*	62.7%	61.8%	51.1%	58.4%
Cooperation of respondent				
Very good or good	92.1%	95 3%	95.0%	94 2%
Fair or poor	7.9%	4 7%	5.0%	5 8%
Quality of given information				
Reliable	91.5%	96.5%	98.1%	95 6%
Questionable	8.5%	3.5%	1.9%	4 4%
Interviewer did not guess study status	32.0%	13 7%	7.3%	17 1%
n	287	322	319	928

* Day interviews were done between 9.00 and 17:00 h.

The cooperation of respondents in the three groups was similarly good for more than 90% of the interviews. The interviewers felt that the cases' interviews were less reliable than that of the hospital referents, which were also less reliable than that of the population referents However, less than 5% of all the interviews were considered as questionable or unreliable.

At the end of the questionnaire, the interviewers were asked to note whether they thought the subject was a case or a referent. They attributed the right study status to 92.7% of the population referents, 86 3% of the hospital referents and 68.0% of the cases. The correct guesses observed after the interview for the cases are lower than what could have been expected, some of the psychiatric patients might have been in a recurring stage of disease and their disorganized thought processes would be evident in the course of a 10 to 25-minute telephone interview The interviewers, all of whom had experience in the occupational health field knew the purpose of the study, they were however not informed as to the study status of the subjects they had to interview.

G HOSPITAL ADMISSION INFORMATION

The distribution of cases and hospital referents by diagnostic category (for the final diagnosis) is shown in Tables V-7 and V-8. For the cases, 'Organic psychotic conditions' constituted 11 3% of the main diagnoses, followed by 'Other psychoses' (32 0%) and non-psychotic mental disorders (56 7%). These figures cannot be directly compared to published mental health statistics however, because since 1978, first admissions' data are not separated from readmissions, and moreover the 8th revision of the International Classification of Disorders (ICD 8) was used at that time

The hospital referents had a variety of diagnoses, with the largest group from cardiovascular disorders (34 1%), followed by digestive disorders (16.3%) and cancers (14 4%) These proportions were consistent with the general morbidity pattern of Quebec males in 1982-83, except for a slight underrepresentation of respiratory disorders [Statistics Canada 1986b 89-95].

The success of the matching procedure can be evaluated from Table V-9. The average age and date of admission were the same for both cases and hospital referents. The observed difference in date of admission was due to a practical problem. Data on admission for the hospital referents was only available after some delay caused by computer processing in Quebec City. Consequently, hospital referents for the cases admitted between April 1984 and March 1985 had to be selected from the 1983-84 computer lists The length of stay of the cases during the key admission was two and a half times longer than that of the hospital referents.

Table V-7 Main diagnostic categories of cases

	Percentage	*n*
Organic psychotic conditions		
Senile and presenile organic psychotic conditions (ICD-9 290)	3.4%	13
Alcoholic psychoses (ICD-9 291)	6 3%	24
Drug psychoses (ICD-9 292)	0.3%	1
Transient organic psychotic conditions (ICD-9 293)	0.5%	2
Other organic psychotic conditions (chronic) (ICD-9 294)	0.8%	3
Other psychoses		
Schizophrenic psychoses (ICD-9 295)	4.5%	17
Affective psychoses (ICD 9 296)	13.1%	50
Paranoid states (ICD-9 297)	5 5%	21
Other nonorganic psychoses (ICD-9 298)	8 9%	34
Neurotic disorders, personality disorders and other non-psychotic mental disorders		
Neurotic disorders (ICD-9 300)	10.7%	41
Personality disorders (ICD-9 301)	3.7%	14
Alcohol dependence syndrome (ICD-9 303)	5.5%	21
Drug dependence (ICD 9 304)	0 3%	1
Non dependent abuse of drugs (ICD-9 305)	1.0%	4
Special symptoms or syndromes not elsewhere classified (ICD-9 307)	0.8%	3
Adjustment reaction (ICD-9 309)	15.0%	57
Specific non-psychotic mental disorders following organic brain damage (ICD-9 310)	2.1%	8
Depressive disorder, not elsewhere classified (ICD-9 311)	15.5%	59
Disturbance of conduct, not elsewhere classified (ICD-9 312)	0.3%	1
Other diagnoses*	1.8%	7
Total	100.0%	381

* These men were primarily hospitalized in psychiatry but received a main diagnosis for their physical disorder. Three men had an associated psychiatric diagnosis of 'Other psychoses' and 4 men of non-psychotic mental disorders

Table V-8 Main diagnostic categories of hospital referents

	Percentage	*n*
Infectious and parasitic diseases (ICD-9 001-139)	1.6%	6
Neoplasms (ICD-9 140-239)	14.4%	55
Endocrine, nutritional and metabolic diseases and immunity disorders (ICD-9 240-279)	4.2%	16
Diseases of blood and blood-forming organs (ICD-9 280-289)	1.1%	4
Diseases of the nervous system and sense organs (ICD-9 320-389)	4.7%	18
Diseases of the circulatory system (ICD-9 390-459)	34.1%	130
Diseases of the respiratory system (ICD-9 460-519)	6 8%	26
Diseases of the digestive system (ICD-9 520-579)	16 3%	62
Diseases of the genitourinary system (ICD-9 580-611)	7.1%	27
Diseases of the skin and subcutaneous tissue (ICD-9 680-709)	1.6%	6
Diseases of the musculoskeletal system and connective tissue (ICD-9 710-739)	3.4%	13
Symptoms, signs and ill-defined conditions (ICD-9 780-799)	3.4%	13
Factors influencing health status and contact with health services (ICD-9 'V' codes)	0 8%	3
Complications of surgical and medical care (ICD-9 996-999)	0.5%	2
Total	100.0%	381

Table V-9 Data available from hospital charts

	Cases	Hospital referents	Overall
Average age at admission (years)	54.1	54.1	54.1
S D	8 7	8 7	8 7
Average year of admission	82.7	82.6	82.7
S D	1 2	1 0	1 1
Average length of stay (days)	43.5	16.6	30.1
S D	76 4	22 7	49 6
Information on direction at discharge	61.7%	24.7%	43.2%
Information on occupation	79.3%	83.7%	81 5%
Information on alcohol intake	72.2%	79.3%	75 7%
n	381	381	762

Destination of the patient at discharge was of interest to us for tracing purposes; the information was available 2 5 times more often for the cases than for the referents. This situation could be a reflection of the fact that a much higher proportion of psychiatric patients are likely to be sent to special homes or long care facilities compared to general hospital patients; it may also show that care is more socially oriented in psychiatry units

Information on occupations and alcohol intake was scrutinized in the medical records and findings similar to those of the pilot study were made Minimal job information, e g. a job title, was present in an average of 81 5% of the records, some qualitative or quantitative information on alcohol intake could be found in 75 7% of the medical records The difference between cases and hospital referents lies in the quality of the information available The psychiatric records contained more job histories and quantitative estimates of alcohol intake than the general hospital records

The average age of the population referents at the date of admission of the case was 54 2 years (S D =8 8 years). All but 4 of these referents were selected from the same electoral polling subdivision, thus providing a very good geographical matching.

H NON-PARTICIPANTS

The referents who did not participate in the study were rather older than the cases (Table V-10) The untraced cases had a distribution of diagnoses similar to that of the whole series, whereas uncooperative cases had more diagnoses among the "Other psychoses' category (in particular 'Affective psychoses' and 'Other nonorganic psychoses') No clear pattern of diagnoses emerged for both untraced and uncooperative hospital referents. The non-participants resided all over the city with no evident cluster in any area

I SUMMARY

A very good participation rate was achieved: 91.7% of the whole study population agreed to give some information and 88.6% of them completed the questionnaire. We could not locate 3 7% of the sample overall, and 4.5% were uncooperative; more cases were untraced (7 6%) and uncooperative (5.8%) compared to the referents. The cases who did not participate in the study were younger than the average, whereas the referent subjects were either very close to the average age or slightly older

Table V-10 Average age of the non-participants

	Cases	Hospital referents	Population referents	Overall
Untraced				
Average age (years)	51.6	56.8	53 2	52.8
S.D	8 7	7 5	7 6	8 3
n	29	9	5	43
Uncooperatives				
Average age (years)	51.0	53.4	54.9	52 9
S D	6 4	9 5	6 5	7 2
n	22	13	17	52

The three study groups were similar in highest level of education attained and in social class of their family when they were a child; however, the cases resembled more the population referents in place of birth and, for Canadian born citizens, in mother tongue. At the time of the interview, the proportion of deceased hospital referents was 2.4 times higher than that of deceased cases (27.3% *vs.* 11.5%), and there were 6 times more deaths among cases than among population referents.

The same proportion of subjects in the three groups held a part-time job at some point and reported occupational exposure to lead and pesticides. The picture was not as clear for other occupational characteristics. more cases had solvent exposure outside their main job and stopped work for periods of 6 months and more for health reasons. They also worked a few years less than the referents

A higher proportion of cases were current smokers and more of them had been consuming 14 drinks of alcohol and more during the last 10 years, compared to the referents The lifetime alcohol intake had also been much larger among the cases than among any referent group Cases had experienced meningitis and convulsions in the same proportion as the hospital referents, but their rate of head injury (with loss of consciousness) and of stroke was slightly higher.

The characteristics of the interviews were similar in the three groups, except for a greater percentage of surrogate interviews for cases and hospital referents, which made their interviews more comparable. Despite the effort taken to hide the study status of the subjects, the interviewers correctly guessed the status of 68.0% of the cases, 86.3% of the hospital referents and 92 7% of the population referents.

The cases' final diagnoses were divided up as follows: 11.3% of 'Organic psychotic conditions' (ICD-9 codes 290-294), 32.0% of 'Other psychoses' (ICD-9 codes 295-298) and 56 7% of 'Neurotic disorders, personality disorders and other non-psychotic mental disorders' (ICD-9 codes 300-312). The hospital referents suffered from various disorders, 34.1% of them within the category of 'Diseases of the circulatory system' (ICD-9 codes 390-459). The age matching was very close for the three groups, and so was the geographical matching.

VI. Main results

A- INTRODUCTION

This chapter presents the results obtained from paired comparisons between cases and their hospital referents The methodological aspect of this thesis - the comparison of hospital and population referents - is presented separately in Chapter VII

1) Exposure variables

Three continuous variables were computed according to the three cut-off points used to assess the intensity of solvent exposure: the number of years exposed at low levels and higher (1/0 and above), of years exposed at moderate levels and higher (2/1 and above), and of years exposed at high levels (3/2 and above) These three continuous variables are thus not exclusive, e g exposure to low levels and higher also include exposure to moderate levels and to high levels Exposure was further categorized according to three durations: any duration, 10 years or more, and 25 years or more

At the start of the study - and thus before any analysis of the data - solvent exposure was considered to be 'important' at a moderate level or higher, and for 10 years or more A moderate level was defined as a rating of 2/1 and above (see Chapter III Research protocol) After inspection of the reliability studies data (Chapter IV Reliability and validity studies), I also chose to focus on exposure to high levels because it became obvious that I had a tendency to overestimate the intensity of exposure compared to expert raters

To address the second objective of the study, three indices of weighted exposure to solvents were computed For a given job, the weighted exposure at a moderate level or higher would be the percentage of the work week exposed at that level, times the number of years, the weighted exposures were then added up for each intensity cut-off point - low exposure and higher, moderate exposure and higher, and high exposure The first and the last years exposed to each of the three levels were used to explore the existence of critical latency periods

Lastly, two exclusive indices of cumulative exposure were computed to explore exposure-response relationships The three continuous exposure indices were first reorganized to produce mutually exclusive indices, i e number of years exposed at low levels, moderate levels and high levels It had been decided that the intensity levels were to be related conceptually to threshold limit values 'low' intensity at less than 30% of the TLV, 'moderate' at 30 to 50% of the TLV and 'high' at above 50% of the TLV The mid-points of these ranges were used as weights - 0 15 for 'low' levels, 0.40 for 'moderate' levels and 0.75 for 'high' levels - to create the two cumulative indices:

cumulative years exposed or 'solvent-years', and cumulative weighted exposure (taking into account the percentage of the work week exposed).

Several variables might be related to both the disease and the exposure under study: for example age, alcohol intake, and exposures to lead and pesticide. Age at admission is a major possible confounding factor and referents had been matched thus in the study design. It was categorized in decades for some analyses: 40 to 49, 50 to 59 and 60 to 69 years. Two variables depicting alcohol intake were computed: weekly alcohol intake during the 10 years before the interview and lifetime consumption of alcohol. The weekly alcohol intake has also been categorized as for the Canada Health Survey: less than 14 drinks, and 14 drinks and more per week. Lead and pesticides are potential neurotoxicants and reported exposure to any of them was checked for any difference between cases and referents.

Diagnostic category, within mental disorder, was of interest because of the lack of agreement, in previous studies, on categories of disease carrying risk. Mental disorders were divided according to the broad subdivisions of the International Classification of Diseases as psychotic (ICD-9 codes 290-298) and non-psychotic conditions (ICD-9 codes 300-316). More refined subdivisions would have been informative, but the number of subjects in each was too small to be meaningful.

2) Analytical sequence

Matching was retained in all analyses, except for the prevalence of solvent exposure discussed later in this section. Two approaches were used: i) using all the available data, and ii) restricting analyses to pairs where both members had completed the interview. In each, the three duration cut-off points were used.

It was mentioned above that two substantial solvent exposure cut-off points would be considered: 'moderate levels and above' and 'high levels'. Each analysis used sequentially both of these cut-off points, the results will be presented first using the *a priori* decided substantial level (moderate levels and above), and then using exposure at high levels.

Odds ratios, together with their 90% confidence intervals, were first calculated from contingency tables. The choice of a 90% C.I. allows immediate identification of odds ratios significantly raised at the conventional 0.05 level, according to a one-sided test, a focus justified by the unilateral nature of the hypotheses of this study, namely that psychiatric patients were more exposed than their hospital referents.

The second analytical step was to verify whether the risk was modified by age at admission, and then to control for reported alcohol intake, and exposure to lead and

pesticides. The cases were also stratified into two large diagnostic categories psychotic (ICD-9 codes 290-298) and non-psychotic (ICD-9 codes 300-316)

Thirdly, conditional logistic regression was used to assess the effect of alcohol intake while controlling for age at admission, total number of years worked, solvent exposure outside the main jobs, and other possible confounders and effect modifiers

Lastly, crude exposure-response relationships were investigated using the exclusive indices of cumulative solvent exposure

3) Exposed job categories

As mentioned in Chapter IV on reliability and validity studies, all the job titles described in both studies A and B were pooled, and listed along with the frequencies of the various intensity ratings I attributed to them. The job categories rated as entailing solvent exposure at low levels and higher, for 50% and more of the described job titles were, with their Canadian classification code soldiers (6117), barbers and hairdressers (6143), foremen in fabricating and assembling occupations, Metal products (8510), roofing and waterproofing (8787), locomotive operation (9131), conductors and brakemen, Railway (9133), labourers in the printing industry (9518)

Only 5 job categories were considered to be exposed at moderate levels of solvents and higher service station attendants (5145), textile bleaching and dyeing occupations (8273), bonding and cementing occupations, Rubber and plastic products (8571), aircraft mechanics and repairers (8582), and typesetting and composing occupations (9511).

High exposure levels were consistently attributed for 4 job categories motor vehicle mechanics and repairers (8581), painting and decorating occupations (8595), painters and related occupations, construction industry (8785), and printing press occupations (9512).

4) Extent of exposure

Fifty-four per cent of the cases and fifty-seven per cent of the referents were ever exposed to any level of solvents, whereas 30% of cases and 34% of referents were exposed (any duration) to moderate levels and higher Exposure to high solvent levels at some time during their work history was attributed to 17 3% of cases and 15 4% of referents The proportion of subjects exposed for more than 10 years at high levels was 6.8% for cases, and 8.0% for referents Detailed tables presenting prevalence of exposure can be found as Annex 13.

Averages of thirty to thirty-three years elapsed since first exposure, and eleven to seventeen years between last exposure and admission to hospital, these figures were similar for cases and referents and for the three intensity cut-off points

Slightly more referents were exposed to any level or to moderate levels and higher, whereas cases were more exposed when high levels were considered.

B- DESCRIPTION OF THE PAIRS

Differences between cases and their hospital referents were tested with paired-sample t tests for continuous variables, McNemar chi squares for dichotomous categorical variables [Fleiss 1981: 114], and Stuart-Maxwell chi squares for categorical variables of more than two levels [Fleiss 1981: 120].

Most sociodemographic variables were similar when a matched comparison was performed The average age at admission, 54.1 years, was the same for cases and their hospital referents. There were no differences between cases and referents in mother tongue, educational level or social class of the family when the subject was a child (Tables VI-1a and 1b). There were more than twice as many immigrants amongst cases than amongst referents (15.2% *vs.* 7 4%).

The same proportion of cases and referents reported consuming 14 drinks of alcohol and more during the last 10 years, but cases took much larger quantities - both during the last 10 years and for their lifetime (Tables VI-1a and 1b).

Reported exposure to lead and pesticides at work, and solvents outside main jobs, was similar for both groups (Table VI-2a). Cases worked less than referents and their work histories had more years of unemployment and of unknown working status (Table VI-2b) Amongst the retired subjects, cases stopped work at a younger age than referents These variables changed very marginally when the analysis was restricted to pairs with complete interviews

There was no difference in frequency of head injury (McNemar χ^2=0.08) or stroke (McNemar χ^2=0.04) prior to hospital admission between cases and hospital referents.

C. BASIC ANALYSIS

1) Exposure at moderate levels and higher

a) Unadjusted estimates

The contingency tables used to compute the odds ratios were set up with the SPSS/PC+™ system adapted for IBM-compatible micro computers. The EGRET™ software was used to calculate 90% confidence intervals, according to Breslow and Day's methods [Breslow and Day 1980: 251-253].

Table VI-1a Matched comparison of sociodemographic characteristics: categorical variables

	Number of pairs	Chi square	df	p value
Mother tongue				
French/English/Other	186	4.70*	2	0.05< p <0.10
Immigrant to Canada				
Yes/No	243	6.89**	1	0.005< p <0.01
Educational level				
Primary & less/Secondary & technical/College & university	222	0.83*	2	>0.10
Drank 14 units*** per week and more in the last 10 years				
Yes/No	234	0.61**	1	>0.10

* Stuart-Maxwell χ^2 test

** McNemar χ^2 test

*** 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine = 1 1/2 oz. of spirits

Table VI-1b Matched comparison of sociodemographic characteristics: continuous variables

	Cases	Hospital referents	Number of pairs	t value	p* value
Social class					
Average Blishen scale	347.6	356.3	204	-0.70	0.485
S.D.	118.9	129 3			
Average alcohol intake					
Weekly intake, last 10 years (units**)	20.9	13.5	215	2.55	0.011
S.D.	35.0	24.5			
Lifetime intake (units)	27876.6	18186.3	182	2.50	0.013
S.D.	41958 8	31040.3			

* Paired t test, two-tailed

** 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine= 1 1/2 oz. of spirits.

Table VI-2a Matched comparison of occupational characteristics: categorical variables

	Number of pairs	McNemar Chi square	df	p value
Lead exposure				
No/Yes	243	0.07	1	>0.10
Pesticide exposure				
No/Yes	243	0.15	1	>0.10
Solvent exposure outside main job				
No/Yes	232	1.10	1	>0.10

Table VI-2b Matched comparison of occupational characteristics: continuous variables

	Cases	Hospital referents	Number of pairs	t value	p* value
Total years worked (years)	31.6	34.8	314	-4.43	<0.001
S.D.	12.3	10.2			
Total years not worked (years)	0.49	0.18	381	3.44	<0.001
S D.	1.66	0.68			
Total years of unknown working status (years)	1.9	1.2	362	2.23	0.026
S.D	5.0	3.0			
Average age stopped working (years)	53.8	55.8	129	-2.52	0.013
S.D.	9.9	8.4			

* Paired t test, two-tailed

A crude analysis of the data did not indicate any significantly elevated risk (Table VI-3). There was also no significant difference between cases and referents for continuous exposure variables: the average number of years exposed was 4.6 for cases and 5.7 for hospital referents (t=-1.19, one-tailed p=0.118), and the average weighted exposures were 1.2 for cases and 1.4 for referents (t=-0.65, one-tailed p=0.259).

b) Adjusted estimates

The 90% confidence intervals presented below were calculated according to Johnson and Kotz's methods as reported in Schlesselman [1982: 210], using the TRUE EPISTAT™ software.

1. Age at admission

Age at admission was a matching criterion; it did not markedly modify the effect of solvent exposure on the risk of mental disorder (Table VI-4). The older age group (60 to 69 years) had elevated non-significant risks for 10-year and 25-year exposures.

There was again not much difference between risk estimates obtained from all the subjects and those obtained when the analysis was restricted to complete interviews.

The averages of continuous exposure variables increased with age, which was to be expected, but no statistically significant differences were found between cases and their referents (Table VI-5). Hospital referents had slightly higher average weighted exposure, except for the older age group where the reverse was obtained.

2. Possible confounders

Amongst possible confounders, alcohol intake, and exposure to lead and pesticides had been identified before the study started. As information on these variables was available only from completed questionnaires, analyses of potential confounders were restricted to complete interviews. A true stratified analysis of these variables would have entailed four strata: variable absent among both subjects of the pair, present with the case and absent with the referent, the reverse, and variable present among both subjects of the pair. This was cumbersome, and for some strata, the numbers were very small. The basic analyses were thus restricted to pairs which were homogeneous for the confounder considered; this was a simple approach but unfortunately resulted in a considerable decrease in the sample size - by about half for alcohol intake, by 25% for lead exposure and by about ten percent for pesticide exposure. A better evaluation of these variables was made by mathematical modeling (see the next section).

Table VI-3 Unadjusted estimates of risk, moderate exposure levels and higher

Solvent exposure	Discordant pairs case/referent	Odds ratio	90% C.I.
	All case-referent pairs (n=351)		
Any duration	64/77	0.83	0.63-1.11
10 years or more	44/46	0.96	0.69-1.38
25 years or more	23/28	0.82	0.52-1.30
	Complete interviews (n=244)		
Any duration	45/53	0.85	0.61-1.18
10 years or more	33/34	0.97	0.65-1.45
25 years or more	17/24	0.71	0.42-1.19

Table VI-4 Estimates of risk stratified according to age at admission, moderate exposure levels and higher

Solvent exposure	Age at admission	Discordant pairs case/referent	Odds ratio	90% C.I.
		All case-referent pairs		
Any duration	40-49 years	22/27	0.81	0.47-1.41
	50-59 years	22/24	0.92	0.52-1.62
	60-69 years	20/26	0.77	0.43-1.36
10 years or more	40-49 years	12/15	0.80	0.36-1.73
	50-59 years	17/17	1.00	0.51-1.96
	60-69 years	16/14	1.14	0.55-2.38
25 years or more	40-49 years	1/4	0.25	0.00-2.67
	50-59 years	10/13	0.77	0.32-1.80
	60-69 years	12/11	1.09	0.47-2.56
		Complete interviews		
Any duration	40-49 years	17/16	1.06	0.53-2.12
	50-59 years	14/18	0.78	0.38-1.57
	60-69 years	14/19	0.74	0.36-1.47
10 years or more	40-49 years	9/11	0.82	0.32-2.05
	50-59 years	11/13	0.85	0.37-1.93
	60-69 years	13/10	1.30	0.56-3.10
25 years or more	40-49 years	1/3	0.33	0.00-4.48
	50-59 years	6/12	0.50	0.17-1.38
	60-69 years	10/9	1.11	0.43-2.90

Table VI-5 Paired comparisons between continuous exposure variables, stratified by age at admission, moderate exposure levels and higher. Complete interviews

	Cases	Hospital referents	t value	p* value
	40-49 years (n=78)			
Total years exposed	3.2	3.5	-0.26	0.397
S.D.	6.2	7.6		
Weighted exposure	0.9	1.1	-0.41	0.343
S.D.	2.1	3.0		
	50-59 years (n=84)			
Total years exposed	4.8	6.3	-1.01	0.158
S.D.	9 6	11.3		
Weighted exposure	1.1	1.6	-0.99	0.163
S.D.	2.9	3.5		
	60-69 years (n=82)			
Total years exposed	5.7	7.1	-0.70	0.241
S.D.	11 0	13.9		
Weighted exposure	1.6	1.5	0.20	0.422
S.D.	3.6	3 1		

* Paired t test, one-tailed

Correction for alcohol intake was made by restricting the analysis to pairs where both members drank less than 14 alcohol units per week, or drank 14 units and more per week during the last 10 years before the interview.

The odds ratios were consistently higher, with wider confidence intervals, among pairs that had a similar alcohol intake (Table VI-6) compared to the unadjusted odds ratios (Table VI-3). None of the risk estimates were significantly raised however.

Correction for lead exposure consisted in restricting the analysis to pairs where both subjects answered either 'yes' or 'no' to the question on lead exposure at work. The 'corrected' odds ratios (Table VI-6) changed very marginally compared to the unadjusted ones (Table VI-3).

Correction for pesticide exposure was made in the same way as for lead exposure. Thus, adjustment lowered all the odds ratios; again, no risk estimate was significantly raised at the 90% level (Table VI-6).

Adjustment for weekly alcohol intake and reported lead exposure did not change the averages of the continuous variables, and there was still no difference between cases and referents (Table VI-7). After adjustment for reported pesticide exposure, the continuous exposure variables changed only slightly, but sufficiently for the referents to be exposed significantly more years (Table VI-7).

3. Diagnostic category

The ICD-9 diagnostic categories were pooled into two broad groups: psychoses (ICD-9 codes 290-299) and non-psychotic conditions (ICD-9 codes 300-316). There was no significant increase in risk (Table VI-8), although the estimates tended to be higher for non-psychotic diagnoses compared to the psychotic ones. The risk estimates computed from all the available pairs were very similar to those calculated from complete interviews.

There was no significant difference between cases and referents, when continuous variables were considered separately for psychotic and non-psychotic diagnoses (Table VI-9), although referents tended to be somewhat more exposed than cases, and this, for both large diagnostic categories.

2) Exposure at high levels

a) Unadjusted estimates

A slightly elevated - but non significant - odds ratio was found for exposure at high levels of solvents for any duration (Table VI-10): no increase was discernible with the 10-year and 25-year cut-off points. The pattern remained the same when all pairs were included in the analysis and when it was restricted to complete interviews.

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			
Any duration	[illegible]	[illegible]	[illegible]
10 years or more	[illegible]	[illegible]	[illegible]
25 years or more	[illegible]	[illegible]	[illegible]

Table VI-7 Paired comparisons between continuous exposure variables, adjusted for possible confounders, moderate exposure levels and higher. Complete interviews

	Cases	Hospital referents	t value	p* value
Adjusted for alcohol intake (n=130)				
Total years exposed	4.7	4.6	0.08	0.468
S.D.	9.4	10.6		
Weighted exposure	1.2	1.1	0.42	0.338
S.D	3.1	2 7		
Adjusted for lead exposure (n=183)				
Total years exposed	4.2	4.9	-0.62	0.268
S D	9.1	10.4		
Weighted exposure	1.2	1.2	-0.15	0.440
S D	3.1	3.0		
Adjusted for pesticide exposure (n=216)				
Total years exposed	4.3	5.8	-1.65	0.050
S D	8.7	11.4		
Weighted exposure	1.0	1.4	-1.33	0.092
S D	2.6	3.2		

* Paired t test, one-tailed

Table VI-8 Estimates of the risk of mental disorder with solvent exposure, stratified by large diagnostic group, moderate exposure levels and higher

Solvent exposure duration	Discordant pairs case/referent	Odds ratio	90% C.I.
	All case-referent pairs		
PSYCHOSES, ICD-9 codes 290-298 (*n*=149)			
Any duration	21/38	0.55	0.35-0.88
10 years or more	19/22	0.86	0.52-1.45
25 years or more	10/14	0.71	0.36-1.41
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=202)			
Any duration	43/39	1.10	0.76-1.61
10 years or more	26/24	1.08	0.68-1.73
25 years or more	13/14	0.93	0.49-1.75
	Complete interviews		
PSYCHOSES, ICD-9 codes 290-298 (*n*=109)			
Any duration	17/27	0.63	0.38-1.05
10 years or more	16/16	1.00	0.56-1.79
25 years or more	9/11	0.82	0.39-1.71
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=135)			
Any duration	28/26	1.08	0.69-1.69
10 years or more	17/18	0.94	0.54-1.65
25 years or more	8/13	0.61	0.29-1.29

Table VI-9 Paired comparisons between continuous exposure variables, stratified by large diagnostic group, moderate exposure levels and higher. Complete interviews

	Cases	Hospital referents	t value	p* value
PSYCHOSES, ICD-9 codes 290-298 (*n*=109)				
Total years exposed	4.6	5.5	-0.65	0.259
S.D.	9.6	10.9		
Weighted exposure	1.0	1.3	-0.83	0.205
S.D.	2.3	3.2		
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=135)				
Total years exposed	4.6	5.8	-1.02	0.156
S.D	8.9	11.7		
Weighted exposure	1.3	1.4	-0.17	0.433
S D	3.4	3.2		

* Paired t test, one-tailed

Table VI-10 Unadjusted estimates of risk, high exposure levels

Solvent exposure	Discordant pairs case/referent	Odds ratio	90% C.I.
	All case-referent pairs (*n*=359)		
Any duration	48/39	1.21	0.84-1.74
10 years or more	21/24	0.88	0.53-1.43
25 years or more	8/9	0.89	0.40-1.98
	Complete interviews only (*n*=244)		
Any duration	35/25	1.40	0.91-2.15
10 years or more	15/17	0.88	0.49-1.58
25 years or more	6/6	1.0	0.39-2.59

There was also no difference between cases and referents when continuous exposure variables were considered: the average number of years exposed was 2.2 for cases and 2.1 for hospital referents (t=0.22, one-tailed p=0.414), and the average weighted exposures were 0.74 for cases and 0.66 for referents (t=0.35, one-tailed p=0.364).

b) Adjusted estimates

1. Age at admission

Age at admission again modified the relationship between solvent exposure and the risk of mental disorder (Table VI-11). The older age group (60 to 69 years) consistently presented higher - but non significant - risks than the two younger groups.

There was again little difference between risk estimates obtained from all the subjects and those obtained when the analysis was restricted to complete interviews.

The averages of continuous exposure variables increased with age, which was to be expected, but no statistically significant differences were found between cases and their referents (Table VI-12). Hospital referents had slightly higher average exposure when both cut-off points - moderate levels and higher, and high levels - were considered, except for the older age group where the reverse was obtained.

2. Possible confounders

The odds ratios were consistently higher, with wider 90% confidence intervals, among pairs that had a similar weekly alcohol intake (Table VI-13) compared to the unadjusted odds ratios (Table VI-10). None of the risk estimates were significant however. The main difference observed at high levels of exposure (compared to moderate levels and higher) was that the risks were all more than 1.00.

The odds ratios corrected for reported lead exposure (Table VI-13) changed very marginally compared to the unadjusted ones (Table VI-10). Adjustment for reported pesticide exposure lowered all the odds ratios; again, no risk estimate was significant at the 90% level.

The continuous exposure variables changed only slightly after correction for alcohol intake, and reported lead and pesticide exposures (Table VI-14); only weighted exposure after adjustment for alcohol intake was close to being significantly higher for cases.

3. Diagnostic category

Stratifying the analysis according to diagnostic category showed a significant increase in risk for any duration of exposure among non-psychotic diagnoses (Table VI-15); this increase was consistent but not significant at the 10-year and 25-year cut-off points. The trend remained unchanged when all case/referent pairs were used in the analysis and when only complete interviews were retained.

Table VI-11 Estimates of risk stratified according to age at admission, high exposure levels

Solvent exposure	Age at admission	Discordant pairs case/referent	Odds ratio	90% C.I.
		All case-referent pairs		
Any duration	40-49 years	12/15	0.80	0.36-1.73
	50-59 years	20/16	1.25	0.65-2.42
	60-69 years	16/8	2.00	0.84-5.00
10 years or more	40-49 years	4/8	0.50	0.12-1.81
	50-59 years	8/10	0.80	0.29-2.13
	60-69 years	9/6	1.50	0.50-4.79
25 years or more	40-49 years	0/3	0.00	0.00-2.94
	50-59 years	4/5	0.80	0.16-3.59
	60-69 years	4/1	4.00	0.37-∞
		Complete interviews		
Any duration	40-49 years	9/8	1.12	0.41-3.15
	50-59 years	14/11	1.27	0.57-2.90
	60-69 years	12/6	2.00	0.72-6.03
10 years or more	40-49 years	2/5	0.40	0.03-2.45
	50-59 years	5/7	0.71	0.19-2.50
	60-69 years	8/5	1.60	0.48-5 83
25 years or more	40-49 years	0/2	0.00	0.00-7.27
	50-59 years	2/3	0.67	0.05-6.01
	60-69 years	4/1	4.00	0.37-∞

Table VI-12 Paired comparisons between continuous exposure variables, stratified by age at admission, high exposure levels. Complete interviews

	Cases	Hospital referents	t value	p* value
	40-49 years (n=78)			
Total years exposed	1.3	1.7	-0.58	0.283
S.D.	3.6	5.9		
Weighted exposure	0.5	0.6	-0.26	0.396
S.D.	1.8	2.4		
	50-59 years (n=84)			
Total years exposed	2.1	2.4	-0.33	0.370
S D.	6.6	7.2		
Weighted exposure	0.8	0.8	-0.02	0.494
S.D.	2.7	2.7		
	60-69 years (n=82)			
Total years exposed	3.1	2.0	1.00	0.161
S.D.	8.0	6.5		
Weighted exposure	0.9	0.6	0.82	0.208
S.D	2.7	2.1		

* Paired t test, one-tailed

Table VI-13 Estimates of risk adjusted for possible confounders, high exposure levels. Complete interviews

Solvent exposure duration	Discordant pairs case/referent	Odds ratio	90% C.I.
	Adjusted for alcohol intake (n=130)		
Any duration	18/8	2.25	0.97-5.53
10 years or more	9/6	1.50	0.50-4.79
25 years or more	4/3	1.33	0.23-9.04
	Adjusted for lead exposure (n=183)		
Any duration	28/19	1.47	0.84-2.63
10 years or more	12/14	0.86	0.39-1.89
25 years or more	5/6	0.83	0.21-3.13
	Adjusted for pesticide exposure (n=216)		
Any duration	28/23	1.22	0.71-2.09
10 years or more	10/17	0.59	0.26-1.30
25 years or more	3/6	0.50	0.08-2.29

Table VI-14 Paired comparisons between continuous exposure variables, adjusted for possible confounders, high exposure levels. Complete interviews

	Cases	Hospital referents	t value	p* value
Adjusted for alcohol intake (n=130)				
Total years exposed	2.5	1.8	0.92	0.180
S.D.	7.0	6.4		
Weighted exposure	0.9	0.5	1.45	0.075
S.D.	2.9	1.9		
Adjusted for lead exposure (n=183)				
Total years exposed	2.3	2.3	-0.04	0.484
S.D.	6.6	7.2		
Weighted exposure	0.8	0.8	0.08	0.468
S.D.	2.7	2.7		
Adjusted for pesticide exposure (n=216)				
Total years exposed	1.8	2.2	-0.79	0.215
S.D.	5.4	6.9		
Weighted exposure	0.6	0.7	-0.70	0.241
S.D.	2.0	2.5		

* Paired t test, one-tailed

Table VI-15 Estimates of the risk of mental disorder with solvent exposure, stratified by large diagnostic group, high exposure levels

Solvent exposure duration	Discordant pairs case/referent	Odds ratio	90% C.I.
	All case-referent pairs		
PSYCHOSES, ICD-9 codes 290-298 (*n*=154)			
Any duration	21/27	0.77	0.47-1.25
10 years or more	9/16	0.56	0.28-1.12
25 years or more	2/7	0.29	0.08-1.07
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=205)			
Any duration	26/12	2.17	1.22-3.85
10 years or more	12/8	1.50	0.71-3.18
25 years or more	6/2	3.00	0.78-11.49
	Complete interviews		
PSYCHOSES, ICD-9 codes 290-298 (*n*=109)			
Any duration	18/18	1.00	0.58-1.73
10 years or more	8/12	0.67	0.31-1.41
25 years or more	2/6	0.33	0.09-1.28
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=135)			
Any duration	17/7	2.43	1.16-5.08
10 years or more	7/5	1.40	0.53-3.67
25 years or more	4/0	∞	N/A*

* N/A: non available

There was no difference between cases and referents, when continuous variables were considered separately for psychotic and non-psychotic diagnoses (Table VI-16). However, cases were twice as exposed as referents among non-psychotic conditions, whereas referents were slightly more exposed than cases among psychotic conditions.

D- MATHEMATICAL MODELING

An efficient way to control for many extraneous variables is by use of multivariable regression analysis [Kleinbaum *et al.* 1982: 315]. The linear logistic regression model is appropriate when the dependent variable (the disease outcome) is dichotomous and the independent variables contain both continuous and categorical variables [Hanley 1983]. It is computationally simpler than the probit model and many programs have been developed for the purpose.

The logistic model takes the following form [Schlesselman 1982: 228]:

$$p_x = p(d = 1 \mid x)$$
$$= 1/\{1 + \exp [- (\beta_o + \beta_1 x_1 + \ldots + \beta_p x_p)] \}$$

where p_x = probability of disease corrected for the variables x
d = presence (d=1) or absence (d=0) of disease
β's = logistic parameters representing the effect of the x's - adjusted for the effects of the other variables in the equation - on the probability of disease.

The risk estimate is derived directly from this equation through the following relationship [Schlesselman 1982: 237]:

$$\Psi(x^*: x) = \exp [\beta_1(x_1^* - x_1) + \ldots + \beta_p(x_p^* - x_p)]$$

where x^* = variables x from one individual
x = variables x from another individual
$\Psi(x^*: x)$ = odds ratio for x^* *versus* x

The analyses were performed with the conditional logistic regression option of the EGRET™ software.

Table VI-16 Paired comparisons between continuous exposure variables, stratified by large diagnostic group, high exposure levels. Complete interviews

	Cases	Hospital referents	t value	p* value
PSYCHOSES, ICD-9 codes 290-298 (*n*=109)				
Total years exposed	2.0	2.8	-0.81	0.209
S D.	6.1	8.0		
Weighted exposure	0.63	0.86	-0.70	0.242
S.D.	1.83	2.83		
NON-PSYCHOTIC CONDITIONS, ICD-9 codes 300-316 (*n*=135)				
Total years exposed	2.3	1.4	1.38	0.085
S.D.	6 7	5.0		
Weighted exposure	0.82	0.50	1.18	0.119
S.D	2.83	1.96		

* Paired t test, one-tailed

As there was little difference between crude risk estimates obtained from all the available data and those restricted to complete interviews, this analysis was limited to complete interviews, with information on possible confounders. To ease the readability of the different logistic regression models discussed in this section and the next one, Table VI-17 presents the short names of the variables used and their meaning.

Full models containing all the terms of interest as potential confounders or effect modifiers were fitted first at moderate exposure levels and higher for any duration (Tables VI-18 to VI-20); these full models were corrected for age at admission and for numbers of years worked even though their coefficients are not presented in the tables. These models were fitted on complete interviews, first with all diagnoses, and then restricted to pairs where the case had a final diagnosis of i) a psychotic condition (ICD-9 codes 290-299), and ii) a non-psychotic condition (ICD-9 codes 300-316).

After correction for possible confounders, the odds ratio, 0.90 (Table VI-18), was higher than the unadjusted odds ratio, 0.85 (Table VI-3), when all diagnoses were pooled. When the analysis was stratified by main diagnostic category, the odds ratios, 0.49 and 1.38 (Tables VI-19 and VI-20), were somewhat different from the unadjusted odds ratios, 0.63 and 1.08 (Table VI-8, complete interviews). This suggests that adjustment for the variables included in the full model widened the difference between the odds ratios found for psychotic diagnoses compared to non-psychotic ones. Apart from immigrant status, which was significantly associated with mental disorder for all diagnoses, lead exposure was related to a higher risk of psychotic diagnoses (Table VI-19). No interaction term was significant when added to the model, so none was included.

Tables VI-21 to VI-23 present the same models, but with an exposure cut-off point of high levels; these full models were also corrected for age at admission and for numbers of years worked. The odds ratios for any duration of exposure at high levels, 1.46, 0.82 and 2.41, were similar to the unadjusted odds ratios, 1.40, 1.00 and 2.43 (Tables VI-4 and VI-15, complete interviews). Again, correction for possible confounders enlarged the difference between psychotic and non-psychotic diagnoses. No interaction term was significant.

The common picture at the two intensity cut-off points is that when diagnoses were divided into psychotic and non-psychotic categories, solvent exposure appeared to be a risk factor only among the latter category. Two variables maintained the same level of risk regardless of the solvent exposure variable used: being an immigrant was consistently related to the risk of psychiatric disease, and weekly alcohol intake did not appear to change that risk.

Table VI-17 Description of the variables used in mathematical modeling

Variable name	Description
Exposure variables	
EXP2	Exposure at moderate levels and higher, any duration (No=0/Yes=1)
EXP3	Exposure at high levels, any duration (No=0/Yes=1)
CUMYRS	[Years exposed at low levels x 0.15] + [years exposed at moderate levels x 0.40] + [years exposed at high levels x 0.75] (Years)
CUMWGT	[weighted exposure at low levels x 0.15] + [weighted exposure at moderate levels x 0.40] + [weighted exposure at high levels x 0.75]
Possible confounders and other variables	
LEAD	Reported exposure to lead at work (No=0/Yes=1)
PEST	Reported exposure to pesticides at work (No=0/Yes=1)
EXTSOLV	Reported exposure to solvents outside main jobs (No=0/Yes=1)
IMMIGR	Immigrant status (No=0/Yes=1)
WKLQALC	Weekly alcohol intake during the last 10 years (None=0/<14 units*=1/14 units+=2)

* 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine= 1 1/2 oz. of spirits

Table VI-18 Adjusted odds ratios for exposure at moderate levels of solvents and higher, complete interviews, adjusted for age at admission and number of years worked. All diagnoses (*n*=227)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP2	-0.1079 (0.229)	0.638	0.90 (0.61-1.31)
LEAD	0.0434 (0.287)	0.880	1.04 (0.65-1.67)
PEST	-0.0966 (0.413)	0.815	0.91 (0.46-1.79)
EXTSOLV	-0.2142 (0 225)	0.303	0.81 (0.57-1.14)
IMMIGR	1.086 (0.350)	0.002	2.96 (1.67-5.27)
WKLQALC=<14 drinks/week	0.2438 (0 258)	0.344	1.28 (0 83-1.95)
WKLQALC=14 drinks+/week	0.1862 (0 233)	0.424	1.20 (0.82-1.77)

Deviance=294.19

Likelihood ratio statistic on 10 df=20.50 (p=0.025)

Table VI-19 Adjusted odds ratios for exposure at moderate levels of solvents and higher, complete interviews, adjusted for age at admission and number of years worked. Psychotic diagnoses (n=100)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP2	-0.7205 (0.383)	0.060	0.49 (0 30-0 91)
LEAD	0.9492 (0 522)	0.069	2.58 (1 09-6.09)
PEST	-0 6197 (0.672)	0.357	0.54 (0.18-1.63)
EXTSOLV	-0.0030 (0 320)	0.993	1.00 (0 59-1.69)
IMMIGR	1.358 (0.556)	0.015	3.89 (1 56-9 71)
WKLQALC=<14 drinks/week	0.3508 (0 445)	0.431	1.42 (0 68-2 95)
WKLQALC=14 drinks+/week	-0.4493 (0 379)	0.236	0.64 (0 34-1 19)

Deviance=112 96

Likelihood ratio statistic on 10 df=25.67 (p=0 004)

Table VI-20 Adjusted odds ratios for exposure at moderate levels of solvents and higher, complete interviews, adjusted for age at admission and number of years worked. Non-psychotic diagnoses (n=127)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP2	0.3237 (0.318)	0.308	1.38 (0.82-2.33)
LEAD	-0.4637 (0.402)	0.249	0.63 (0.32-1.22)
PEST	0.2285 (0.611)	0.709	1.26 (0.46-3.43)
EXTSOLV	-0.4811 (0.308)	0.118	0.62 (0.37-1.03)
IMMIGR	1.077 (0.511)	0.035	2.94 (1.27-6.80)
WKLQALC=<14 drinks/week	0.2231 (0 357)	0.532	1.25 (0.69-2.25)
WKLQALC=14 drinks+/week	0.5303 (0.333)	0.111	1.70 (0.98-2.94)

Deviance=162.77

Likelihood ratio statistic on 10 df=13.29 (p=0.208)

Table VI-21 Adjusted odds ratios for exposure at high levels, complete interviews, adjusted for age at admission and number of years worked. All diagnoses (*n*=227)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP3	0.3822 (0.289)	0.186	1.46 (0.91-2.36)
LEAD	0.0003 (0.286)	0.999	1.00 (0.62-1.60)
PEST	-0.1573 (0.417)	0.706	0.85 (0.43-1.70)
EXTSOLV	-0.2414 (0.207)	0.243	0.78 (0.56-1 10)
IMMIGR	1.062 (0.348)	0.002	2.89 (1.63-5 13)
WKLQALC=<14 drinks/week	0.2584 (0.258)	0.317	1.29 (0 85-1 98)
WKLQALC=14 drinks+/week	0.1950 (0.233)	0.402	1.21 (0 83-1.78)

Deviance=292.63

Likelihood ratio statistic on 10 df=22.06 (p=0.015)

Table VI-22 Adjusted odds ratios for exposure at high levels, complete interviews, adjusted for age at admission and number of years worked. Psychotic diagnoses (n=100)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP3	-0.1987 (0.397)	0.616	0.82 (0.43-1.57)
LEAD	0.8746 (0.506)	0.084	2.40 (1.04-5.52)
PEST	-0.7336 (0.661)	0.267	0.48 (0.16-1.42)
EXTSOLV	-0.0915 (0.309)	0.767	0.91 (0.55-1.52)
IMMIGR	1.324 (0.546)	0.015	3.76 (1.53-9.23)
WKLQALC=<14 drinks/week	0.3798 (0.436)	0.384	1.46 (0.71-3.00)
WKLQALC=14 drinks+/week	-0.3620 (0.370)	0.329	0.70 (0.38-1.28)

Deviance=116.47

Likelihood ratio statistic on 10 df=22.16 (p=0.014)

Table VI-23 Adjusted odds ratios for exposure at high levels, complete interviews, adjusted for age at admission and number of years worked. Non-psychotic diagnoses (n=127)

Variables in the model	Coefficient (Standard error)	p value	Odds ratio (90% C.I.)
EXP3	0.8806 (0.477)	0.065	2.41 (1 10-5.29)
LEAD	-0.3935 (0.396)	0.321	0.67 (0.35-1.29)
PEST	0.0505 (0.628)	0.936	1.05 (0.37-2.95)
EXTSOLV	-0.4557 (0.306)	0.137	0.63 (0 38-1 05)
IMMIGR	1.061 (0.512)	0.038	2.89 (1.24-6.70)
WKLQALC=<14 drinks/week	0.1928 (0.361)	0.594	1.21 (0.67-2.20)
WKLQALC=14 drinks+/week	0.4852 (0 336)	0.148	1.62 (0.93-2 82)

Deviance=160.12

Likelihood ratio statistic on 10 df=15.94 (p=0.101)

E- EXPOSURE-RESPONSE TREND

Two cumulative exposure indices were used to explore the relationship of exposure to response: i) solvent-years (sum of: years exposed at low levels times 0.15, years exposed at moderate levels times 0.40, and years exposed at high levels times 0.75), and ii) weighted solvent-years (sum of years multiplied by the percentage of the work week exposed at low levels times 0.15, at moderate levels times 0.40 and at high levels times 0.75). This analysis was unmatched.

Solvent-years were stratified so that each stratum would contain more than ten subjects. There was no increased exposure among cases compared to hospital referents when total years exposed were considered (Table VI-24).

As the units of weighted cumulative exposure (years multiplied by the percentage of work week exposed) are less amenable to stratification, cases and referents were compared with an independent-sample t test. The difference was not significant: 2.197 for cases and 1.944 for hospital referents (t=0.37, one-tailed p=0.354).

Each cumulative index of exposure was then inserted in the 'final' logistic regression model described in the previous section of this chapter. Neither cumulative years of exposure (in 5 categories), nor weighted cumulative exposure (CUMWGT) were significantly related to an increased risk.

As for the exposure variables used in the preceding section, immigrant status was always a significant predictor of mental disorder. An alcohol intake of 14 drinks and more, in the last 10 years, appeared to be a significant predictor of non-psychotic mental disorder.

Although non-significant, there was a trend, among non-psychotic conditions, for an increased risk with increased cumulative years of exposure, at least for the three first strata, 1-4 years, 5-9 years and 10-19 years. In fact, the 5 to 9 years stratum always presented the highest risk estimate amongst the exposure strata: for all diagnoses, 1.79 (90% C.I.=0.96-3.32); for psychotic diagnoses, 0.96 (90% C.I.=0.35-2.59); for non-psychotic diagnoses, 2.27 (90% C.I.=0.93-5.52).

F- SUMMARY

Thirty-two per cent of subjects (cases plus referents) were exposed to moderate solvent levels and higher at some point during their work history; when the cut-off point for exposure was increased to high levels, 16% of the subjects were so exposed.

Table VI-24 Unadjusted risk estimates according to cumulative solvent exposure. Unmatched analysis

Solvent-years	Cases	Hospital referents	Mantel-Haenszel Odds ratio	90% C.I.
0	199	197	*	
1-4	75	94	0.79	0.57-1.09
5-9	38	30	1.25	0.79-2.00
10-19	28	33	0.84	0.51-1.37
20 +	9	14	0.64	0.28-1.42
Unknown duration	16	9		
Unknown exposure	16	4		
Total	381	381		

Crude global O.R.**=0.91 (90% C.I.=0.71-1.18)

Trend χ^2= 0.695 p=0.404

Heterogeneity χ^2= 4.083 p=0.395

Linearity χ^2= 3.388 p=0.336

* Reference level

** 'Unknown duration' exposure was included for the computation of the crude global odds ratio.

The case-referent pairs were similar on many sociodemographic and occupational variables: mother tongue, educational level, social class of the family during their childhood, reported lead and pesticide exposure at work, reported solvent exposure outside work, and proportion who took 14 drinks of alcohol and more during the ten years preceding the interview.

The cases had a higher proportion of immigrants, they drank more alcohol both during the last ten years and during their life time, they worked fewer years and stopped work at an earlier age than their referents.

A simple analysis, based on contingency tables, did not show any significantly increased risk, although odds ratios were higher with high intensity levels.

Risks increased with age at admission, at the high exposure levels (complete interviews); although the risks were non significant, the trend was the same at the three duration cut-off points: any duration, 10 years or more and 25 years or more.

After adjustment for alcohol intake, increased odds ratios were found at high levels. This pattern was not found at moderate exposure levels, perhaps because of the removal of half of the pairs because of discordance on weekly alcohol intake. Neither adjustment for lead or pesticide exposure changed the risk estimates.

Separation of the pairs into 2 diagnostic categories, psychotic conditions (ICD-9 codes 290-299) and non-psychotic conditions (ICD-9 codes 300-316), revealed systematically higher risks among the non-psychotic diagnoses compared to the psychotic ones. There was a statistically significant increased risk (O.R.=2.41, 90% C.I.=1.10-5.29) when the 'high' cut-off point was used, among non-psychotic conditions, for any duration of exposure. Lead exposure was associated with an increased risk of psychotic disorder at both intensity cut-off points.

Paired t tests between continuous exposure variables - total years exposed and weighted exposure - did not show statistically significant differences for any of the analyses mentioned above, and this, for any exposure intensity or duration cut-off point.

Conditional logistic regression analyses revealed the same findings: immigrant status was the only variable consistently associated with an increased risk of mental illness, whatever the exposure variable present in the model; when all pertinent variables were incorporated in the model, the risk was higher when the 'high' cut-off point was used compared to the 'moderate and higher'; risk estimates were higher among non-psychotic diagnoses compared to psychotic.

A simple analysis did not show any statistically significant exposure-response trend; however, there was an increased risk for the 5 to 9 year stratum. When cumulative years of exposure (CUMYRS) were incorporated into a logistic model, the 5

to 9 years stratum always showed the higher odds ratio over the other strata. There was again a tendency for the risk estimates to be higher among the non-psychotic diagnoses compared to the psychotic ones. There was no difference in cumulative weighted exposure (CUMWGT) between cases and referents.

VII. Comparison of hospital and population referents

A methodological question addressed in this thesis was whether a neighborhood referent group would have given different results from the hospital referent group selected. Chapter V, Description of the study population, described each of the three groups of subjects based on information obtained from the questionnaires. After reviewing the literature and the part of the protocol dealing with population referents, this chapter will focus on differences and similarities between the two referent groups. The impact of the selection of the referent group will then be discussed.

A- REVIEW OF LITERATURE

Following selection of cases, selection of appropriate referents is of the utmost importance in case-referent studies. The ideal referent group has been defined as one which is "... exactly the same as the study group in all respects except for the characteristics which are to be studied" [Abramson 1984: 58]. The most important, logically, is that the referent group should be representative of the population from which the cases derived. This implies a representativeness at the levels of i) the opportunity for exposure to the risk factor(s) (e.g. to be living or travelling to an area where the exposure can occur), ii) the susceptibility to develop the disease under study (e.g. to still have the organ in which the disease can develop), and iii) the similarity of the methods and quality of subject selection and of data collection [Cole 1979; McDonald 1981: 393; Schlesselman 1982: 76; Miettinen 1985a; Knottnerus 1987; Schlesselman and Stadel 1987]. However greater comparability and overmatching might be difficult to differentiate and need careful thought applied to each study situation.

1) Characteristics of two types of referents

a) Hospital referents

Hospital controls are "... readily available, have time to spare and are cooperative" [Cole 1979]; this probably applies to subjects interviewed while still in hospital. They mostly have the same willingness to collaborate as the cases - thus lessening the recall bias that is typical of patients interviewed over and over on possible exposures, especially in university hospitals - and they were also submitted to the same selection factors that brought them to the same hospital(s) as the cases [Cole 1979; Mausner and Kramer 1985: 160].

A possible drawback to using hospital referents is the possibility that the condition(s) for which they were treated have some links with the risk factor(s) under study. Selecting hospital referents from a wide array of diagnoses has been advocated as

a method of diluting that potential link [Cornfield and Haenszel 1960; Axelson 1979; Cole 1979; Schlesselman 1982: 78; Mausner and Kramer 1985: 161].

It remains necessary nevertheless to carefully examine the underlying assumptions that i) these referents constitute an 'unbiased estimate' of the prevalence of the risk factor(s) under study among the entire population of interest not suffering from the disease [Cornfield and Haenszel 1960], and that ii) these subjects are representative of the 'universe' of patients who would attend the same hospital(s) if they become sick [Tuyns *et al.* 1977]. Unfortunately, it is usually difficult to define the population from which the cases arose [Breslow 1982: 35], and it is quite likely that hospital admission and selection criteria vary with types of disorders [Tuyns *et al.* 1977].

b) Population referents

Population referents are generally thought to be an ideal choice when cases are selected from a population-based source; they are healthy and can represent quite well the people living in the area, which increases the generalizability of the results of the study [Cole 1979; Monson 1980: 145; Mausner and Kramer 1985: 160]. Of course, choosing referents from the general population avoids the selective factors of illness and attendance for medical care [Abramson 1984: 58]. Several authors also argue that population referents give a more accurate picture of exposure in the population from which the cases arose - if that population can be defined properly [Sartwell 1974; Tuyns *et al.* 1977; Ibrahim and Spitzer 1979; Lilienfeld and Lilienfeld 1980: 207; Shuster and Cook 1983; Stavraky and Clarke 1983; Abramson 1984: 59; Miller 1984].

Disadvantages have also to be recognized: there has to be a list from which to randomly select the referents; and, most importantly, population referents have been reported to be less cooperative, thus theoretically producing responses of poorer quality [Cole 1979; Breslow 1982: 34; Mausner and Kramer 1985: 160]. If neighborhood referents are selected, there is the possibility of overmatching, especially if the study is made in a rural area where homogeneous socioeconomic surroundings can be expected [Breslow and Day 1980: 28]. But then overmatching threatens any matching to a certain extent, and the ideal solution might very well be not to match but to adjust for confounding or modifying variables during analysis, that is if a much larger number of referents is available.

2) Selecting the appropriate referent group

This issue can be addressed along two theoretical trends: viewing referent selection as a design issue characteristic of the case-referent study, with the randomized clinical trial as the scientific example of excellence towards which to aim [Feinstein 1985a],

and viewing referent selection on its own merits as an independent scientific endeavour, and an "... approach to harvesting the information in the study base..." [Miettinen 1985a; Miettinen 1985b: 23].

The randomized clinical trial example requires selection of the study groups according to scientific requirements on qualification for admission into the study, unbiased 'allocation of maneuvers' - in our case, solvent exposure and non-exposure - and unbiased detection of outcomes [Feinstein 1985a]. This means that i) exclusion criteria that would have been valid in the context of a randomized clinical trial have to be defined, then ii) biases that could be related to the exposure opportunity ('allocation of maneuvers') have to be identified and avoided, and finally iii) a source of cases that would have included the referents if they had developed the disease under study (unbiased detection of the outcomes) has to be selected [Feinstein 1985a; Feinstein 1985b: 539-543].

Miettinen considers that the critical operation before selecting a referent group is to adequately define *a posteriori* the population from which the cases arose ('base population'), and then to sample it properly [Miettinen 1985a]. Theoretically, the base for a case-referent study would be the set of individuals who, if they had developed the disease of interest, would be cases in the study: people admitted to the same facilities, for conditions that are 'interchangeable' with the studied disease as a reason for being admitted to a medical care facility, and which are not related to the exposure(s) of interest [Miettinen 1985a]. Comparable accuracy of information could be insured by selecting referents whose replies to questionnaires are influenced by the same factors as for cases - e.g. the hospital setting *per se*, or the type of disease they have; Miettinen suggests, for example, taking as referents for a study of a congenital malformation, other series of malformation(s) instead of normal babies [Miettinen 1985a].

Unfortunately, in the 'real' world, we know little about the determinants of hospital admission (except for diseases which almost always bring the subject to consult, as perforated appendicitis does) and, moreover, etiologic factors of diseases are not clear enough for us to say that a given disease is not related to the risk factor(s) under study [Tuyns *et al.* 1977]. Some of the diseases included in the referent series might be related to some, but not all, of the determinants of the disease under study; and also, a reference series with diseases that are too similar to the investigated disease could cause more harm than good if the exposure under study is related to some of the reference diseases - e.g. solvents being related to several types of malformations [Axelson 1985].

3) Selecting more than one referent group

Cornfield and Haenszel recommended a few decades ago the use of both hospital and general population referents in retrospective studies as a safeguard against bias originating from unrepresentativeness of one of the control groups [Cornfield and Haenszel 1960]. Later, some authors advocated using 2 or more referent groups so that consistent results obtained with the different groups would strengthen inferences drawn from the study [Sartwell 1974; Ibrahim and Spitzer 1979; Feinstein 1985b: 545-546]. There was also a debate in the Journal of Chronic Diseases in 1983, where participants agreed at the end that studies should include both hospital and population referents to help reveal biases not foreseen during the planning stages of the study [Feinstein and Horwitz 1983; Shuster and Cook 1983; Stavraky and Clarke 1983].

In eight encountered studies where more than one type of referents were used, 5 discussed reasons for selecting more than one referent group; five studies obtained the same results with both referent groups, whereas three mentioned discrepancies [Oleinick *et al.* 1966; McDonald *et al.* 1970; Collaborative Group for the Study of Stroke in Young Women 1973; Modan *et al.* 1975; Thériault *et al.* 1978; Jain *et al.* 1980; Vernick and Kuller 1982; French *et al.* 1985].

4) Summary

The controversy concerning what constitutes the best referent group will probably never be settled. Logically, an appropriate referent group should be chosen after careful consideration of the objectives of the study and the nature of the case group - without regard to the 'directionality' of reasoning 'from cause to effect' or 'from effect to cause' that leads to differentiating 'cohort' *versus* 'case-control' designs [Miettinen 1988]. Thus, the referent group should be closely comparable to the case group on i) the opportunity for exposure to the risk factor(s), ii) the susceptibility to develop the disease under study, and iii) the similarity of the methods of subject selection and of data collection.

B- PROTOCOL

To permit investigation of the methodological question of the study, a series of neighborhood referents was chosen for comparison with the hospital referents. The population referents were selected from the September 1984 provincial electoral lists which subdivide into electoral divisions and polling subdivisions; each of the latter gather individuals in groups of about 100 households living on the same street or adjacent ones. These divisions and subdivisions were identified for each case using his address at the time of the key psychiatric admission. A maximum of four subjects,

matched on the age of the case at admission (±2 years), was then selected from the same polling subdivision as the case using a random number table. If no male of the appropriate age was found in that polling subdivision, the next one was screened and the eligible referents were chosen from it. Among those eligible referents, the first one with a valid telephone number was chosen. A few population referents, selected at the end of the study, were chosen from the 1985 electoral lists because the 1984 ones were not readily available any more.

To ensure the comparability of treatment between the study subjects, 'triplets' were formed - a case with a hospital and a population referent - and then interviewed as such. The letters were sent out to each member of the triplet at the same time, and the subjects were interviewed by telephone to obtain their work history. Solvent exposure was assessed as reported in Chapter III (Research protocol) and lifetime occupational exposures were compared within each hospital referent/population referent pair.

As for the cases, the hospital referents were Quebec residents at the time of their admission, and both types of referents were still living in the Province or an adjacent one at the start of the study in April 1985.

C- DIFFERENCES AND SIMILARITIES

1) Description of the pairs

The extent of solvent exposure is reported with the three intensity cut-off points used in the previous chapter: 'low and higher', 'moderate and higher', and 'high'. Fifty-seven per cent of the hospital and sixty-one per cent of the population referents were ever exposed to low levels and higher, while 34% of hospital and 38% of population referents were exposed at moderate levels and more. When exposure to high levels was considered, 15.4% of hospital and 17.4% of population referents were ever exposed; overall, 8.0% of hospital and 9.1% of population referents were exposed at high levels for 10 years or more.

About thirty years elapsed since the first exposure, and 13 years since the last exposure to the hospital admission. These figures were similar between the two referent groups and between cases and hospital referents, for the three intensity cut-off points. A greater proportion of population referents were exposed at each of the three intensity cut-off points.

The rest of the analyses were all matched. Paired-sample t tests, McNemar and Stuart-Maxwell chi square tests were used to assess differences between the two referent groups. Some differences emerged: more population referents were

immigrants, and more of them spoke English as their mother tongue or were raised in a bilingual family, whereas more hospital referents spoke French (Table VII-1a).

Educational level and social class of the family during the childhood of the referents were similar. The same proportion of each referent group took 14 drinks of alcohol and more per week during the last 10 years (Table VII-1a), but hospital referents had a higher average weekly intake during the last 10 years and there was no difference between their average lifetime alcohol intake (Table VII-1b). The population referents were significantly older than the hospital referents (54.2 *vs.* 53.9 years at the cases' admission to hospital).

There was no difference in reported exposure to lead or pesticides, and to solvent exposure outside main jobs (Table VII-2a). There was also no difference between total years worked, years not worked and years of unknown working status; population referents retired at a slightly - though significantly - older age (Table VII-2b).

2) Exposure differences and similarities

Differences between solvent exposure among both referent groups were assessed similarly to the method used to compare cases and hospital referents: contingency tables were prepared and exposure odds ratios were computed with their 95% confidence intervals (approximate method), and paired-sample t tests were computed. The confidence intervals were set at 95% because there was no prior hypothesis about one of the referent groups being more exposed than the other.

a) Unadjusted estimates

No statistically significant difference was found in the odds of exposure for the two referent groups, at both intensity cut-off points, and for all durations; each referent group was more exposed than the other on some occasions, without following any evident pattern (Table VII-3).

There was also no difference between the two groups on continuous exposure variables (Table VII-4): the hospital referents were more exposed than the population referents when 'moderate levels and higher' was the cut-off point, and the reverse occurred at 'high levels'.

b) Adjusted estimates

1. Age at admission

Here again, there was no statistically significant difference between the two referent groups on the odds of exposure to solvents. However, at moderate intensity levels, more hospital referents tended to be exposed in the older age groups - 50-59 and 60-69 years old (Table VII-5).

Table VII-1a Matched comparison of sociodemographic characteristics: categorical variables

	Number of pairs	Chi square	df	p value
Mother tongue				
French/English/Both	208	10.85*	2	0.001< p <0.01
Immigrant to Canada				
Yes/No	272	16.02**	1	<0.001
Educational level				
Primary & less/Secondary & technical/College & university	249	3.13*	2	>0.10
Drank 14 units*** per week and more in the last 10 years				
Yes/No	267	3.22**	1	0.05< p <0.10

* Stuart-Maxwell χ^2 test

** McNemar χ^2 test

*** 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine = 1 1/2 oz. of spirits

Table VII-1b Matched comparison of sociodemographic characteristics: continuous variables

	Hospital referents	Population referents	Number of pairs	t value	p* value
Social class					
Blishen scale	354.8	338.3	247	1.50	0.136
S.D.	129.5	117.5			
Alcohol intake					
Weekly intake, last 10 years (units**)	14.9	11.1	253	2.02	0.044
S.D.	26.2	17.4			
Lifetime intake (units)	20354.3	15887.8	226	1.53	0.128
S.D.	35251 3	27978.9			

* p value of the paired-sample t test (two-tailed)

** 1 alcohol unit= 1 beer (12 ozs.)= 7 to 8 ozs. of cider= 4 ozs. of wine= 1 1/2 oz. of spirits.

Table VII-2a Matched comparison of occupational characteristics: categorical variables

	Number of pairs	McNemar Chi square	df	p value
Lead exposure				
No/Yes	271	0.34	1	>0.10
Pesticide exposure				
No/Yes	271	0.35	1	>0.10
Solvent exposure outside main job				
No/Yes	266	2.40	1	>0.10

Table VII-2b Matched comparison of occupational characteristics: continuous variables

	Hospital referents	Population referents	Number of pairs	t value	p* value
Total years worked (years)	34.5	33.4	333	1.68	0.094
S.D.	10.2	12.0			
Total years not worked (years)	0.18	0.20	381	-0.36	0.719
S.D.	0.68	0.71			
Total years of unknown working status (years)	1.2	1.2	359	-0.12	0.901
S.D.	2.9	4.9			
Average age stopped working (years)	58.2	59.7	90	-2.22	0.029
S.D.	7.4	6.5			

* Paired-sample t test, two-tailed

Table VII-3 Unadjusted estimates of exposure, moderate exposure levels and higher, and high exposure levels. Complete interviews (n=272)

Solvent exposure Duration	Discordant pairs hospital/population	Odds ratio	95% C.I.
Moderate levels and higher			
Any duration	66/67	0.98	0.68-1.42
10 years or more	48/47	1.02	0.66-1.59
25 years or more	27/18	1.50	0.76-2.98
High levels			
Any duration	38/41	0.93	0.57-1.51
10 years or more	26/25	1.04	0.56-1.94
25 years or more	8/11	0.73	0.24-2.15

Table VII-4 Paired comparisons between continuous exposure variables. Complete interviews (n=272)

	Hospital referents	Population referents	t value	p* value
Exposure at moderate levels and higher				
Total years exposed	6.4	5.5	0.94	0.346
S.D.	11.9	10.3		
Weighted exposure	1.6	1.3	0.88	0.380
S.D.	3.6	3.1		
Exposure at high levels				
Total years exposed	2.3	2.7	-0.54	0.587
S.D.	2.7	8.2		
Weighted exposure	0.8	0.8	-0.20	0.840
S.D.	2.8	2.8		

* Paired-sample t test, two-tailed

Table VII-5 Estimates of exposure stratified according to age at admission, moderate exposure levels and higher. Complete interviews

Exposure duration	Age at admission	Discordant pairs hospital/population	Odds ratio	95% C.I.
Any duration	40-49 years	19/23	0.83	0.41-1.65
	50-59 years	24/27	0.89	0.48-1.65
	60-69 years	23/17	1.35	0.66-2.79
10 years or more	40-49 years	12/17	0.71	0.29-1.66
	50-59 years	23/18	1.28	0.63-2.60
	60-69 years	13/12	1.08	0.43-2.75
25 years or more	40-49 years	2/5	0.40	0.03-2.99
	50-59 years	15/7	2.14	0.75-6.60
	60-69 years	10/6	1.67	0.50-6.06

At high levels, population referents were systematically more exposed than their hospital match among the 60 to 69 years old (Table VII-6).

A similar pattern emerged when continuous exposure variables were compared: at moderate levels and higher, the hospital group was more exposed than the population one at the two older age groups, 50-59 and 60-69 years (Table VII-7), whereas at high levels, population referents were more exposed among the 60 to 69 years old (Table VII-8). One difference reached statistical significance: weighted exposure at moderate levels and higher among the 50 to 59 years old (hospital referents being more than twice as exposed as the population group).

2. Possible confounders

In the last chapter, adjustment for possible confounders caused the sample size to be considerably reduced without bringing answers that were different to the ones obtained with the continuous variables. I decided to restrict the adjusted analyses to the continuous variables for the two referent groups comparison.

There was no difference on average years of exposure and weighted exposure at both intensity cut-off points among the 155 pairs who were homogeneous on their proportion of weekly alcohol intake (Table VII-9).

Adjusting for reported lead and pesticide exposures slightly modified the averages of the continuous exposure variables, without increasing the differences between the two groups (Tables VII-10 and VII-11).

c) Cumulative exposure

As for the case/hospital referent comparisons, two cumulative exposure indices were used to explore the existence of a systematic exposure-response relationship: i) solvent-years ({years exposed at low levels X 0.15} + {years exposed at moderate levels X 0.40} + {years exposed at high levels X 0.75}), and ii) weighted solvent-years ({years X % of work week at low levels X 0.15} + {years X % of work week at moderate levels X 0.40} + {years X % of work week at high levels X 0.75}). Solvent-years were stratified as for the case/hospital referent comparison. There was no overall increased odds of exposure among any group, except for the stratum of 5 to 9 years exposed, where the population group was significantly more exposed than the hospital group (Table VII-12).

The weighted cumulative exposure (years multiplied by the percentage of work week exposed) for referents were compared with an independent-sample t test. The difference was not significant: 1.944 for hospital referents and 2.796 for population referents ($t=-1.08$, two-tailed $p=0.279$).

Table VII-6 Estimates of exposure stratified according to age at admission, high exposure levels. Complete interviews

Exposure duration	Age at admission	Discordant pairs hospital/population	Odds ratio	95% C.I.
Any duration	40-49 years	12/13	0.92	0.36-2.33
	50-59 years	16/13	1.23	0.52-2.92
	60-69 years	10/15	0.67	0.25-1.70
10 years or more	40-49 years	7/7	1.00	0.27-3.68
	50-59 years	14/10	1.40	0.54-3.73
	60-69 years	5/8	0.62	0.14-2.43
25 years or more	40-49 years	1/0	∞	0.00-∞
	50-59 years	6/5	1.20	0.27-5.59
	60-69 years	1/6	0.17	0.00-1.79

Table VII-7 Paired comparisons between continuous exposure variables, stratified by age at admission, moderate exposure levels and higher. Complete interviews

	Hospital referents	Population referents	t value	p* value
	40-49 years (*n*=89)			
Total years exposed	3.3	4.5	-1.00	0.321
S.D.	6.9	8.2		
Weighted exposure	0.8	1.0	-0.77	0.441
S.D	2.0	2.1		
	50-59 years (*n*=94)			
Total years exposed	8.4	6.1	1.34	0.184
S.D.	12.6	10 3		
Weighted exposure	2.5	1.1	2.61	0.011
S.D.	4.8	2.2		
	60-69 years (*n*=83)			
Total years exposed	7.8	5.9	0.93	0.356
S.D.	14.8	12 2		
Weighted exposure	1.6	2.0	-0.76	0.452
S.D	3.2	4.6		

* Paired t test, two-tailed

Table VII-8 Paired comparisons between continuous exposure variables, stratified by age at admission, high exposure levels. Complete interviews

	Hospital referents	Population referents	t value	p* value
	40-49 years (n=89)			
Total years exposed	1.6	1.6	-0.03	0.976
S D.	5 0	4.5		
Weighted exposure	0.5	0.6	-0.56	0.577
S.D.	1.8	1.8		
	50-59 years (n=94)			
Total years exposed	3.7	2.9	0.58	0.565
S.D.	9.1	8.4		
Weighted exposure	1.4	0.6	1.57	0.120
S.D.	4.0	2.1		
	60-69 years (n=83)			
Total years exposed	1.7	3.8	-1.53	0.130
S D	6.2	10.7		
Weighted exposure	0.5	1.3	-1.71	0.091
S.D	1.8	4.1		

* Paired t test, two-tailed

Table VII-9 Paired comparisons between continuous exposure variables, adjusting for weekly alcohol intake. Complete interviews (n=155)

	Hospital referents	Population referents	t value	p* value
	Exposure at moderate levels and higher			
Total years exposed	7.2	6.8	0.25	0.802
S.D.	12.5	11.3		
Weighted exposure	1.7	1.7	0.05	0.959
S.D.	3.6	3.4		
	Exposure at high levels			
Total years exposed	2.7	3.2	-0.53	0.595
S.D.	7 4	9 0		
Weighted exposure	0.9	1.0	-0.40	0.690
S.D.	2.9	3.0		

* Paired t test, two-tailed

Table VII-10 Paired comparisons between continuous exposure variables, adjusting for lead exposure. Complete interviews (n=198)

	Hospital referents	Population referents	t value	p* value
Exposure at moderate levels and higher				
Total years exposed	5.9	5.2	0.70	0.487
S.D.	11.7	10.1		
Weighted exposure	1.4	1.4	0.13	0.893
S.D.	3.5	3.4		
Exposure at high levels				
Total years exposed	2.1	2.8	-0.95	0.345
S.D.	6.8	8.6		
Weighted exposure	0.7	0.9	-0.56	0.574
S.D.	2.8	3.1		

* Paired t test, two-tailed

Table VII-11 Paired comparisons between continuous exposure variables, adjusting for pesticide exposure. Complete interviews (n=246)

	Hospital referents	Population referents	t value	p* value
Exposure at moderate levels and higher				
Total years exposed	6.4	5.4	0.99	0.323
S.D.	11.9	10.4		
Weighted exposure	1.6	1.3	0.88	0.377
S.D.	3.6	3.2		
Exposure at high levels				
Total years exposed	2.4	2.7	-0.37	0.711
S.D.	7.2	8.3		
Weighted exposure	0.8	0.8	-0.02	0.988
S.D.	2.9	2.9		

* Paired t test, two-tailed

Table VII-12 Unadjusted odds of exposure according to cumulative solvent exposure. Unmatched analysis

Solvent-years	Hospital referents	Population referents	Mantel-Haenszel Odds ratio	95% C.I.
0	197	174	*	
1 - 4	94	85	0.98	0.67-1.42
5 - 9	30	50	0.53	0.31-0.89
10-19	33	29	1.00	0.57-1.78
20 +	14	13	0.95	0.41-2.22
Unknown duration	9	12		
Unknown exposure	4	18		
Total	381	381		

Crude global O.R.**=0.84 (95% C.I.=0.62-1.13)

Trend χ^2= 0.000 p=0.993

Heterogeneity χ^2= 6.775 p=0.148

Linearity χ^2= 6.775 p=0.079

* Reference level

** 'Unknown duration' exposure was included for the computation of the crude global odds ratio.

D. SUMMARY

An average of thirty-six per cent of both referent groups were ever exposed to moderate solvent levels and higher, three per cent more than the cases and hospital referents' average. About 16% of hospital and population referents were exposed to high levels at some point during their work, which is similar to the average for the cases and hospital referents.

The two referent groups were similar on most sociodemographic variables: educational level, social class of the family during their childhood, lifetime alcohol intake, exposure to lead and pesticides, exposure to solvents outside their jobs, total years worked and total years not worked.

The two groups were statistically different on four aspects: population referents had more immigrants among them; a greater proportion had been raised in an English or a bilingual speaking family; their retirement age was older than that of the hospital referents; and hospital referents drank more alcohol during the last 10 years. A major difference between the two referent groups was already shown in Chapter V (Description of the study population, Table V-6): the low percentage of surrogate interviews made with the population referents, 6.0%, compared to the hospital referents, 32.6%, and to the cases, 31.0%.

The unadjusted odds of solvent exposure were the same for both groups, except for a few times where one of the groups would be more exposed, without following any identifiable pattern.

Stratification for age at admission revealed two trends: hospital referents were more exposed at moderate levels and higher among the 50 to 69 years old, whereas population referents were more exposed to high levels after 60 years of age.

Average number of years exposed to solvents and weighted exposure were consistent with the results obtained from contingency tables; however, hospital referents had a statistically higher weighted exposure at moderate levels and higher among the 50 to 59 years old.

Adjustment for lead or pesticide exposure at work, and for solvent exposure outside work, did not modify the averages of the continuous exposure variables.

Lastly, there was no difference among the two referent groups on cumulative exposure to solvents, except for the stratum of 5 to 9 years, where the population referents were significantly more exposed than the hospital referents.

E. CONCLUSIONS

As was foreseen from the unmatched comparisons between the three study groups (Chapter V. Description of the study population), population referents were more similar to cases on immigrant status, but dissimilar on educational level - population referents being better educated. They had a lower alcohol intake and worked more years than the cases (with less years of unknown working status), and they retired later than the cases.

Using population referents would have increased the crude exposure estimates at moderate levels and higher, and decreased them at high levels of exposure, resulting in an overall levelling of the odds ratios around one. The effect of age at admission and the suggestion of increased risk in the 5 to 9 years of exposure stratum would have disappeared.

As it was impossible to extrapolate on the effect of using population referents on diagnostic categories - psychotic *versus* non-psychotic diagnoses - a matched comparison between cases and population referents was made. With complete interviews, the risks at moderate levels remained of the same magnitude, and the increase at high levels vanished.

Thus, if population referents had been used instead of hospital referents, the tendency of increasing risks with age at admission, with high levels of exposure, with exposures between 5 and 9 years, and with non-psychotic diagnoses, would all have disappeared.

Which one of the two referent groups was more appropriate?

Population referents appeared to be more representative in regard to opportunity for exposure to solvents, as sociodemographic factors are linked to employment opportunities and the neighbors were more similar to cases than hospital referents were. This could be partly imputed to sociodemographic differences inherent to patients from psychiatric hospitals compared to psychiatric patients from general hospitals; general hospital patients were used as referents, whereas most cases came from two psychiatric hospitals (see the next chapter for a further discussion on this point).

The second requirement for a sound referent group, in this study, is that of the susceptibility of seeking care - having developed a mental disorder - and to subsequently be treated in hospital. Neither referent group appeared to be the more appropriate according to this requirement. It is extremely hazardous to assume that treatment in hospital corresponds to similar help seeking behavior in patients with different diseases; this behavior probably depends on the perception by the patient of the severity of the disorder. The ideal hospital referent group would be patients who had the choice to

be treated in hospital or on an external basis, but decided to be hospitalized: it is a complicated concept of which I could find no appropriate example. The same reasoning applies to population referents: probably not all of them would seek hospital treatment if they developed a mental disorder, but those who would, would most likely be found in the same hospitals as the cases.

Hospital referents were clearly more adequate regarding the requirement of comparability of sources of subjects and methods of data collection: they were identified from the same type of source and had the same proportion of surrogate interviews than the cases (and thus work histories of comparable precision).

All this considered, there was in fact, very little difference between the two referent groups, although hospital referents appear to constitute a slightly more adequate referent group in this study. The rule that cases selected from hospitals should be compared to referents chosen from the same hospital, and that cases selected from a whole population should be compared to referents issued from the same population, bears some sense and should prevail on the other requirements of representativeness of the referent group.

VIII. Discussion

This study was designed to investigate whether occupational solvent exposure was related to mental disorders, and to characterize that relationship. The following sections will discuss the study findings in relation to previous findings and to the findings of Study B, an associated study; lastly, the strengths and weeknesses of the study will be examined in terms of methods and subjects.

To simplify the reading, the odds ratios - computed as approximates of relative risks - will be referred to as risks in the following discussion.

A. STUDY FINDINGS

1) Solvent exposure

a) Main research question

The main question of this study asked whether cases ascertained from mental services and hospitals had a higher frequency of solvent exposure than hospital referents or, in other words, was there evidence of an increased risk of mental disorder among solvent-exposed subjects?

Two of the six studies on long term effects of solvent exposure discussed in the Review of literature found a significantly increased relative risk of all mental disorder diagnoses among solvent-exposed workers [Axelson *et al.* 1976; Olsen and Sabroe 1980]. Two further studies demonstrated significantly increased risks for some psychiatric diagnoses [Mikkelsen 1980; Lindström *et al.* 1984]. A fifth study found an increased (but non significant) relative risk of encephalopathia [Rasmussen *et al.* 1985]. The risks ranged from 1.6 to 3.4; some of these were crude risks, most were adjusted at least for age, and some for alcohol intake and previous head injury. Our crude estimates of risk for any duration of solvent exposure, both non-significant, were respectively 0.85 at moderate levels and higher, and 1.40 at high exposure levels; the risks for exposures of 10 years and more became 0.97 and 0.88 at the same intensities. Adjustment for age, number of years worked, alcohol intake, lead and pesticide exposure, solvent exposure outside work and immigrant status, gave slightly increased (still non-significant) risks of respectively 0.90 and 1.46 at 'moderate' and 'high' levels; with a '10 years and more' cut-off point, the adjusted risks became respectively 1.20 and 0.90.

However, there were differences between studies in the methods used to define the cases and to ascertain solvent exposure. The four Scandinavian studies published until 1984 used as cases men who had been awarded disability pensioning for

neuropsychiatric reasons; these men had conceivably been treated in psychiatry prior to their retirement. The 1985 study chose a series of men, between 50 and 80 years old, evaluated in hospital after they had applied for nursing home accomodation; these men were somewhat older than our series and could have had the opportunity to work longer before becoming disabled. We selected men who were first admitted to hospital for psychiatric treatment; they were thus at an early stage of disability and could conceivably have worked a few more years before retiring.

Solvent exposure was defined, for most studies, as membership in a few trades: painters, carpetlayers, cabinet makers and varnishers; crude exposure-response cut-off points, if any, were used: more than 30 years of exposure [Axelson *et al.* 1976], more than 4000 hours of indoor, or indoor and outdoor exposure [Olsen and Sabroe 1980]. In our study, solvent exposure was assessed for each subject according to his work history, and exposure-response cut-off points of 'moderate levels and higher' and 'high levels' were used with three durations (any, 10 years and more, 25 years and more). Except for the 1985 one, which found a non-significant increased risk, the previous studies had all restricted their study population to construction trades among which a higher proportion of solvent exposure could be expected; this increased their chance of finding significant relationships between solvent exposure and mental disorders despite their small sample sizes.

b) Secondary research questions

Two additional questions were addressed in this study: was it possible to identify certain diagnostic categories of mental disorders more strongly associated with solvent exposure, and could the nature of this association be characterized in terms of types of solvents involved, existence of an exposure-response relationship or of an identifiable latency period?

1. Diagnostic categories

The four earlier studies found increased risks of 2.0 to 5.5 for some combination of non-psychotic diagnoses: Axelson [1982] for 'nervositas' (ICD-8 code 790); Olsen and Sabroe [1980], and Mikkelsen [1980] for non-psychotic diagnoses (ICD-8 codes 300-315); Lindstrom *et al.* [1984] for 'neurosis, persona pathologica, psychosomatic disease and nervositas' (ICD-8 codes 300, 301, 305 and 790). Our definition of non-psychotic disorders was similar to that of the Danish, Olsen and Sabroe, and Mikkelsen, and we found crude risks of 1.08 (90% C.I.=0.69-1.69) at 'moderate levels and higher', and of 2.43 (90% C.I.=1.16-5.08) at 'high levels' for these diagnoses; the adjusted risks were 1.38 (90% C.I.=0.82-2.33) at 'moderate levels and higher', and 2.41 (90% C.I.=1.10-5.29) at 'high levels'.

Three of them also found increased risks for dementia, ranging from 2.0 to 3.4: Axelson [1982], Olsen and Sabroe [1980] and Mikkelsen [1980]. In this study, the number of subjects with dementia was too small (43 subjects) to be meaningful; we found crude risks ranging from 0.71 to 1.00 depending on the intensity level considered and whether all subjects or only complete interviews were considered.

2. Age

Axelson *et al.* [1976] reported 'weak confounding' introduced by age, without presenting the corresponding risk ratios. However, their tables allowed the calculation of risk ratios corresponding to 35-44, 45-54 and 55-64 years at start of pensioning; the risks increased with each age stratum, which is what we found. The other studies did not mention age apart from stating that the referents were matched for age at pensioning.

These differences in risk with age at admission, although referents were matched for age, might be interpreted as cohort effects. The older group might have had higher exposures than was accounted for during exposure assessment, and could have been more able, when they were younger, to cope with the neuropsychological effects of solvents. Hospital admission determinants might very likely have been different a few decades ago, especially for psychiatric treatment.

3. Types of solvents

The types of solvents specified in the Scandinavian studies were turpentine and mixtures of aliphatic and aromatic hydrocarbons within the C_6-C_{10} range [Axelson *et al.* 1976], solvents contained in lacquers, glues and paints [Olsen and Sabroe 1980] and white spirits [Mikkelsen 1980]. We did not have detailed information on the types of solvents used by the subjects, but rather on the job titles for which at least 50% were classified as being exposed to moderate or high levels of solvents (painters, motor vehicle mechanics, printing press occupations; service station attendants, textile bleaching and dyeing occupations, bonding and cementing occupations in the plastics industry, aircraft mechanics and typesetting and composing occupations). These job titles entail exposures to almost every chemical class of solvents: mixtures of aliphatic, cyclic and aromatic hydrocarbons, halogenated hydrocarbons, alcohols, ethers, esters, and refined petroleum solvents (kerosene, naphthas, white spirits, mineral spirits, etc).

4. Exposure-response relationship

Two of the studies published between 1976 and 1984 reported a rough relationship of exposure to response, over all age groups, through dichotomizing the duration of exposure: less than or equal to 30 years and more than 30 years [Axelson *et al.* 1976], and more than 4000 hours of indoor exposure [Olsen and Sabroe 1980]. No clear

exposure-response trend was found in this thesis study with a cumulative index weighted for intensity of exposure, adjusted or not for the percentage of work week exposed; however, a consistent increase in risk estimates was found for exposures lasting 5 to 9 years. An unmatched analysis - not reported in this thesis - using the 30 years and more of Axelson *et al.* [1976] did not show any increased risk with the 'moderate and higher' cut-off point, but showed an increase within the older age group (60 to 69 years at admission) at 'high' levels: risk ratios of 1.64 for less than or equal to 30 years of exposure, and 3.19 for more than 30 years of exposure.

A lack of exposure-response relationship could have several interpretations, of which two are predominant: individual susceptibility might be an important determining factor, or exposure assessment was technically inadequate. Host susceptibility is certainly a major etiological factor of mental disorder, and solvent exposure could act as a triggering agent in a predisposed person. The increased risk for the 5 to 9 years of exposure might also suggest that susceptible subjects who were heavily exposed for less than 10 years have decided to quit their solvent exposed job, that is, after the onset of some effects of solvents. However, retrospective exposure assessment is likely to have a major impact: it is always difficult to perform, and subject to many sources of error. We had no reliable data on intensity or duration of exposure, and the model that would be appropriate to describe the exposure-response relationship was unknown: the exposure assessment procedure used in this thesis might not have been sensitive enough to detect a systematic exposure-response relationship

5. Latency period

None of the previously mentioned studies addressed the possibility of the existence of a latency period. The only pertinent data available to us in this study was the number of years since first solvent exposure: no significant difference was found for any of the study groups, which all had been exposed for the first time about 30 years before hospital admission. This does not rule out the existence of a latency period, but shows that the three study groups had very similar years of first exposure.

2) Comparability of cases and referents

Cases had a proportion of immigrants, 15.7%, higher than that of their hospital referents, 6.5%, but similar to that of population referents, 17.9%. It is beyond the scope of this thesis to discuss this issue further. Cases and hospital referents had comparable proportions of surrogate interviews, 31.0% and 32.6%, whereas population referents had a much lower rate of interviews with other respondents than the subject himself.

Cases also had a lower educational level than the two referent groups - although not significantly lower than hospital referents. Higher death rates among cases compared to the general population (here, neighborhood referents) have been documented for a few decades [Babigian and Odoroff 1969; Black *et al.* 1985]. This was thus expected to happen in the case group.

The higher alcohol intake among cases might reflect the fact that 11.8% of them had a final diagnosis directly related to alcohol intake (alcoholic psychosis or alcohol dependence syndrome); when secondary diagnoses were also considered, 22.6% of cases presented an alcohol related diagnosis. There was no difference on the overall percentage of cases and referents reporting exposure to either lead or pesticides at work, and adjustment for these two variables did not change the risk estimates at any intensity of exposure; however significantly more cases with a psychotic diagnosis reported lead exposure at work.

Cases worked significantly less than both hospital and population referents (32 *versus* 35 years). This could conceivably have shortened the period during which they could have been exposed to solvents. Indeed, although there was no difference between the groups on the first year of exposure to solvents, at any intensity of exposure, the period between the last exposure to high solvent levels and hospital admission was 4 years longer for cases compared to referents.

3) Comparison with Study B

This thesis project, also called Study A, was part of a larger project - funded by the Institut de recherche en santé et en sécurité du travail du Québec - which included Study B, mentioned earlier; I participated in both studies. All following Study B results are taken from the final report submitted to the funding agency [Cherry and McDonald 1988]; however, further analysis is underway. A paper was also presented at the Sixth International Symposium on Epidemiology in Occupational Health, held in Stockholm, Sweden, in August 1988 [Cherry *et al.* 1988].

The main groups in Study B were 319 cases of organic brain disorders and referents with other psychiatric diagnoses, selected from the same hospital. In Study A, cases were chosen mainly from psychiatric hospitals and all mental disorders (except mental retardation) were included in the case definition; the referent series was selected from the nearest general hospital. Thus no direct comparisons between Study A and Study B results can be made, although their results can be examined in parallel; Study B results will be presented first.

Based on 'moderate levels and higher' and 'high levels', at both '10 years and more' and '25 years and more' of exposure, Study B showed higher risks of solvent exposure

among cases with organic mental disorders compared to general psychiatric referents, although not all significant at α=0.05.

For Study B, when odds ratios were computed after stratification according to age at admission, the risks decreased from 3.0 for the 40 to 49 years old, to 2.0 and 1.2 respectively for the 50 to 59, and 60 to 69 years old, at 'moderate levels' of solvents; the risk of exposure was thus much higher among younger people with organic diagnoses compared to other psychiatric patients, but the difference between these cases and other psychiatric patients tended to disappear with increasing age.

In Study B, at 'moderate levels' of solvents for 10 years and more, the risk was markedly increased for organic cases who had an associated diagnosis related to alcoholism (from 1.46 to 5.7).

The main sociodemographic differences between Study A and Study B subjects were that more subjects in Study B came from rural areas, and they were on average older because of the case definition of organic mental disorders - which are diagnosed at an older age. A higher proportion of subjects in Study B reported pesticide exposure (6.3% in Study B *vs.* 5.5% in Study A), and their father held more often a 'low status' job when the subject was a child (68.5% in Study B *vs.* 60.6% in Study A), which is to be expected in a population with a higher proportion of rural inhabitants.

The contact rates were slightly higher in Study B (more than 91.6% for each group) than in Study A (94.2% in the referent groups, but 86.3% in the case group); possibly due to the fact that younger and less disabled psychiatric patients may be more mobile, especially in a large city.

Study A did not find that the subgroup of patients with organic mental disorders were more exposed than their general hospital referents. The odds ratios increased with age in Study A, where cases with any psychiatric diagnosis were compared to general hospital referents.

The impact of an associated diagnosis related to alcoholism was inconsistent in Study A, and because of the small numbers of organic disorders, the following analyses were not reported in the results. When cases were divided into organic and non-organic diagnoses according to the definition used in Study B (organic diagnoses: ICD-9 codes 290, 294, 310.1 and 331), the risks were higher for subjects with an alcohol-related diagnosis among the organic diagnoses at 'moderate levels' for 10 years and more (1.67 *versus* 0.83 for non-organic diagnoses); at 'high' levels, the pattern was less clear, although higher risks were again related to alcohol diagnoses. When cases were divided into psychotic (ICD-9 codes 290 to 299) and non-psychotic diagnoses (ICD-9 codes 300 to 316), no increased risk was discernible at moderate levels' for 10 years and

more, but at 'high levels', there were increased risks when psychotic diagnoses were associated to alcohol-related diagnoses - 1.5, *versus* 0.43 with no alcohol-related diagnosis - whereas no such trend was discernible among non-psychotic diagnoses.

Less surrogate interviews were done in Study A, probably due in part to the subjects' younger age. Study A population had twice as many foreign-born subjects (overall 13.3%) compared to Study B (overall 6.7%), again reflecting urban/rural differences. Lastly, more Study A subjects reported an alcohol intake of at least 14 drinks per week during the last 10 years (30.5% *vs.* 23.5% for Study B), and lead exposure at work (15.8% *vs.* 8.8% for Study B).

B. DESIGN FEATURES

Selection and information biases are of special concern in case-referent studies, and of special interest here, are the problems related to assessment of mental disorders, of retrospective solvent exposure, and of subjects' selection.

1) Problems with assessment of mental disorders

Three aspects of disease assessment are especially problematic for mental disorders, and could possibly lead to selection bias: completeness of disease ascertainment, reliability and validity of the diagnoses.

a) Complete ascertainment

Two main approaches have been used in the definition of psychiatric cases: reliance on diagnoses recorded in hospitals and clinics, and psychiatric interview or interview with a psychometric questionnaire [Dohrenwend and Dohrenwend 1982]. Rates of mental disorder based on cases under treatment are around 1-3% [Bahn *et al.* 1966; Dohrenwend and Dohrenwend 1982], whereas those from population studies reach 20% [Denis *et al* 1973; Dohrenwend and Dohrenwend 1982]. The first approach is necessarily incomplete because of the inadequacy of treatment rates (with or without hospital admission) to describe the prevalence or incidence rates in a community; the second approach is unaffordable due to the enormous cost of surveying everyone in a given area [Anderson 1978; Dohrenwend and Dohrenwend 1982], and most of the cases defined that way would not be severe cases.

The importance of complete case ascertainment depends on the purpose of the study; this may be great if the object is to estimate the need for better services in a given geographical area; on the other hand incomplete ascertainment may be quite adequate if certain age groups or certain diagnostic categories are of interest. In this study, the purpose was to identify men who had to be admitted to hospital because they were unable to function at home or at work; thus the fact that they were treated in hospital was used

as a surrogate index of the severity of their mental dysfunction. A problem might arise if a different percentage of cases and referents are treated in hospital; however this study was not designed to assess that issue.

b) Reliability of diagnosis

According to Weissman and Klerman [1978], there are five sources of variance in the diagnosis of mental disorders: the subject, the occasion when the problem becomes manifest, the source of information, the observer and the diagnostic criteria used. Not much can be done to reduce most of these sources of error, but knowing that they exist helps to put into perspective data obtained from diagnostic classification lists.

A review of the most important studies published between 1950 and 1977 - when the DSM-III classification system was introduced - showed that only sociopathic behavior, organic brain syndrome and schizophrenia obtained acceptable agreement between psychiatrists, as measured by a Kappa statistic above 0.50 [Eaton 1986: 20]. The best percentage agreement reported between psychiatrists in the literature (77%) was in a study where psychiatrists trained at the same institution made their diagnoses after seeing videotapes of patients' interviews [Kendell 1973]. Spitzer and Williams [1985] reported that one third of the factors contributing to disagreement between psychiatrists were inconsistencies on the interviewers' side (leading to information, observation and interpretation variance) while the rest was the result of nomenclature ambiguities (leading to criterion variance).

That lack of agreement between psychiatrists does not help in identifying specific diagnostic categories more at risk; this could lead, for example, to making different diagnoses for the same clinical entity presenting in a 45-year old man and a 65-year old one. It could also mean that cases from different hospitals (or areas or countries) are not necessarily similar, even when they are classified in the same diagnostic categories. These reliability problems may be partly responsible for the lack of consistency of the findings, so far, regarding the diagnostic categories susceptible to reflect chronic solvent insult on the central nervous system.

c) Validity of diagnosis

A study like this one is affected mainly by the validity aspects dealing with characterization of the disease entity and with etiological theories. Spitzer and Williams [1985] mention face validity (how accurately does the classification describe the characteristics of the disorder) and descriptive validity (how specific are the characteristic features to that category) as facilitating communication. Construct validity is the extent to which evidence supports the etiological theories underlying a given disorder [Spitzer and Williams 1985].

This study was not designed to evaluate validity of the psychiatric (or non-psychiatric) diagnoses used. Consequences of face validity and descriptive validity problems are conceivably similar to those of lack of diagnosis reliability in psychiatry: difficulty in comparing diagnostic categories from different studies and thus to elaborate coherent etiological theories explaining solvent effects.

d) Characteristics of hospital admission records

According to Anderson [1978], the main factors affecting hospital statistics are medical care (medical practice, illness behavior and organization of care), and the information system (diagnostic coding and diagnostic fashion).

Although we did not deliberately select hospital admission as an index of the severity of mental disorder, it can be considered as such despite the importance of illness behavior and organization of care as admission determinants. In hospital settings, diagnoses are coded for administrative purposes. The coding is usually performed by more than one nosologist, and university affiliated hospitals have student nosologists who tend to apply more rigorously the rules of the International Classification of Diseases - e.g. the rule is to put 'addiction to cigarette', a mental disorder code (ICD-9 code 305.1), whenever smoking is associated with lung cancer: it was done inconsistently in the reviewed charts.

These characteristics again jeopardize conclusions that can be drawn from the results - on risks being specific to certain diagnostic categories for example - and also the extent of diagnoses' comparisons that is possible with other countries.

2) Problems with retrospective assessment of occupational exposure

a) Reliability of questionnaire data

Because of the absence of environmental measurements in previous decades and even today, most retrospective assessments of occupational exposure have to rely on records or questionnaires. As mental disorders are not likely to have been widely associated with solvent exposure in general, recall bias was not foreseen to be a problem here. The occupational information provided is usually more accurate when the subject himself gives the interview - in contrast to a surrogate respondent [Williams Pickle *et al.* 1983] - although a few studies proved that close relatives can give valid occupational exposure information [Martin and Butcher 1982; Pershagen and Axelson 1982; Coggon *et al.* 1985; Shalat *et al.* 1987; Bond *et al.* 1988]. In this study, the same proportion of surrogate respondents were found among cases and hospital referents (30% and 32%): their respective work histories should have been equally precise. Only 6% of interviews of population referents were done with surrogates, which could mean that

their work histories were more reliable but less comparable than that of the other groups.

The accuracy of the reported work history also appears to be better when the subject has held only a few jobs [Bourbonnais *et al.* 1987; Rosenberg *et al.* 1987; Bond *et al.* 1988], when he is more educated [Bourbonnais *et al.* 1987], and when the time lapse between the jobs and the interview is minimal [Rosenberg *et al.* 1987; Bond *et al.* 1988]. These aspects of accuracy are more problematic: in our study, cases tended to have had more jobs and to be less educated than the hospital referents, although these differences were not statistically significant; population referents had significantly higher levels of education than the cases.

The interviewer's awareness of the status of the interviewed subject could have been a problem here. Regardless of the care taken in hiding the study status prior to the interview, the interviewers still correctly identified 68.0% of the cases, 86.3% of the hospital referents and 92.7% of the population referents. Nonetheless, as explained earlier, the interviewer focused on obtaining a complete job history and was not allowed to probe for solvent exposure; this set of rules may have offset the information bias. Another type of interviewer effect is also possible: Baumgarten *et al.* [1983], when looking at the validity of reported employer name and employment dates, found that one interviewer elicited less agreements than the other interviewers, although not significantly so. One of our interviewers, who interviewed 81.4% of the total sample, completed the questionnaire with a higher proportion of referents than the others, because she stayed longer with us, and referents - especially population ones - were less cooperative and had to be contacted several times before agreeing to give an interview. She had also correctly guessed the study status of a larger proportion of the subjects than the two other interviewers (85.1% *versus* 69.0% and 64.6%).

b) Supplementation of missing data

When no contact was made with the subject or a surrogate respondent, I used the job titles (and job history when available) recorded in the medical chart of the subject. Strauss *et al.* [1978] demonstrated that occupations obtained by means of a psychiatric history presented a 96.7% agreement between the patient, a close family member and the medical record. This could partly explain the consistency of the unadjusted risk estimates computed from all available information with those calculated from completed questionnaires. However, no information was available on the potential confounding factors and no adjustment could be made for them, resulting in the restriction of some analyses to complete interviews.

c) Retrospective exposure assessment

A complete work history is a good basis for retrospective exposure assessment, especially when only one or a few occupational factors are considered; it is also rarely inherentently plagued with bias [Hémon 1986].

The translation of work histories into exposure histories has been done with only a few methods so far: i) using a checklist of exposures (e.g. asbestos) [McDonald *et al.* 1970]; ii) using a job-exposure matrix - or occupation and exposure linkage system [Hoar *et al.* 1980; Hsieh *et al.* 1983; Ravnskov *et al.* 1983; McDonald *et al.* 1987] (from the job title, exposure is defined as a few categories based on exposure intensity or exposure likelihood - e.g. no exposure, low exposure, moderate exposure and high exposure, or not likely, possible and probable exposures); and iii) a hybrid version of the exposure matrix in conjunction with a case-by-case evaluation of the job history by chemists [Siemiatycki *et al.* 1981; Gérin *et al.* 1985].

The first method works best when only one or very few specific substances are investigated; organic solvents cover a wide variety of substances and would thus be difficult to study with that approach. Very few job-exposure matrices have been published or are publicly available, and they were developed in other countries, which limits their applicability to our study. The third method has been used in a study of cancer cases; it was costly and somewhat complicated to apply to our data.

The method I used to assess solvent exposure has been described in Chapter III, Research protocol, and its reliability was verified by comparing my results to that of experts using the same method. The level of crude agreement obtained was lower than that of the cancer study using the third method described earlier [Goldberg *et al.* 1986] - 53-60% compared to 93-98.5% - but there were four categories to agree upon in our trial, compared to only two in that of Goldberg and colleagues (presence or absence).

Random misclassification of organic solvent exposure is likely to occur when exposure is estimated retrospectively from job histories obtained by an interview. This misclassification should not invalidate the results because the exposure assessment was done without knowing the status of the subject. It could however obscure the relationship between mental disorders and solvent exposure, and possibly blur a systematic exposure-response relationship.

3) Subject selection

a) Case group

1. Selection criteria

Our selection criteria had the following justifications. A first admission avoided chronic patients who have not been working for many years, which would reduce the

number of 'man-years at work' and the possibility of finding a link between work with solvents and the development of mental disorders. A minimal length of stay of 5 nights excluded cases admitted for social reasons and helped to insure a certain 'severity' of the disorder. Lastly, men aged 40 years and more have had the time and possibility of being exposed at work; if organic solvents contribute to psychiatric disorders, they are more likely to have an effect after at least a few years of exposure.

2. Sample size

In pair-matched case-referent studies, sample size requirements depend on i) the level of risk to be detected, ii) frequency of exposure in the referent population and also iii) the level of acceptable uncertainty (type I and type II errors) in interpreting the results. According to the studies on long term effects of organic solvents, an odds ratio of approximately 2 was expected. We were uncertain as to what percentage of the general population of Quebec was exposed to organic solvents; however, an assumption of 5% seemed reasonably conservative. A smaller α (0.05) seemed more important to lower the chances of falsely concluding on a positive association between solvent exposure and mental disorder, than to conclude wrongly that there was no association (higher β, 0.20). The optimal sample size would have been 392 pairs, but we obtained 381 pairs With the actual percentage of solvent exposure in the referent population, 17 8% (exposure at moderate levels and higher, for 10 years and more), and the final sample size used in the unadjusted analyses (259 matched pairs), the detectable risk was slightly below 1.7. That smallest detectable risk was higher when analyses were performed on subgroups, and it went up to 2.5 when the cases were stratified into two large diagnostic categories (psychotic and non-psychotic diagnoses), with sample sizes around 100.

3. Representativeness

As mentioned earlier, hospitalized cases are not representative of all persons suffering from and treated for a mental disorder In order to obtain our calculated sample size, our case series had to be selected from two types of hospitals: psychiatric hospitals and the psychiatric ward of a general university hospital. To verify whether patients admitted to psychiatric hospitals were different than general hospital ones on sociodemographic factors, both groups were compared.

Three times as much organic psychoses and twice as much neurotic problems were found among the psychiatric hospitals' cases, whereas there was twice as much depressive disorders among the general hospital's cases. The pattern of hospital admissions to public mental and general hospitals in the United States is not the same, but still depicts differences in the patients found in various types of hospitals: twice as

much organic brain syndromes, alcohol related disorders and schizophrenia in mental hospitals, and four times as much neuroses in general hospitals [Gruenberg 1980]. In our study, patients admitted to psychiatric hospitals were also older, and there was a slightly higher proportion of them who had only primary school education.

As most cases came from the two large psychiatric hospitals of a major North American city, it still allowed a reasonable generalization of the results. Moreover, this case-referent design permitted the selection of a comparison group while taking into account, at least partially, a potential sociodemographic bias through approximate matching on area of residence.

b) Referent groups

1. Selection criteria

It was decided to match cases and referents on age because it is related to the opportunity for employment and, therefore, of being occupationally exposed to solvents. Age is also a well known determinant in most diseases, and mental disorders are not an exception - which can be verified by a simple scanning of hospital statistics.

Matching on date of hospital admission appeared to be important due to the seasonal variations in the occurrence of mental disorders and of numerous acute or subacute diseases, and to the time related variations in the labour market (recession, high unemployment, etc.).

Area of residence was of concern because of the availability of hospital treatment facilities, the average socio-economic level of neighbors and the presence of job opportunities (or at least to availability of transportation to the possible employers). The matching was close in the selection of population referents but less so in the selection of hospital referents.

The only diagnosis that caused the rejection of a hospital referent was that of liver cirrhosis, which is closely related to high alcohol intake. Even though diagnoses of nervous system diseases might be correlated with solvent exposure - due to the toxicity of many solvents on the peripheral nervous system - they were not outright excluded from the study. Individual final diagnoses from that category have been examined and only one hospital referent had a diagnosis coherent with solvent exposure, namely peripheral neuropathy without diabetes or high alcohol intake.

In order to have some confidence that the reference subjects were not previously hospitalized for psychiatric treatment, their medical record was scrutinized with that in mind in order to eliminate such subjects. As the equivalent was not possible for population referents, the last question asked during the interview inquired about all hospital admissions since the individual was 21 years old. Although a certain amount of

underreporting is expected to occur, it can, at least, be quantified as the cases were asked the same question. In this study, 49.5% of the cases who completed the interview (142/287) reported their hospital admission in psychiatry. Five hospital referents and 4 population referents reported a previous hospital admission in psychiatry; they were replaced by another referent. Unfortunately, 3 population referents were kept in the study by error after reporting a psychiatric hospitalization. Assuming the same amount of underreporting of psychiatric in-treatment than for the cases, the hospital referent group would contain 5 ex-psychiatric patients (for 322 complete interviews), and the population referent group, 7 of them (for 319 complete interviews) These small expected numbers of misclassified 'non-diseased' subjects should not have had a major effect on the risk estimates, but if they did have any, it would have been to bring the estimates toward the null value.

A possible bias results from the fact that hospital referents were not selected according to an incidence criterion - i e. it was not necessarily their first admission for that condition whereas is was so for the cases - because it would have unnecessarily lengthened the subject selection stage which had already lasted about ten months. The expected consequences would be to have more 'chronic' patients among the hospital referents group, resulting in more unemployment or early retirement, and most probably, a higher number of deceased subjects (with a correspondingly higher number of surrogate interviews). These consequences were partly verified in this study, but the cases still worked fewer years than the referents before the key admission

2. Representativeness

The validity of case-referent studies rests for a good part on the selection of an adequate comparison group. This issue was discussed with some detail in the preceding chapter. The usual rule is to select the referent group in the same way as the case group was chosen, e.g. from patients in the same hospital but with other types of problems. The fact that the case series in this study (unlike Study B) came mainly from psychiatric hospitals precluded from doing just that. However, selecting patients from the nearest general hospital, appeared to be a useful method to obtain a certain comparability of the health care seeking behaviour patterns, although it does not necessarily insure comparable hospital admission practices It is conceivable that some of the hospital referents, less inclined to seek help, would not have been treated in hospital if they had suffered from a psychiatric disorder, and thus should not have been included in the referent group.

The observed sociodemographic differences between the case series from the two types of hospitals might reflect some unforeseen determinants of hospital admission;

this could mean that selecting hospital referents was really appropriate only for cases from the general hospital. An analysis of the data restricted to the general hospital cases and their referents, although limited because of the resulting sample size (60 pairs, of which 37 had complete interviews), produced higher risk estimates both at 'moderate levels' of solvents and at 'high levels'. The crude estimates for any duration of solvent exposure, both non-significant, were respectively 1.14 at moderate levels and higher, and infinite at high exposure levels - *versus* respectively 0 85 and 1.40 for the total case group; the risks for exposures of 10 years and more both became 1 00 at the same intensities - *versus* respectively 0.97 and 0.88 for the total case group.

3 Hospital *versus* population referents

To address the methodological question of the appropriateness of a population referent group, we selected referents from the neighborhood of the cases. The polling subdivision lists allowed the selection of referents from the immediate neighborhood of the cases (the assumption being here that people living in the same neighborhood are relatively homogeneous on sociodemographic factors such as social class, life habits, etc.)

The population referents were slightly, though significantly, older than the hospital referents (54 2 *versus* 53.9 years at the cases' admission to hospital); this discrepancy could be caused by the fact that age only was available on the electoral lists that served to select population referents, and not date of birth as was the case for the hospital referents When they agreed to give the interview, population referents were as helpful as hospital referents, and the interviewers felt that the information they provided was slightly more reliable than that given by the hospital referents A few more population referents (4 5%) than hospi , referents (3 4%) refused to give an interview

Population referents were more similar to cases for mother tongue, immigrant status and other sociodemographic factors homogeneous within a given neighborhood. However, their work histories were likely to have been more accurate because only 6% of their interviews were done with surrogates.

On the whole, there was very little difference between the two referent groups, although hospital referents appeared to constitute a slightly better referent group in this study.

C-SUMMARY

There was no increased relative risk of mental disorder with occupational solvent exposure, using the *a priori* defined exposure criterion (exposure at moderate levels and

and higher, for 10 years and more). No particular diagnostic category appeared to present an increased risk over the others.

However, when the exposure criterion was set at a higher level - justified by the results of a reliability study showing that I tended to overestimate exposure - the odds ratios increased for any duration of exposure, but not for an exposure of 10 years and more. There was a significantly increased risk of non-psychotic disorders for high levels of exposure.

No systematic exposure-response relationship could be demonstrated, but there was some suggestion of an increased odds ratio for subjects exposed for 5 to 9 years, whereas the odds ratios were below one for shorter and for longer exposures.

Selection biases probably exist but were difficult to assess. Incomplete case ascertainment and the fact that psychiatric treatment in hospital concerns only part of the mentally ill, reflect hospital admission determinants that are very difficult to identify, and apply during the selection of the referent group.

Information biases should not have affected the results, given that roughly the same proportion of interviews were with surrogates among both the cases and the hospital referents.

Reliability and validity problems of psychiatric diagnoses, coupled to inconsistencies of hospital statistics, could blur the diagnostic categories susceptible to reflect solvents' chronic insult to the central nervous system; this could partly explain the lack of consistency in the previous studies regarding specific diagnostic entities.

The exposure assessment procedure used was the best that could be done, given the retrospective type of available data; added to random misclassification of exposure, it could however have been too imprecise to detect a subtle effect of solvents.

The major problem was probably, as in many epidemiological studies, a certain inadequacy of the referent group used. Patients from general hospitals were used as referents for cases selected from psychiatric hospitals; although help seeking behavior and hospital admission practices are probably different for physical and mental disorders. Psychiatric patients from general hospitals were younger and slightly more educated than cases selected from the psychiatric hospitals, this increases the likelihood of existence of selective determinants that could not be accounted for by choosing referents from general hospitals.

IX. Conclusion

No increased relative risk of being admitted to hospital for psychiatric treatment was found among men exposed to moderate levels of organic solvents and higher. However, the results of this study suggest an increased risk among men exposed to high levels of solvents Some of this increase appears to be imputable to subjects exposed at high levels for 5 to 9 years. Cases with a diagnosis of non-psychotic mental illness were significantly more exposed to high levels of solvents than their referents, whereas it was not so for cases with a diagnosis of psychotic mental illness.

The fact that no systematic exposure-response relationship could be demonstrated, and that subjects who had been exposed for 5 to 9 years presented an increased risk of mental disorders, could indicate a triggering effect of solvents on predisposed individuals.

The inconsistent results from previous studies on the diagnostic categories at risk, combined to findings in study B - that among psychiatric patients, cases of organic mental disorders (psychotic diagnoses) are more exposed to solvents, appear to concur in a theory of triggering effects. Exposure to a sufficiently high solvent intensity could deteriorate predisposed subjects to the point of requiring hospital treatment; the nature of the actual psychiatric diagnosis could be determined by the personality of each subject

The selection of an appropriate referent group was an important challenge in this study, and it could have been better dealt with if cases and referents could have been selected from different wards of the same hospitals.

More similar studies are needed in North America to further explore the relationships between occupational exposure to organic solvents and mental illness.

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ANNEXES

Annex 1

Disease categories and sub-categories used to define cases
ICD-9

PSYCHOSES (290-299)

Organic psychotic conditions (290-294)

290 Senile and presenile organic psychotic conditions
- 290.0 Senile dementia, simple type
- 290.1 Presenile dementia
- 290.2 Senile dementia, depressed or paranoid type
- 290.3 Senile dementia with acute confusional state
- 290 4 Arteriosclerotic dementia
- 290.8 Other
- 290.9 Unspecified

291 Alcoholic psychoses
- 291.0 Delirium tremens
- 291.1 Korsakov's psychosis, alcoholic
- 291.2 Other alcoholic dementia
- 291 3 Other alcoholic hallucinosis
- 291 4 Pathological drunkenness
- 291 5 Alcoholic jealousy
- 291 8 Other
- 291 9 Unspecified

292 Drug psychoses
- 292.0 Drug withdrawal syndrome
- 292.1 Paranoid and/or hallucinatory states induced by drugs
- 292 2 Pathological drug intoxication
- 292 8 Other
- 292.9 Unspecified

293 Transient organic psychotic conditions
- 293 0 Acute confusional state
- 293.1 Subacute confusional state
- 293 8 Other
- 293.9 Unspecified

294 Other organic psychotic conditions (chronic)
- 294 0 Korsakov's psychosis or syndrome (nonalcoholic)
- 294.1 Dementia in conditions classified elsewhere
- 294.8 Other
- 294 9 Unspecified

Other psychoses (295-299)

295 Schizophrenic psychoses
- 295.0 Simple type
- 295.1 Hebephrenic type
- 295.2 Catatonic type
- 295 3 Paranoid type
- 295 4 Acute schizophrenic episode
- 295 5 Latent schizophrenia
- 295.6 Residual schizophrenia
- 295.7 Schizoaffective type
- 295.8 Other
- 295 9 Unspecified

296 Affective psychoses
296.0 Manic-depressive psychosis, manic type
296 1 Manic-depressive psychosis, depressive type
296 2 Manic-depressive psychosis, circular type but currently manic
296.3 Manic-depressive psychosis, circular type but currently depressed
296 4 Manic-depressive psychosis, circular type, mixed
296 5 Manic-depressive psychosis, circular type, current condition not specified
296.6 Manic-depressive psychosis, other and unspecified
296.8 Other
296 9 Unspecified

297 Paranoid states
297 0 Paranoid state, simple
297 1 Paranoia
297 2 Paraphrenia
297.3 Induced psychosis
297 8 Other
297 9 Unspecified

298 Other nonorganic psychoses
298 0 Depressive type
298.1 Excitative type
298 2 Reactive confusion
298 3 Acute paranoid reaction
298.4 Psychogenic paranoid psychosis
298 8 Other
298 9 Unspecified

NEUROTIC DISORDERS, PERSONALITY DISORDERS AND OTHER NON-PSYCHOTIC MENTAL DISORDERS (300-316)

300 Neurotic disorders
300 0 Anxiety states
300.1 Hysteria
300 2 Phobic state
300 3 Obsessive-compulsive disorders
300.4 Neurotic depression
300.5 Neurasthenia
300 6 Depersonalization syndrome
300.7 Hypochodriasis
300 8 Other neurotic disorders
300 9 Unspecified

301 Personality disorders
301 0 Paranoid personality disorder
301 1 Affective personality disorder
301 2 Schizoid personality disorder
301 3 Explosive personality disorder
301 4 Anankastic personality disorder
301 5 Hysterical personality disorder
301 6 Asthenic personality disorder

301.7 Personality disorder with predominantly sociopathic or asocial manifestation
301.8 Other personality disorders
301.9 Unspecified

302 Sexual deviations and disorders
302.0 Homosexuality
302.1 Bestiality
302.2 Paedophilia
302.3 Transvestism
302.4 Exhibitionism
302.5 Trans-sexualism
302.6 Disorders of psychosexual identity
302.7 Frigidity and impotence
302.8 Other
302.9 Unspecified

303 Alcohol dependence syndrome

304 Drug dependence
304.0 Morphine type
304.1 Barbiturate type
304.2 Cocaine
304.3 Cannabis
304.4 Amphetamine type and other psychostimulants
304.5 Hallucinogens
304.6 Other
304.7 Combinations of morphine type drug with any other
304.8 Combinations excluding morphine type drug
304.9 Unspecified

305 Nondependent abuse of drugs
305.0 Alcohol
305.1 Tobacco
305.2 Cannabis
305.3 Hallucinogens
305.4 Barbiturates and tranquillizers
305.5 Morphine type
305.6 Cocaine type
305.7 Amphetamine type
305.8 Antidepressants
305.9 Unspecified

306 Physiological malfunctions arising from mental factors
306.0 Musculoskeletal
306.1 Respiratory
306.2 Cardiovascular
306.3 Skin
306.4 Gastrointestinal
306.5 Genitourinary
306.6 Endocrine
306.8 Other
306.9 Unspecified

307 Special symptoms or syndromes not elsewhere classified
- 307.0 Stammering and stuttering
- 307.1 Anorexia nervosa
- 307.2 Tics
- 307.3 Stereotyped repetitive movements
- 307.4 Specific disorders of sleep
- 307.5 Other and unspecified disordres of eating
- 307.6 Enuresis
- 307.7 Encopresis
- 307.8 Psychalgia
- 307.9 Other and unspecified

308 Acute reaction to stress
- 308.0 Predominent disturbance of emotions
- 308.1 Predominant disturbance of consciousness
- 308.2 Predominant psychomotor disturbance
- 308.3 Other
- 308.4 Mixed
- 308.9 Unspecified

309 Adjustment reaction
- 309.0 Brief depressive reaction
- 309.1 Prolonged depressive reaction
- 309.2 With predominant disturbance of other emotions
- 309.3 With predominant disturbance of conduct
- 309.4 With mixed disturbance of emotions and conduct
- 309.8 Other
- 309.9 Unspecified

310 Specific nonpsychotic mental disorders following organic brain damage
- 310.0 Frontal lobe syndrome
- 310.1 Cognitive or personality change of other type
- 310.2 Postconcussional syndrome
- 310.8 Other
- 310.9 Unspecified

311 Depressive disorder, not elsewhere classified

312 Disturbance of conduct not elsewhere classified
- 312.0 Unsocialized disturbance of conduct
- 312.1 Socialized disturbance of conduct
- 312.2 Compulsive conduct disorder
- 312.3 Mixed disturbance of conduct and emotions
- 312.8 Other
- 312.9 Unspecified

316 Psychic factors associated with diseases clasified elsewhere

Annex 2

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents

Reference	Organic solvents	Subjects	Summary of results
Grandjean *et al.* 1955 (Switzerland)	Trichloroethylene (TRI)	50 workers in mechanical engineering, doing metal degreasing No referents	- 28% with neurological changes (modification of vision, reflexes, cutaneous sensivity) - 36% with vegetative system problems (fine tremors, excess perspiration) - 34% with slight to moderate psycho-organic syndrome (half of which were without cause) - exposure-response relationship with frequency of reported symptoms
Bardodej and Vyskocil 1956 (Czechoslovakia)	TRI	12 dry cleaners (2 women) 55 metal degreasers (30 women) (8 ex-workers)	- prenarcotic symptoms: headache, sleepiness, nausea, tinnitus (up to 66% of workers) - vegetative nervous system signs (intolerance to heat and alcohol, hot flushes, increased heart beat: up to 46% of workers) - neurasthenic syndrome (irritability, emotional lability, loss of psychic control, etc.: up to 25%)
Smith 1970 (England)	TRI	130 workers Referents: 63 unexposed 112 lead exposed	- complaints of fatigue (75%) and dizziness (56%); intolerance to alcohol and tobacco - more complaints among the more exposed
Hanninen 1971 (Finland)	Carbon disulfide (CS_2)	Workers in viscose rayon factory: I. 50 exposed intoxicated II. 50 exposed no symptoms III. 50 non exposed	- performance in psychomotor and visual test: group II acted more like group I than like group III - discriminant analysis: group II had poor visual performance, impaired dexterity, disturbances in manual coordination - group I had impairment in performances involving vigilance, manual dexterity and intelligence

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Hänninen *et al.* 1976 (Finland)	Toluene, xylene, butyl acetate, white spirit, acetone, etc.	100 car painters 101 referents	- impairment in visual intelligence and verbal memory, reduction in emotional reactivity - no difference in mean reaction times
Lindstrom *et al.* 1976 (Finland)	Styrene	98 workers in reinforced polyester plastic products 43 referents	- poorer visuomotor accuracy and psychomotor performance - inverse correlation between visuomotor accuracy, psychomotor performance, vigilance, and high mandelic acid concentration in urine
Hane *et al.* 1977 (Sweden)	Paint solvents	52 house painters 52 referents	- lower mean scores on tests measuring intellectual capacity and psychomotor coordination - lower performance on memory test and reaction time test
Gun et al. 1978 (Australia)	TRI	8 metal degreasers 8 non exposed referents (all female subjects)	- increased choice reaction time among exposed subjects, even when exposure to TRI was well below the 100 ppm TLV
Knave *et al.* 1978 (Sweden)	Jet fuel (87.5% saturated hydrocarbons 12% aromatic hydrocarbons)	30 jet motor factory workers 30 referents	- more acute symptoms: dizziness, headache, nausea, etc. - more symptoms of neurasthenia, anxiety or depression - higher score of psychiatric symptoms on interview - lower performance on psychological tests demanding attention and high sensorimotor speed - differences in EEG parameters - lower nerve action potentials for sural, higher sensory nerve conduction velocity for ulnar (distal part), higher motor nerve conduction velocity for median

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Knave *et al.* 1979			- higher occurrence of neurasthenic symptoms in exposed subjects (fatigue, anxiety, mood changes, memory difficulties, psychosomatic symptoms)
Elofsson *et al.* 1980 (Sweden)	Toluene, xylene, styrene, ethanol, butanol, MEK, MBK, MIBK, methyl acetate, methylene chloride, TRI, white spirit, (all < 1/2 of TLV)	80 heavily exposed car and industrial painters 2 referent groups of 80 workers from electronics industry	- decrease in nerve conduction velocity in long sensory fibers - more items indicative of neurasthenic syndrome - decrease in reaction time, manual dexterity, perceptual speed, short term memory
Lindstrom 1980 Lindström and Martelin 1980 (Finland)	Halogenated hydrocarbons, aromatic hydrocarbons, paint solvents, styrene	56 solvent poisoned workers 98 styrene exposed workers 43 unexposed construction workers	- decline in visuomotor performances and performances indicating freedom from distractability (solvent-poisoned workers) with an exposure-response relationship - styrene workers differed only slightly from unexposed workers on psychological performances - personality factor analysis solvent-poisoned group had indications of psycho-organic deterioration; styrene workers had few emotional reactions, low anxiety and low number of neurotic signs
Seppaläinen *et al.* (1980) (Finland)	Halogenated hydrocarbons, trichloroethylene, paint solvents	107 solvent poisoned workers: 48 male, 59 female	- women showed a wide-range decline in verbal and performance scales of WAIS compared to Finnish population - men had more difficulties in memory and concentration than women - some relation between long duration of exposure and poorer performance on some psychomotor tests

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Anshelm-Olson *et al.* 1981 (Sweden)	Mixture of solvents with MEK (> Swedish TLV's)	42 steel workers in the production of plastic coated sheets	- simple reaction time measured before, 6 months and 21 months after ventilation improvement: consistent improvement over each measurement period, for morning and end of shift
Gregersen and Stigsby 1981 (Denmark)	White spirit, perchloroethylene, styrene, toluene	7 painters 6 dry cleaners 10 plastic boat industry workers 31 rotogravure workers 28 referents	- no difference in means of auditory reaction time - wider range of reaction times with unchanged mean - significantly lower concentration, attention and abstraction scores
Anshelm Olson 1982 (Sweden)	Xylene, toluene, butanol, ethanol	47 paint manufacture workers 47 referents	- significantly lower simple reaction time at the highest exposure - lower performance of exposed on dots and visual memory tests - exposed reported more symptoms on questionnaire
Iregren 1982 (Sweden)	Toluene (around TLV's)	34 printers 2 referent groups: spray painters and non-exposed (referent groups are subsets of Elofsson *et al.* 1980)	- printers had poorer reaction times than the 2 referent groups - other test results are similar to those of the non-exposed; painters did more poorly on these tests
Routhier *et al.* 1982 (France)	TRI	188 workers in screw-cutting plant (96 exposed less than TLV and 47 > TLV)	- more symptoms of fatigue, tremors, trigeminal geminal neuritis, drunkenness, dizziness - only fatigue and trigeminal neuritis are associated with urinary trichloroacetic acid

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Boudène *et al.* 1983 (France)	TRI	124 metal degreasers: I- 55 men, 10 women II- 18 men, 3 women III- 32 men, 6 women	- complaints of dizziness (23% of subjects), intolerance to alcohol (21%) - decrease in performance on psychometric tests for blood trichloroethanol > 10 mg/l
Cherry *et al.* 1983 (England)	Styrene Styrene Methylene chloride, methanol 1,1,1-trichloroethane, toluene, xylene	27 fibre glass boat makers 20 fibre glass panel makers 56 film makers 15 paint makers	- visual analogue scales for sleepiness, physical and mental tiredness, general good health: no difference at beginning of shift, but significant deterioration among exposed at end of shift - mood deterioration negatively correlated with blood solvent levels in the first three groups - simple reaction time: slower in morning and no difference at end of shift for styrene and methylene chloride; slower at both times for paint solvents
Lindström and Wickström 1983 (Finland)	White spirit (around 40 ppm)	219 maintenance house 229 referents	-significant difference in 'chronic' symptoms - forgetfulness, sensitization, dizziness, weakened sense of smell; 'acute' symptoms - feeling ill, nausea, runny nose. - poorer performance in visual memory test - prolonged simple reaction time
Struwe and Wennberg 1983 (Sweden)	Toluene, xylene, styrene, ethanol, butanol, MEK, MBK, MIBK, methyl acetate, white spirit. Toluene (90%), xylene & petrol	80 exposed car & industrial painters 80 referents 37 printers	- painters presented more fatigue, nervousness and lack of manual dexterity (neurasthenic syndrome) - painters had general decrease in conduction velocity and action potential amplitude for peripheral nerves - printers: large decrease in nerve action potential for sural nerve only; no increase in psychiatric symptoms

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Gregersen *et al.* 1984 (Denmark)	White spirit, perchloroethylene, styrene, toluene	65 solvent exposed: painters, dry cleaners, boat builders, photogravure printers 33 unexposed workers: electricians & warehousemen	- significantly more acute symptoms: somnolence, anorexia, headache, vertigo, inebriation, alcohol potentiation - significantly more 'demential' symptoms: impaired memory and concentration, fatigability, emotional instability, irritability - no difference in neurological symptoms - significantly more emotional changes, poorer performance in all the tests, more cerebral asthenopia - no effect on reaction time except for larger range
Mutti *et al.* 1984 (Italy)	Styrene (Levels between 10 and 300 ppm)	50 workers fabricating fiberglass silos 50 sex-, intelligence and age-matched controls	- significant impairment of verbal learning skills among workers with urine mandelic and phenylglyoxylic acid sums > 150mmole/mole creatinine - significant impairment of logical memory and visuo-constructive abilities with MA+PGA sums > 300 mmole/mole creatinine
de Grosbois and Mergler 1985 (Canada)	Ethyl ether and alcohol	71 exposed workers in an explosive factory 74 unexposed workers: public servents and hospital workers	- higher frequency of prenarcotic symptoms (slower reflexes after work, inebriation, slurred speech, distraction, dreamliness) among exposed workers - higher frequency of mood changes, fatigue, insomnia, memory and concentration problems, hand tremors and dizziness among exposed workers - more symptoms reported among the more exposed group compared to the less exposed
Maizlish *et al.* 1985 (USA)	Paint solvents, glues, lacquers, printing solvents (isopropanol, hexane)	124 exposed and 116 non-exposed workers (office furniture, automotive parts, printing)	- poorer memory span among exposed - no relation between behavioral test performance and solvent concentration

Epidemiological studies on acute and subacute neurobehavioral effects of organic solvents (continued)

Reference	Organic solvents	Subjects	Summary of results
Maizlish *et al.* 1987			- no relation between solvent concentration and neurological function tests' results - mild neuropathy among 16% of study group
Valciukas *et al.* 1985 (USA)	Paint solvents	74 shipyard painters 74 controls matched for sex, race, age, education	- increased prevalence of acute neurological symptoms among painters - decrements in CNS function tests (Block design, Digit symbol, Embedded figures) among painters - performance on tests related to chronic symptoms
Ekberg *et al.* 1986 (Sweden)	Glues (alcohol-based and contact adhesives)	25 floorlayers exposed for > 20 years 25 floorlayers exposed for 5-10 years 50 age-matched carpenters	- increased prevalence of neuropsychiatric symptoms among floorlayers with long experience - visuo-analytical impairment associated with exposure to alcohol-based glues; perceptual impairment associated with exposure to contact glues
Winchester and Majdar 1986 (New-Zealand)	Paint, adhesives, printing solvents (mainly toluene)	42 exposed workers 42 non-exposed workers matched for age, sex, race, education	- higher prevalence of dizziness and headache among exposed - higher prevalence of memory and concentration problems among exposed - increased simple reaction time among exposed under 30 years old
Mikkelsen 1987 (Denmark)	Mixed solvents paint solvents & white spirit	94 painters 99 bricklayers	- association between solvent exposure and any degree of dementia -no clear association with performance on psychometric tests and clinical signs of peripheral neuropathy -association with neurological findings of dyscoordination and with cortical and central measures of cerebral atrophy on computarized tomography scan

Annex 3

Study questionnaire

McGill University
School of Occupational Health

Identification number ☐☐☐☐☐

Date of Interview _____

Beginning _____ ___h End_____ ___h

Length of interview ☐☐☐ min.

Study on occupation and mental health

A. GENERAL INFORMATION

1. a) I would first like to make sure that I am speaking to the right person
I have here that your age is _____ years. Is that correct? ☐ Does not know

b) Can you give me your date of birth _____ ☐ Does not know
D M YR

[Date of birth given by 1 Subject
2 Other]

I would now like to ask you a few general questions.

2. Were you born in Canada? a) Yes —> Was this to an anglophone family?
1 Francophone
2 Anglophone
3 Other (specify) _____

b) No —> If not, where were you born? _____

c) —> What year did you come to Canada? 19____

3. a) Can you remember what your father or guardian's job was when you were a child? (What type of work did he do?)

1 yes (specify) _____

7 female parent or guardian

8 does not know

9 refusal

b) Can you remember what type of company he worked for? (What did they do?)

1 yes _____

7 female parent or guardian

8 does not know

9 refusal

4. a) At what age did you leave primary school _____ Years

b) Did you go on to secondary school?

1 yes —> at what age did you leave it? _____ Years

2 no —> (GO TO QUESTION 4d)

c) After secondary school, did you go on to college, university or other studies?

1 yes —> When was this? 19___ to 19___
Was it full-time ☐, or part-time ☐ ?

2 no

d) Did you receive any technical training or a trade course?

1 yes: _____ When was this? 19___ to 19___
Was it full-time [ ], or part-time [ ]?

2 no

Check approximate year ended full time schooling 19___

B. OCCUPATIONAL HISTORY

Now I would like to know some details about every job you held since you finished school in 19____, starting with the first and going up to the present day.

5. What type of company were you working for? In what city was it located? Do you remember its name?	6. Did you have more than one job with this company?	7. Can you describe to me in a few sentences, what you did in this job? (during a typical work day/week)	8. When did you start this job? When did you finish it?
Type of Co. _____ City (location) _____ Name of Co. _____ A)	Title (starting by the first) Other job If yes →		From 19___ To 19___ ____ mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. _____ City (location) _____ Name of Co. _____ B)	Title Other job If yes →		From 19___ To 19___ ____ mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. _____ City (location) _____ Name of Co. _____ C)	Title Other job If yes →		From 19___ To 19___ ____ mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. _____ City (location) _____ Name of Co. _____ D)	Title. Other job If yes →		From 19 To 19___ ____ mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. _____ City (location) _____ Name of Co. _____ E)	Title Other job If yes → Page 4		From 19___ To 19___ ____ mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.

Now I would like to ask some questions about your exposure to chemicals and similar substances in the course of your work. This question is very important to the study, so I hope you will be able to give us the details we need for each of your jobs. It should not take too long.

12. In the course of your normal work, did you handle, inhale or ingest any of the following substances?

	(a) Glues	(b) Plastic or Rubber Fumes	(c) Lead	(d) Gasoline Oils	(e) Paints Varnishes Dyes	(f) Solvents Alcohols	(g) Pesticides or Herbicides	(h) Metal Cleaners or Degreasers
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8
Specify								
A)								
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8
Specify:								
B)								
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8
Specify.								
C)								
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8
Specify.								
D)								
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8
Specify.								
E)								

Examples
Glues Industrial adhesives, rubber or spirit based glues, epoxy.
Solvents Acetone, carbone tetrachloride, varsol, mineral spirits, methanol.
Cleaners or degreasers Trichlorethylene or products such as "cleaning fluid" or "neutrl".

9. During these years, did you ever stop working for 6 months or more for other reasons like strikes, military service, etc.?

1 yes a) in 19 ___ for ___ mths./yrs.
because of
b) in 19 ___ for ___ mths./yrs.
because of
c) in 19 ___ for ___ mths./yrs.
because of
2 no, never
8 does not know
9 refusal

10. During these working years, did you ever hold a part time job along with your main job?

1 yes a) in 19 ___ for ___ mths./yrs.
work ___ hrs./week
b) in 19 ___ for ___ mths./yrs.
work ___ hrs./week
c) in 19 ___ for ___ mths./yrs.
work ___ hrs./week
2 no
8 does not know
9 refusal

11. Since you have been working, did you ever hold a job where you were regularly laid off for several months each year?

1 yes a) in 19 ___ for ___ mths./yrs.
work
b) in 19 ___ for ___ mths./yrs.
work
c) in 19 ___ for ___ mths./yrs.
work
2 no
8 does not know
9 refusal

11A. Check
Last day at work
___ month ___ year

5a) What type of company were you working for? In what city was it located? Do you remember its name?	6a). Did you have more than one job with this company?	7a). Can you describe to me in a few sentences, what you did in this job? (during a typical work day/week)	8a) When did you start this job? When did you finish it?
Type of Co. _____ City (Location) _____ Name of Co. _____ I)	Title (starting by the first) _____ _____ _____ Other job If yes →	_____ _____ _____ _____ _____ _____	From 19___ To 19___ _____mths./yrs ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. City (Location) _____ Name of Co.: _____ G)	Title _____ _____ _____ Other job If yes →	_____ _____ _____ _____ _____ _____	From 19___ To 19___ _____mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. City (Location) _____ Name of Co. _____ H)	Title _____ _____ _____ Other job If yes →	_____ _____ _____ _____ _____ _____	From 19___ To 19___ _____mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co. City (Location) _____ Name of Co. _____ I)	Title _____ _____ _____ Other job If yes →	_____ _____ _____ _____ _____ _____	From 19___ To 19___ _____mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.
Type of Co City (Location) _____ Name of Co. _____ J)	Title _____ _____ _____ Other job If yes → Check and use additional sheet [ ]	_____ _____ _____ _____ _____ _____	From 19___ To 19___ _____mths./yrs. ☐ Full-time ☐ Part-time ____h/wk.

12a) In the course of your normal work, did you handle, inhale or ingest any of the following substances?

	(a) Glues	(b) Plastic or Rubber Fumes	(c) Lead	(d) Gasoline Oils	(e) Paints Varnishes Dyes	(f) Solvents Alcohols	(g) Pesticides or Herbicides	(h) Metal Cleaners or Degreasers
Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8

Specify: _____

F)

Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8

Specify. _____

G)

Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8

Specify: _____

H)

Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8

Specify: _____

I)

Yes	1	1	1	1	1	1	1	1
No	2	2	2	2	2	2	2	2
Doesn't know	8	8	8	8	8	8	8	8

Specify: _____

J)

13. During all these years at work, did 5 you ever stop working for 6 months or more because of health-related problems (accident, illness, etc.)?

1 yes a) In 19___ for ___ mths/yrs.
because of _____
b) In 19___ for ___ mths/yrs.
because of _____
c) In 19___ for ___ mths/yrs.
because of _____

2 no, never

8 does not know

9 refusal

11A. Check
Last day at work
_____month _____year

I would now like to check with you some types of jobs and activities which are *particularly important* in our study.

14. Whether at work, at home or anywhere else, were you ever involved in		15. Was this as part of your job? If no, specify.	16. When was that? (In what years?)	17. How many hours a week were you doing this?
a) Cabinet making or wood working	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
b) Diesel engine operation	1 yes 2 no	1 yes 2 no _____	from 19__to 19 _ from 19__to 19__	____h/week ____h/week
c) Machine or engine maintenance	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
d) House painting, paid by someone else	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
e) Dry cleaning	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
f) Manufacturing of fibre glass boats	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
g) Fur or leather processing, stuffing animals	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
h) Spraying of trees or weeds	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
i) Processing of photographs	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week
j) Printing (textile, paper)	1 yes 2 no	1 yes 2 no _____	from 19__to 19__ from 19__to 19__	____h/week ____h/week

C. HOBBIES

18a. During your adult life, did you have any practical hobby that involved the use of paints[ ], glues[ ], solvents[ ], cleaners[ ], or other similar products? _____

1 yes 2 no 8 does not know 9 refusal

18b. What was the hobby?	18c. The chemical product?		
1) _____	1) _____	From 19___to 19___	____h/week
2) _____	2) _____	From 19___to 19___	____h/week
3) _____	3) _____	From 19___to 19___	____h/week

D. PERSONAL HABITS

Here are a few questions on smoking and drinking habits

19.a) Have you ever smoked cigarettes regularly?

1 yes 2 no (—> Q 20)

b) Do you still smoke?

1 yes 2 no ——————> stopped _____ year(s) ago.

c) On average, how many cigarettes do (did) you smoke a day? _____ cig./day

20 a) Have you ever drunk beer, cider, wine or alcohol regularly, that is once a week or more?

1 yes 2 no 8 does not know 9 refusal

		Beer/Cider	Wine	Alcohol (Spirits)
b)	During the last 10 years or so, did you drink beer, cider, wine or alcohol once a week or more?	[ ] Yes [ ] No	[ ] Yes [ ] No	[ ] Yes [ ] No
c)	If yes —> How many bottles/glasses did you drink approximately on average each week?	_____ bottles per week	_____ glasses per week	_____ glasses per week
d)	For how many years have you been drinking (did you drink) approximately this amount?	_____ years	_____ years	_____ years
e)	Since you were 21 years old, was there there ever a time when you drank much more?	1 yes 2 no 8 does not know 9 refusal	1 yes 2 no 8 does not know 9 refusal	1 yes 2 no 8 does not know 9 refusal
f)	What age were you when you started to drink more?	_____ years	_____ years	_____ years
g)	How much did you drink then?	_____ bottles per week	_____ glasses per week	_____ glasses per week
h)	For how long?	_____ years	_____ years	_____ years

Comments on alcohol consumption history _____

_____

_____

E. MEDICAL HISTORY

I will finish by asking you about some ailments or diseases that you may have had.

21. Has a doctor ever told you that you had:		22. What treatment did you receive for this problem?	23. In what year was this?
a) Meningitis or infection of the brain	1 yes 2 no	_____ [ ] none [ ] does not know	in 19
b) Convulsions			
1. as an infant	1 yes 2 no	_____ [ ] none [ ] does not know	in 19
2. as a child	1 yes 2 no	_____ [ ] none [ ] does not know	in 19
3. since then	1 yes 2 no	_____ [ ] none [ ] does not know	in 19
c) A head injury with loss of consciousness	1 yes 2 no	_____ [ ] none [ ] does not know	in 19
d) Stroke or other illness of that kind	1 yes 2 no	_____ [ ] none [ ] does not know	in 19

8

24. Since you were 21 years old, have you ever been hospitalized?

1 yes 2 no 8 does not know 9 refusal

a) When? _____ What was the medical problem? _____

b) When? _____ Medical problem _____

d) When? _____ Medical problem _____

d) When? _____ Medical problem _____

25. Finally, do you think that any of your jobs has affected your health?

This ends the questionnaire. Thank you very much for the time you took for this interview. Your cooperation in this study will be very useful. You can be assured that all information obtained from this questionnaire will be kept strictly confidential. If ever we need additional information, can we call you? [ ] Yes [ ] No

I. INTERVIEWER'S REMARKS

1) - Persons who gave information (Relationship with subject)

2) - Type of interview
1 - Telephone/home
2 - Telephone/hospital
3 - Personal/home
4 - Personal/hospital
5 - Other _____

3) - Language of interview
1 - French
2 - English

4) - Was the cooperation of person interviewed.
1 - very good 2 - good 3 - fair 4 - poor

5) - Interview seems
1 - very reliable 2 - reliable
3 - questionable 4 - unreliable

6) - Other comments (problems, etc.)

7) [ ] The subject revealed where he was hospitalized before Question 24
[ ] The interviewer thinks she knows the subject status (case or referant)
[ ] The interviewer has no idea of the subject status

Interviewer's initials [ ][ ]

Université McGill
Ecole de santé au travail

Numéro d'identification ☐☐☐☐☐

Date de l'entrevue _____

Début ____ : ____ h Fin ____ : ____ h

Durée de l'entrevue ☐☐☐ min.

Etude sur le travail et la santé mentale

A. RENSEIGNEMENTS GENERAUX

1. a) J'aimerais d'abord vérifier que je parle à la bonne personne
J'ai ici pour votre âge ____ ans. Est-ce exact? ☐ Ne sait pas

b) Pouvez-vous me donner votre date de naissance ___ ___ ___ (J M A) ☐ Ne sait pas

[Date de naissance donnée par 1 sujet lui-même
2 quelqu'un d'autre]

Je voudrais maintenant vous poser quelques questions d'ordre général.

2. Etes-vous né au Canada? a) Oui —> Etait-ce dans une famille francophone?
1 francophone
2 anglophone
3 autre (préciser) _____

b) Non —> Si non, dans quel pays êtes-vous né? _____

c) —> En quelle année êtes-vous arrivé au Canada? 19____

3. a) Pouvez-vous vous rappeler quel métier faisait votre père ou votre tuteur quand vous étiez enfant? (Quel type de travail faisait-il?)
1 oui: (préciser) _____
7 élevé par sa mère ou une autre femme
8 ne sait pas
9 refus

b) Pouvez-vous vous souvenir du type de compagnie où il travaillait? (Que faisait-elle?)
1 oui _____
7 élevé par sa mère ou une autre femme
8 ne sait pas
9 refus

4. a) A quel âge avez-vous quitté l'école primaire? _____ ans

b) Avez-vous continué à l'école secondaire?
1 oui à quel âge l'avez-vous quittée? _____ ans
2 non —> (ALLEZ A LA QUESTION 4 d)

c) Après l'école secondaire, avez-vous fait des études collégiales ou universitaires ou d'autres études?
1 oui —> Quand était-ce? de 19___ à 19___
Etait-ce à plein temps ☐, ou à temps partiel ☐?
2 non

d) Avez-vous suivi un cours technique ou un cours de métier?
1 oui —> Quand était-ce? de 19___ à 19___
Etait-ce à plein temps ☐, ou à temps partiel ☐?
2 non

Vérification. année approximative de la fin de l'étude à plein temps: 19____

B. HISTOIRE DE TRAVAIL

J'aimerais maintenant obtenir quelques renseignements sur chacun des emplois que vous avez eus depuis que vous avez quitté l'école en 19____, en commençant par le premier et en terminant par le plus récent.

5. Pour quelle sorte de compagnie travailliez-vous? Dans quelle ville était-elle située? Vous souvenez-vous de son nom?	6. Avez-vous eu plusieurs emplois à cette compagnie?	7. Pouvez-vous me décrire en quelques phrases en quoi consistait votre travail à ce poste? (au cours d'une journée ou d'une semaine typique)	8. Quand avez-vous commencé cet emploi? Quand l'avez-vous terminé?
Sorte de cie Ville (endroit) Nom de cie A)	Titre (commencer par le premier) Autre emploi Si oui →		de 19____ à 19____ ____mois/ans [ ] temps plein [ ] temps partiel ____h/sem.
Sorte de cie Ville (endroit) Nom de cie B)	Titre Autre emploi Si oui →		de 19____ à 19____ ____mois/ans [ ] temps plein [ ] temps partiel ____h/sem.
Sorte de cie Ville (endroit) Nom de cie C)	Titre Autre emploi Si oui →		de 19____ à 19____ ____mois/ans [ ] temps plein [ ] temps partiel ____h/sem.
Sorte de cie Ville (endroit) Nom de cie D)	Titre Autre emploi Si oui →		de 19____ à 19____ ____mois/ans [ ] temps plein [ ] temps partiel ____h/sem.
Sorte de cie Ville (endroit) Nom de cie E)	Titre Autre emploi Si oui → Page 4		de 19____ à 19____ ____mois/ans [ ] temps plein [ ] temps partiel ____h/sem.

Maintenant, j'aimerais vous poser quelques questions sur les produits chimiques et autres substances auxquels vous avez été exposé au travail. Cette question est très importante pour notre étude et j'espère que vous serez en mesure de nous donner les détails nécessaires pour chacun de vos emplois. Ceci ne devrait pas être long.

12. Pendant votre travail habituel, avez-vous manipulé, respiré ou ingéré quelques-unes de ces substances?

	(a) Colles	(b) Fumée de plastiques et Caoutchouc	(c) Plomb	(d) Essence Huiles	(e) Peinture Vernis Teintures	(f) Solvants Alcools	(g) Pesticides ou Herbicides	(h) Nettoyeur à métal ou dégraisseur
oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

A)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

B)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

C)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

D)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

E)

Exemples
Colles adhésifs industriels, colles à base de caoutchouc ou solvants epoxy.
Solvants ou alcools acétone, tétrachlorure de carbone, essences minérales, varsol, méthanol.
Nettoyeurs ou dégraisseurs trichloréthylène ou produits comme "cleaning fluid" ou "neutri".

9. Pendant ces années, avez-vous cessé de travailler 6 mois ou plus pour d'autres raisons grèves, service militaire, etc.?

1 oui a) en 19___pendant____mois/ans
pour _____
b) en 19__ pendant __ mois/ans
pour _____
c) en 19___pendant____mois/ans
pour _____

2 non, jamais

8 ne sait pas

9 refus

10. Pendant ces années de travail, avez vous déjà eu un travail à temps partiel en même temps que votre emploi principal?

1 oui a) en 19__ pendant __ mois/ans travail __ h/sem.
b) en 19__ pendant __ mois/ans travail _____h/sem.
c) en 19__ pendant __ mois/ans travail __ h/sem.

2 non

8 ne sait pas

9 refus

11. Depuis que vous travaillez, avez vous déjà eu un emploi ou vous étiez régulièrement mis à pied plusieurs mois chaque année?

1 oui a) en 19__ pendant____mois/ans travail
b) en 19__pendant__ mois/ans travail
c) en 19__ pendant____ mois/ans travail

2 non

8 ne sait pas

9 refus

11 A. Vérification
dernier jour au travail
_____mois _____an

5a) Pour quelle sorte de compagnie travailliez-vous? Dans quelle ville était-elle située? Vous souvenez-vous de son nom?	6a). Avez-vous eu plusieurs emplois à cette compagnie?	7a). Pouvez-vous me décrire en quelques phrases en quoi consistait votre travail à ce poste? (au cours d'une journée ou d'une semaine typique)	8a). Quand avez-vous commencé cet emploi? Quand l'avez-vous terminé?
Sorte de cie Ville (endroit) Nom de cie I)	Titre (commencer par le premier) Autre emploi Si oui		de 19_____ à 19_____ _____mois/ans temps plein temps partiel ___h/sem.
Sorte de cie Ville (endroit) Nom de cie G)	Titre Autre emploi Si oui		de 19_____ à 19_____ _____mois/ans temps plein temps partiel ___h/sem.
Sorte de cie Ville (endroit) Nom de cie H)	Titre Autre emploi Si oui		de 19_____ à 19_____ _____mois/ans temps plein temps partiel ___h/sem.
Sorte de cie Ville (endroit) Nom de cie I)	Titre Autre emploi Si oui		de 19_____ à 19_____ _____mois/ans temps plein temps partiel ___h/sem.
Sorte de cie Ville (endroit) Nom de cie J)	Titre Autre emploi Si oui→Cocher ☐ et utiliser une feuille additionnelle.		de 19_____ à 19_____ _____mois/ans ☐ temps plein ☐ temps partiel ___h/sem.

12a). Pendant votre travail habituel, avez-vous manipulé, respiré ou ingéré quelques-unes de ces substances?

	(a) Colles	(b) Fumée de plastiques et caoutchouc	c) Plomb	(d) Essence Huiles	(e) Peinture Vernis Teintures	(f) Solvants Alcools	(g) Pesticides ou Herbicides	(h) Nettoyeur à métal ou dégraisseur
oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

F)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

G)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Preciser. _____

H)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Preciser _____

I)

oui	1	1	1	1	1	1	1	1
non	2	2	2	2	2	2	2	2
ne sait pas	8	8	8	8	8	8	8	8

Préciser _____

J)

13. Pendant toutes ces années de travail, avez-vous cessé de travailler 6 mois ou plus pour des raisons de santé (accidents, maladie, etc.) 5

1 oui a) en 19___ pendant_____ mois/ans
pour _____
b) en 19___ pendant_____ mois/ans
pour _____
c) en 19___ pendant_____ mois/ans
pour _____

2 non, jamais

8 ne sait pas

9 refus

11 A. Vérification
dernier jour au travail
_____ mois _____ an

Maintenant j'aimerais revoir avec vous quelques types de travail et d'activité particulièrement importants pour notre étude.

14. Que ce soit à votre travail ou non, avez-vous déjà fait de la/ l'/ du		15. Etait-ce au cours de votre emploi? Si non, préciser.	16. Quand était-ce? (En quelle année?)	17. Combien d'heures par semaine faisiez-vous cela?
a) Ebénisterie ou menuiserie	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
b) Opération de de moteurs diesel	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
c) Entretien de machines ou de moteurs	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
d) Peinture domestique à contrat	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
e) Nettoyage à sec	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
f) Fabrication de bateaux en fibre de verre	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
g) Traitement du cuir, de la fourrure, empaillage d'animaux	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
h) Arrosage d'arbres ou de mauvaises herbes	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
i) Développement de photographies	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.
j) Imprimerie (textile, papier)	1 oui 2 non	1 oui 2 non_____	de 19__ à 19__ de 19__ à 19__	_____h/sem. _____h/sem.

C LOISIRS

18 a. Depuis que vous êtes adulte, avez-vous pratiqué un passe-temps où vous employiez de la peinture ☐, de la colle ☐, des solvants ☐, des nettoyeurs ☐, ou d'autres produits de cette nature? _____

1 oui 2 non 8 ne sait pas 9 refus

18b. Quel était ce passe-temps?	18 c. Le produit chimique?		
1)_____	1)_____	de 19___ à 19___	___h/sem.
2)_____	2)_____	de 19___ à 19___	___h/sem.
3)_____	3)_____	de 19___ à 19___	___h/sem.

D. HABITUDES DE VIE

Voici maintenant quelques questions sur votre consommation de cigarettes et d'alcool.

19. a) Avez-vous déjà fumé la cigarette régulièrement?

1 oui 2 non (—> Q 20)

b) Fumez-vous encore?

1 oui 2 non ——→ cessé depuis _____ ans.

c) En moyenne combien fumez-fumiez-vous de cigarettes par jour?_____cig./jour

20. a) Avez-vous déjà bu de la bière, du cidre, du vin ou de l'alcool régulièrement, c'est-à-dire une fois par semaine ou plus?

1 oui 2 non 8 ne sait pas 9 refus

		Bière ou cidre	Vin	Alcool (spiritueux)
b)	En général, pendant les dix dernières années, buviez-vous de la bière ou du cidre/du vin/de l'alcool une fois par semaine ou plus?	☐ oui ☐ non	☐ oui ☐ non	☐ oui ☐ non
c)	Si oui —> A peu près combien de bouteilles/verres avez-vous bu par semaine en moyenne ? non ⌐	_____ bouteilles par sem.	_____ verres par sem.	_____ verres par sem.
d)	Depuis combien d'années buvez-vous (Pendant combien d'années avez-vous bu) à peu près cette quantité?	_____ ans	_____ ans	_____ ans
e)	Depuis l'âge de 21 ans, y a-t-il eu une période où vous buviez beaucoup plus?	1 oui 2 non 8 ne sait pas 9 refus	1 oui 2 non 8 ne sait pas 9 refus	1 oui 2 non 8 ne sait pas 9 refus
f)	A quel âge avez-vous commencé à boire plus?	_____ ans	_____ ans	_____ ans
g)	Quelle quantité buviez-vous alors?	_____ bouteilles par sem.	_____ verres par sem.	_____ verres par sem.
h)	Pendant combien de temps?	_____ ans	_____ ans	_____ ans

Commentaires sur l'histoire de consommation d'alcool _____

E. HISTOIRE MEDICALE

Je vais maintenant terminer avec quelques questions sur des malaises ou des maladies que vous auriez pu avoir auparavant.

21. Est-ce qu'un médecin vous a déjà dit que vous souffriez de/d'		22. Quel traitement avez-vous reçu pour ce problème?	23. En quelle année était-ce?
a) Méningite ou infection au cerveau	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	en 19_____
b) Convulsions			
1. Lorsque vous étiez bébé	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	en 19_____
2. Lorsque vous étiez enfant	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	en 19_____
3. Plus tard	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	En 19_____
c) Coup à la tête avec perte de connaissance	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	en 19_____
d) Accident cérébro-vasculaire (caillot au cerveau) ou une autre maladie du même genre	1 oui 2 non	_____ ☐ Aucun ☐ Ne sait pas	En 19_____

8 24. **Depuis l'âge de 21 ans, avez-vous été hospitalisé?**

1 oui 2 non 8 ne sait pas 9 refus

a) Quand?_____ **Pour quelle raison médicale?**_____

_____

_____

b) Quand?_____ **Raison médicale?**_____

_____

_____

c) Quand?_____ **Raison médicale?**_____

_____

_____

d) Quand?_____ **Raison médicale?**_____

_____

_____

25. **Finalement, pensez-vous que l'un de vos emplois a affecté votre santé?**

_____

_____

_____

Cecl termine le questionnaire. Merci beaucoup du temps que vous avez consacré à cette entrevue. Votre collaboration dans cette étude sera très utile. Vous pouvez être assuré que tout renseignement obtenu dans ce questionnaire sera gardé entièrement confidentiel. Si jamais nous avons besoin d'autres renseignements, seriez-vous disponible?

__ oui __ non

F. REMARQUES DE L'INTERVIEWER

1) - Personnes ayant fourni des renseignements (lien avec le sujet):

_____

_____

2) - Type d'entrevue
1. téléphone/domicile
2. téléphone/hôpital
3. en personne/domicile
4. en personne/hôpital
5. autre. _____

3) - Langue de l'entrevue
1. français
2. anglais

4) - La coopération de la personne interrogée était:

1 - très bonne 2 - bonne 3 - moyenne 4 - pauvre

5) - L'entrevue semble 1 - très valable 2 - valable 3 - discutable 4 - peu valable

6) - Autres commentaires (problèmes, etc.)

_____

_____

7) ☐ Le sujet a révélé où il a été hospitalisé avant la question 24

☐ L'interviewer croit connaître le statut du sujet (cas ou témoin)

☐ L'interviewer ignore tout du statut du sujet

Initiales de l'interviewer ☐☐

Annex 4

Hospital extraction sheet

No dossier médical _____ No d'identification ☐☐☐☐☐

Nom de l'hôpital _____ ☐ Homme ☐ 40-69 ans ☐ 5 jours + ☐ 1ère admission ☐ Diagnostic final ☐ Dx associé

Adresse _____

Cas-étude A ☐
étude B ☐
Témoin-étude A ☐
étude B ☐

Cas et témoins hospitaliers

Informations extraites du dossier médical

Nom du patient _____ Date de naissance |__|__|__|__|
(Apparie a) An Mois Jour

Adresse a la 1ère admission _____ Tél (____) ____-____

_____

Langue maternelle ☐ francais ☐ anglais ☐ autre

1ere admission |__|__|__|__| An Mois Jour Radiation |__|__|__|__| An Mois Jour

Destination au conge ☐ Domicile
☐ Autre _____

Diagnostic - final au congé (ou actuel) ___ _____ ☐☐☐.☐

(CIM-) - secondaires _____ ☐☐☐.☐

_____ ☐☐☐.☐

_____ ☐☐☐.☐

Nom du (des) medecin(s) traitant(s) _____

Occupation habituelle mentionnée
feuille d'admission oui ↓ non, anamnese / notes infirmieres ↓

Poste _____ _____

_____ _____

Consommation d'alcool _____

Hospitalisations subsequentes ☐ Aucune au même endroit

2ème admission |__|__|__|__| An Mois Jour Radiation |__|__|__|__| An Mois Jour

3ème admission |__|__|__|__| An Mois Jour Radiation |__|__|__|__| An Mois Jour

4ème admission |__|__|__|__| An Mois Jour Radiation |__|__|__|__| An Mois Jour

5ème admission |__|__|__|__| An Mois Jour Radiation |__|__|__|__| An Mois Jour

Autres remarques pouvant servir à retracer le sujet.

Adresse la plus recente _____ Tél (____) ____-____

_____

Autre(s) contact(s) Nom _____ Tél (____) ____-____

Adresse _____

Lien avec le sujet _____

Nom _____ Tél (____) ____-____

Adresse _____

Lien avec le sujet _____

Autres remarques _____

_____

_____

_____

_____

Informations extraites le _____ par _____

An / Mois / Jour

Annex 5

Identification sheet

Identification des sujets

Nom du sujet _____ No identification ☐☐☐☐☐

Adresse _____ No tél (___)___-____

_____ Langue _____

Age en 1985 (ou au moment du décès) _____ ans

Autre(s) personne(s) à interviewer

1- Nom _____

Adresse _____ No tél (___)___-____

_____

Lien avec le sujet _____

Raison pour interviewer un substitut _____

_____

2- Nom _____

Adresse _____ No tel (___)___-____

_____

Lien avec le sujet _____

Raison pour interviewer un substitut _____

_____

3- Nom _____

Adresse _____ No tél (___)___-____

_____

Lien avec le sujet _____

Raison pour interviewer un substitut _____

_____

Démarches effectuées

Lettre envoyée le _____ ☐ au sujet lui-même

☐ à _____

Date	Jour de la semaine	Heure	Commentaires et resultats

Annex 6

Introductory letter

McGill University

School of Occupational Health
Ecole de Sante au Travail
Charles Meredith House (514) 392-4568

Dear Sir,

A research team of McGill University is carrying out a survey on health and occupation. The purpose of this study is to look at the work history of people and find out if some occupational exposures are related to certain health problems.

Your name has been chosen, using scientific methods of sampling, either from hospital listings or from electoral lists. Your participation in this study is very important; however, your collaboration is entirely voluntary.

In a few days, a member of our team will telephone and ask you to answer a 15-30 minute questionnaire on all occupations you have held since you left school. If the interviewer calls when you are busy, please do not hesitate to suggest another time so that the questionnaire can be completed in the most convenient manner for you. The information that will be collected is entirely confidential and only an identification number will appear on the questionnaire itself.

We hope that you will be able to spare the amount of time required to answer this questionnaire. If you have any question on the study, you can talk to one of the team at 392-8932.

Yours sincerely,

Dr. J. Corbett McDonald
Professor

France Labrèche
Study coordinator

Si vous désirez les informations en français, s.v.p. téléphonez à 392-8932.

Postal address 1130 Pine Avenue West, Montreal, PQ, Canada H3A 1A3

McGill University

School of Occupational Health
Ecole de Santé au Travail
Charles Meredith House (514) 392-4568

Cher monsieur,

Une équipe de chercheurs de l'Université McGill fait actuellement une enquête sur la santé et le travail. Le but de cette étude est de voir si l'exposition à certains produits dans le milieu de travail est reliée à des problèmes de santé.

Votre nom a été choisi, par des méthodes scientifiques d'échantillonnage, à partir de listes d'hospitalisations ou de listes électorales.

Votre collaboration à cette étude est très importante; cependant votre participation est tout à fait volontaire. Dans quelques jours, un membre de notre équipe vous téléphonera pour vous demander de répondre à un questionnaire de 15 à 30 minutes sur tous les emplois que vous avez eus depuis votre sortie de l'école. Si cette personne téléphone à un moment où vous êtes occupé, n'hésitez pas à lui demander de vous rappeler plus tard, à un moment qui vous conviendra mieux. Les renseignements que nous recueillerons seront confidentiels et votre nom n'apparaîtra pas sur le questionnaire lui-même.

Nous espérons que vous trouverez le temps nécessaire pour répondre au questionnaire. Si vous avez des questions au sujet de l'étude, vous pouvez communiquer avec notre équipe à: 392-8932. Merci à l'avance de votre collaboration.

Veuillez agréer nos salutations distinguées,

Dr. J. Corbett McDonald, MD
Professeur titulaire

France Labrèche
Coordonnatrice de l'étude

If you would prefer information in English, please telephone at: 392-8932

Postal address 1130 Pine Avenue West, Montreal, PQ, Canada H3A 1A3

Annex 7

Short letter for uncooperative subjects

McGill

School of Occupational Health
Ecole de Sante au travail
Charles Meredith House
McGill University

Postal address
1130 Pine Avenue West
Montreal PQ Canada H3A 1A3

(514) 398-4198

I telephoned you a few weeks ago, about an important medical project we are doing on the effects of work on health. Unfortunately, you were too busy at the time to talk to us about your work. All we really want to know is what your main jobs have been and whether in the course of this work, you were often exposed to vapours from glues, paints, varnishes, solvents or degreasers. If you could possibly let us know the answer to these two questions, it would contribute enormously to our research and we would be most grateful.

Sincerely,

Donna Amyot
Research Assistant
Tel. no.: 398-4236

Simply fill in the two questions below and return this note in the stamped and addressed envelope. On receiving your reply, we shall gladly send you $10.00 to cover any expense.

1. Since leaving school, what have been your main types of jobs?

_____

_____

2. While in these jobs, were you often exposed to? (If yes, please tick __✓__)

glues/adhesives. . . . . ____
paints/varnishes/dyes. . . . . ____
solvents/spirits . . . . . ____
metal cleaners/degreasers. . . . . ____

OR

If none of these, tick here . . . . . ____

Signed: _____

P.S. If you would be willing to answer a few more questions about your jobs, could you tick to show whether you would prefer to do it either by mail ____, or by telephone ( ) _____-_____.

McGill

School of Occupational Health
Ecole de Santé au travail
Chair / Accréditation
McGill University

1130 Pine Avenue West
Montreal, PQ Canada H3A 1A3

(514) 398-4229

Je vous ai téléphoné il y a quelque temps, au sujet de notre important projet médical concernant les effets du travail sur la santé. Malheureusement, vous étiez trop occupé à ce moment pour nous parler de votre travail. Tout ce que nous désirons vraiment savoir est quels ont été vos principaux emplois et si, au cours de votre travail, vous avez souvent été exposé à des vapeurs de colles, de peintures, de vernis, de solvants ou de dégraisseurs. Si vous pouviez nous faire connaître la réponse à ces deux questions, ceci contribuerait énormément à notre recherche et nous vous en serions très reconnaissants.

Bien vôtre,

Donna Amyot
Assistante de recherche
No. tél: (514) 398-4236

Répondez simplement aux deux questions ci-après et retournez-nous cette feuille dans l'enveloppe adressée et timbrée ci-jointe. Lorsque nous recevrons votre réponse, nous serons heureux de vous faire parvenir $10.00 pour vos frais.

1. Depuis que vous avez quitté l'école, quels genres de travaux avez-vous fait principalement?_____

_____

2. Pendant ces emplois, est-ce que vous avez souvent été exposé à des: (si oui, cochez S.V.P. ✓)

colles/adhésifs . . . . . ____

peintures/vernis/teintures . . . . . ____

solvants/alcools . . . . . ____

nettoyeurs à métal/dégraisseurs . . . ____

OU

Si à aucune de ces substances, cochez ici ____

Signé:_____

P.S. Si vous accepteriez de répondre à quelques autres questions sur vos emplois, veuillez cocher ici pour indiquer si vous préférez le faire par la poste ___, ou au téléphone (au no.(____) ____-_____).

Annex 8

Short questionnaire for uncooperative subjects

McGill University

Identification number ☐☐☐☐☐

Date questionnaire is completed _____
Day Month Year

STUDY ON OCCUPATION AND HEALTH

For this study, it is very important for us to know about your jobs. Could you spare a few minutes to answer the questions on this side and send us back this questionnaire in the self-addressed envelope. If you have a few more moments, please turn over and complete the back of this sheet.

1. We believe your present age to be _____ years. Is it correct? _____
   Could you give us your date of birth? _____
   Day Month Year

2. What was your main job during most of your working life? _____
   _____

3. How old were you when you started your first full-time job? _____ years old.

4. In the course of any of your jobs, were you exposed to (i.e. handle, breathe or swallow) any of the following chemical substances? If yes, what year did this start, and for how many years did it last?

   - Glues or adhesive substances ☐ No ☐ Yes → started in 19___, for ___ years.
   - Lead ☐ No ☐ Yes → started in 19___, for ___ years.
   - Gasoline, oils ☐ No ☐ Yes → started in 19___, for ___ years.
   - Paints, varnishes, dyes ☐ No ☐ Yes → started in 19___, for ___ years.
   - Solvents, alcohols ☐ No ☐ Yes → started in 19___, for ___ years.
   - Pesticides, herbicides ☐ No ☐ Yes → started in 19___, for ___ years.
   - Metal cleaners, or degreasers ☐ No ☐ Yes → started in 19___, for ___ years.
   - Other chemical substances ☐ No ☐ Yes → started in 19___, for ___ years.
     - If yes, which one(s)? _____

5. Please list below all the jobs you have held for one year or more since you finished school. If more than 5 jobs, please start with those you held for the longest time.

	What type of company was it?	What was your job title?	Can you briefly describe what you did in this job?	When did you start this job? For how many years did you do it?
A			_____ _____ _____ _____	From 19__ to 19__ For _____ years _____ hours/week
B			_____ _____ _____ _____	From 19__ to 19__ For _____ years _____ hours/week
C			_____ _____ _____ _____	From 19__ to 19__ For _____ years _____ hours/week
D			_____ _____ _____ _____	From 19__ to 19__ For _____ years _____ hours/week
E			_____ _____ _____ _____	From 19__ to 19__ For _____ years _____ hours/week

6. Do you think that any of your jobs has affected your health? If so, please explain _____

_____

_____

_____

THANK YOU FOR YOUR HELP WITH THIS STUDY.

McGill

Numéro d'identification ☐☐☐☐☐

Date à laquelle le questionnaire est rempli _____ _____ _____
Jour Mois An

ETUDE SUR LE TRAVAIL ET LA SANTE

Pour cette étude, il nous est très important de connaître vos emplois. Pourriez-vous prendre quelques minutes pour répondre aux questions sur cette page et nous retourner ce questionnaire dans l'enveloppe pré-adressée. Si vous avez un peu plus de temps, veuillez compléter aussi l'endos de cette feuille.

1. Nous croyons que votre âge actuel est _____ ans. Est-ce exact? _____
   Pouvez-vous nous donner votre date de naissance? _____
   Jour Mois An

2. Quel a été votre emploi principal jusqu'à maintenant? _____
   _____

3. Quel âge aviez-vous lorsque vous avez commencé votre premier emploi à plein temps? _____ ans.

4. Pendant n'importe lequel de vos emplois, avez-vous déjà été exposé (en manipulant, respirant ou avalant) à n'importe laquelle des substances chimiques suivantes? Si oui, en quelle année cela a-t-il commencé, et pour combien d'années?

   - Colles ou substances adhésives ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Plomb ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Essence, huiles ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Peintures, vernis, teintures ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Solvants, alcools ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Pesticides, herbicides ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Nettoyeurs à métal, ou dégraisseurs ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
   - Autre(s) substance(s) chimique(s) ☐ Non ☐ Oui ⟶ Début en 19___, pour ____ ans.
     - Si oui, laquelle (ou lesquelles)? _____

5. Veuillez inscrire ici tous les emplois que vous avez eus pendant un an ou plus depuis que vous avez quitté l'école. S'il y en a plus que 5, veuillez commencer par les emplois que vous avez eus pendant le plus longtemps?

	Quelle sorte de compagnie était-ce?	Quel était votre titre d'emploi?	Pouvez-vous décrire brièvement ce que vous faisiez?	Quand avez vous commencé cet emploi? Combien d'années l'avez-vous eu?
A			_____	De 19___ à 19__ Pendant ___ ans ____ heures/semaine
B			_____	De 19__ à 19 Pendant ans ____ heures/semaine
C			_____	De 19___ à 19 Pendant ans ____ heures/semaine
D			_____	De 19___ à 19 Pendant ___ ans ____ heures/semaine
E			_____	De 19___ à 19 Pendant ____ ans ____ heures/semaine

6. Pensez-vous que l'un de vos emplois a affecté votre santé? Si oui, donnez plus de détails.

_____

_____

_____

MERCI D'AVOIR COLLABORE A CETTE ETUDE.

Annex 9

Example of job descriptions presented to raters for the 'Agreement trials'

A

ID#:	023
Type of Industry:	Railroad company
Job title:	Warehouse
Desc. of tasks:	Office work; loading and unloading of railway cars
Year started:	1971
# of years position held:	6 years
Other information:	

ID#:	026
Type of Industry:	Chemical products manufacture
Job title:	Plastics
Desc. of tasks:	Mechanic/helper; did maintenance on machinery; mentions having been exposed to explosions
Year started:	1972
# of years position held:	13 years
Other information:	Exposed to glues in the packaging, to plastic and rubber fumes, lead in thermo power stations, to gasoline and oils, paints, varnishes and dyes, solvents and alcohols and metal degreasers

Annex 10

Example of job histories presented to raters for the 'Job histories assessment' trial

A026-2

	Type of company	Job title	Job description	Years
1	Nil	Nil	Unknown activities No exposure reported	1957
2	Foundry	Unskilled worker	Prepared orders made moulds; did not work in foundry itself Reported exposure: lead	1961
3	Kitchenware company	Toolmaker	Toolmaker on die machine made steel parts; bench fitter No exposure reported	1963
4	Machine shop	Unskilled worker	Worked on die machine made steel parts, milling, etc. No exposure reported	1965
5	Machine repair shop	Bench fitter	Made, cut and worked with parts, repaired hydraulic cylinders No exposure reported	1967
6	Chemical products Co.	Mechanic helper	Company fabricated plastic, did machine maintenance Reported exposure: glues in packaging, plastic fumes, lead in thermal power station, gasoline, paints, solvents (Tripolene C), metal degreasers	1972-85

Annex 11

Coding sheet used by raters for the 'Job histories assessment' trial

NAME:_____

IDENTIFICATION	MORE EXPOSED (CIRCLE ONE OR BOTH)		CONFIDENCE (CIRCLE ONE)			'IMPORTANT' EXPOSURE (1, 2, Neither, Both)			
A008	1	2	0	+	++	1	2	N	B
A020	1	2	0	+	++	1	2	N	B
A026	1	2	0	+	++	1	2	N	B
A027	1	2	0	+	++	1	2	N	B
A028	1	2	0	+	++	1	2	N	B
A037	1	2	0	+	++	1	2	N	B
A038	1	2	0	+	++	1	2	N	B
A048	1	2	0	+	++	1	2	N	B
A049	1	2	0	+	++	1	2	N	B
A050	1	2	0	+	++	1	2	N	B
A051	1	2	0	+	++	1	2	N	B
A053	1	2	0	+	++	1	2	N	B
A057	1	2	0	+	++	1	2	N	B
A060	1	2	0	+	++	1	2	N	B
A062	1	2	0	+	++	1	2	N	B
A067	1	2	0	+	++	1	2	N	B

Annex 12

Example of job titles presented to raters for the 'Job titles coding' trial

8529 — Other Fabricating and Assembling Occupations: Metal Products, n.e.c.

This unit group includes occupations, not elsewhere classified, concerned with fabricating and assembling metal products.

8335 — Welding and Flame Cutting Occupations

This unit group includes occupations concerned with joining, surfacing, cutting or otherwise fabricating and repairing ferrous and non-ferrous metal parts and structures using welding and cutting equipment. It includes activities such as setting up and operating equipment, welding using oxy acetylene, electric arc, metal inert gas or tungsten inert gas equipment; soldering using oxy-acetylene or gas blow torch, soldering iron or electric soldering gun, lead burning, and cutting or perforating using oxy-acetylene cutting torch or electric arc cutting equipment.

8784 — Plasterers and Related Occupations

This unit group includes occupations concerned with applying plaster, stucco, plasterboard and related materials to structural surfaces, fastening laths to walls and ceilings to support plaster or related materials, applying coats of plaster to produce finished surfaces, mouldings and special effects, spraying fireproofing materials on surfaces, and erecting and finishing acoustical ceilings and dry walls.

9131 — Locomotive Operating Occupations

This unit group includes occupations concerned with operating railway locomotives to transport freight and passengers and to move locomotives within yards and servicing and repair areas. Activities include operating controls of locomotive, communicating by radiotelephone, interpreting train orders, signals and railway rules and regulations, and inspecting locomotive to ensure adequate fuel supply and proper functioning of equipment.

8355 — Planing, Turning, Shaping and Related Wood Machining Occupations

This unit group includes occupations concerned with making wooden parts or products by such machines as planing, turning, shaping, routing, boring, morticing and drilling wood stock to desired shape and size. Activities include setting up and operating woodworking machines, measuring and laying out work.

6191 — Janitors, Charworkers and Cleaners

This unit group includes occupations concerned with cleaning building interiors, furnishings and equipment, washing windows, cleaning chimneys and furnaces, and cleaning and repairing venetian blinds.

Annex 13

Prevalence of exposure to solvents

Table A-1 Prevalence of solvent exposure: any level

	Cases		Hospital referents	
Distribution of exposure				
Average years exposed	9.4		10.5	
S.D.	12.7		13.6	
Average years since first exposure	33.0		32.0	
S.D.	10.5		11.1	
Average years since last exposure	11.7		11.5	
S.D.	12.3		13.7	
Exposure in years	*n*	%	*n*	%
0	169	46.3%	161	42.7%
1-9	52	14.2%	72	19.1%
10-19	51	14.0%	37	9.8%
20-29	40	10.9%	48	12.7%
30-39	28	7.7%	34	9.0%
40 +	9	2.5%	16	4.3%
Unknown duration	16	4.4%	9	2.4%
Missing information	16	--	4	--
Total	381	100.0%	381	100.0%

Table A-2 Prevalence of solvent exposure: moderate levels and higher

	Cases		Hospital referents	
Distribution of exposure				
Average years exposed	4.4		5.2	
S D	9.4		10.8	
Average years since first exposure	30.3		30.3	
S D.	12.1		11.6	
Average years since last exposure	12.4		13.5	
S.D	13.7		13.5	
Exposure in years	*n*	%	*n*	%
0	256	70.1%	250	66.3%
1-9	41	11.2%	54	14.3%
10-19	29	7.9%	22	5.8%
20-29	19	5.2%	19	5.1%
30-39	13	3.6%	17	4.5%
40 +	2	0.6%	9	2.4%
Unknown duration	5	1.4%	6	1.6%
Missing information	16	--	4	--
Total	381	100.0%	381	100.0%

Table A-3 Prevalence of solvent exposure: high levels

	Cases		Hospital referents	
Distribution of exposure				
Average years exposed	1.9		2.0	
S.D.	6.3		6.6	
Average years since first exposure	30.6		28.2	
S.D.	12.0		10.6	
Average years since last exposure	17.3		13.4	
S.D.	15.0		12.9	
Exposure in years	*n*	%	*n*	%
0	302	82.7%	319	84.6%
1-9	36	9.9%	27	7.2%
10-19	12	3.3%	13	3.4%
20-29	6	1.6%	10	2.7%
30-39	6	1.6%	6	1.6%
40 +	1	0.3%	1	0.3%
Unknown duration	2	0.5%	1	0.3%
Missing information	16	--	4	--
Total	381	100.0%	381	100.0%