Contact dermatitis caused by alkyl glucosides in the modern cosmetic industry and contact dermatitis in the Canadian aircraft industry

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Abstract (English)

Introduction:

Contact dermatitis is defined as an inflammatory reaction secondary to direct or airborne cutaneous contact with an irritant or sensitizing molecule. Contact dermatitis can significantly impact the quality of life of patients and can lead to loss of work when severe. Contact dermatitis is subdivided into irritant and allergic contact dermatitis. The underlying cutaneous immunologic response determines the nature of the cutaneous reaction.

Allergic contact dermatitis is a delayed type IV hypersensitivity reaction that occurs in certain predisposed individuals and that requires prior epicutaneous sensitization. Cross-reaction can occur when 2 structurally similar allergens are found in two different substances. This similar allergen may activate the immune system and elicit a cutaneous allergic reaction in an individual previously sensitized to the first molecule.

Irritant contact dermatitis is an acute; non-immunologically mediated direct cytotoxic reaction that occurs to some degree in all individuals. It is the most common occupational skin disease and accounts for 70-80% of work-related dermatoses.[1] Upon frequent exposure, some people may develop “hardening” of the skin. This phenomenon is not possible with allergic contact dermatitis.

The cosmetic industry is an important source of potentially sensitizing and irritating ingredients for consumers. New preservatives, surfactants, emollients, sun blockers, perfumes, etc. are constantly being synthetized, and certain molecules such as the family of surfactant alkyl glucosides are being rediscovered by the industry. With

respect to the alkyl glucosides, over the past 15 years, many cases of allergic contact dermatitis have been published, mostly to lauryl and decyl glucosides. The sunscreen ingredient Tinosorb® M contains decyl glucoside as a “hidden” allergen, the likely culprit in most cases of allergic contact dermatitis to this sunscreen ingredient.[2]

The aircraft industry is another important source of contact dermatitis, in this case occupationally related. Materials used in the construction of planes have evolved over the past several years leading to introduction of new potentially highly sensitizing products. Bombardier Aerospace is a Canadian multinational aircraft manufacturer based in Montreal that employs thousands of workers. Contact dermatitis in the aircraft industry has been described in the American and European literature but no Canadian literature is available. The McGill University Health Centre contact dermatitis clinic has tested in the last 25 years over three hundred workers from Bombardier who were affected with occupational dermatoses.

Methods:

As part of my thesis, we retrospectively analysed data for all McGill University Health Centre patients patch tested with decyl glucoside and lauryl glucoside between the years 2009 and 2016. We compiled demographic characteristics and patch test results for all subjects.

We also extracted from the database of McGill University Health Centre contact dermatitis clinic the files of all Bombardier Aerospace workers referred for suspicion of occupational dermatoses between 1990 and 2015. These were subdivided according to demographics, type of work, results of patch testing and final diagnosis.

Results:

Regarding the retrospective analysis of patch test result for the alkyl glucosides, we found that twenty (0.65%) of 3095 patients reacted to decyl glucoside. Fifteen (0.92%) of 1628 patients were positive to lauryl glucoside, with 6 of these also allergic to decyl glucoside, and 9 reacting to lauryl glucoside alone. The sensitization rate increased to 2.2% in the fist 6 months of 2016.

In our research regarding Bombardier Aerospace, we found 305 workers who were investigated for various dermatoses. Fifty-eight percent were 40 years of age or less, and one third were women. The interval between hiring and onset of dermatitis varied from 2 months to 25 years, but in 120 (39%) workers, it occurred during the first 3 years of work. Fifty-one percent of the cases involved assemblers. Composite materials technicians were over-represented, since they provided 27% of the cases, whereas they constitute only 10% of the workforce. Of the 305 workers, 152 suffered from allergic contact dermatitis (ACD) and 96 from irritant contact dermatitis (ICD). Of those with ACD, 82 reacted to commercially available allergens, mostly epoxy resins or chromates. However, 85 (56%) reacted only to products from the workplace.

Conclusion

Our study on Alkyl Glucosides reveals that their sensitizing potential is higher than expected. Cross-reactions are not automatic and multiple glucosides should be tested to increase the rate of detection.

In the aircraft industry, allergic contact dermatitis is more common than irritant because of widespread exposure to highly sensitizing resins and anti-corrosion materials. Cross-

reactions are not automatic and many patients reacted only to products from the workplace. These cases would have been missed had they not been tested with these compounds.

Abstract (French)

Introduction:

La dermatite de contact est définie comme étant une réaction inflammatoire secondaire à un contact direct ou aéroporté avec une molécule irritante ou sensibilisante. La dermatite de contact peut avoir un impact significatif sur la qualité de vie des patients et mener à une perte d'emploi lorsque très sévère. Elle est subdivisée en dermatite de contact allergique ou irritative. La réponse immunologique sous-jacente détermine la nature de la réaction cutanée.

La dermatite de contact allergique est une réaction retardée de type 4 qui se présente chez certains individus prédisposés et qui dépend d'une sensibilisation épicutanée préalable. Une réaction croisée peut avoir lieu quand deux allergènes de structure voisine se retrouvent dans des substances différentes. Cet allergène similaire peut activer le système immunitaire et provoquer une réaction cutanée allergique chez un individu préalablement sensibilisé à la première molécule.

La dermatite de contact irritative est une réaction aiguë, non-immunologique causée par une cytotoxicité directe et qui peut affecter tout individu à des degrés divers. C'est la dermatite professionnelle la plus commune représentant 70-80% des dermatoses reliées au travail.[1] Avec des expositions répétées, certaines personnes

peuvent développer une tolérance cutanée. Ce phénomène n'est pas possible avec une dermatite allergique.

L'industrie cosmétique est une source importante d'ingrédients potentiellement sensibilisants et irritants pour le consommateur. De nouveaux conservateurs, surfactants, émollients, écrans solaires, parfums, etc. sont constamment synthétisés. Certaines molécules, telles celles de la famille des surfactants alkyl glucosides, sont redécouvertes par l'industrie. Dans les 15 dernières années, plusieurs cas d'allergie de contact aux lauryl glucoside et décyl glucoside ont été publiés. Le filtre solaire Tinosorb® M contient le décyl glucoside comme ingrédient caché et celui-ci est probablement la cause de la majorité des cas d'allergie de contact à cet agent anti-soleil.[2]

L'industrie de l'aviation est aussi une autre importante cause de dermatite de contact professionnelle. Les matériaux utilisés dans la construction des avions ont grandement évolués dans les dernières années, amenant l'introduction de produits potentiellement très sensibilisants. La firme Bombardier Aéronautique est une multinationale canadienne reconnue de l'aviation, basée à Montréal, et qui emploie des milliers de travailleurs. La dermatite de contact dans le milieu aéronautique a été décrite dans la littérature américaine et européenne, mais pas dans la littérature canadienne. La clinique des dermatites de contact du centre universitaire de santé McGill a testé, au cours des 25 dernières années, plus de trois cent travailleurs de chez Bombardier Aéronautique victimes de dermatoses professionnelles.

Méthodes :

Au cours de ma maitrise, nous avons analysé de façon rétrospective tous les patients testés au centre universitaire de santé McGill avec l'allergène décyl glucoside,

ainsi que ceux testé au lauryl glucoside depuis 2009. Nous avons compilé les caractéristiques démographiques ainsi que les résultats des tests cutanés de tous les patients. Nous avons extrait les dossiers de tous les travailleurs de chez Bombardier Aéronautique référés à la clinique des dermatites de contact du centre universitaire de santé McGill pour suspicion de dermatose professionnelle entre les années 1990 et 2015. Ils ont été divisés selon leurs caractéristiques démographiques, type de travail, résultat, diagnostic final.

Résultats :

L'analyse rétrospective des résultats des tests épicutanés aux alkyl glucosides a montré que vingt (0.65%) des patients ont réagi au décyl glucoside. Quinze (0.92%) des 1628 patients testés au lauryl glucoside ont été positifs avec seulement 6 patients également allergiques au décyl glucoside. Neuf patients ont réagi au lauryl glucoside seul. Le taux de sensibilisation a augmenté à 2.2% dans les 6 premiers mois de 2016.

Concernant l'étude chez Bombardier Aéronautique, nous avons trouvé que 305 travailleurs ont été investigués pour dermatose. Cinquante-huit pourcent des gens étaient âgés de moins de 40 ans et un tiers était de sexe féminin, proportionnellement à la main-d'oeuvre. L'intervalle entre le début de la dermatite et l'embauche varie entre 2 mois et 25 ans, mais 120 (39%) des cas se sont présentés dans les 3 premières années de travail. Cinquante et un pourcent des cas impliquait les assembleurs. Avec 27% des cas, les techniciens en matériel composite était sur-représentés étant donné qu'ils constituent 10% de la main-d'œuvre. Des 305 employés, 152 ont souffert d'une allergie de contact et 96 d'une irritation de contact. Parmi ceux atteint d'une allergie, 82 ont réagi

aux allergènes commercialement disponibles, surtout les résines époxys et les chromates. Par contre, 85 (56%) ont réagi seulement aux produits du milieu de travail.

Conclusion

Notre étude sur les alkyl glucosides dans l'industrie cosmétique révèle que leur potentiel de sensibilisation est plus grand qu'attendu chez les consommateurs. Les réactions croisées ne sont pas automatiques et plusieurs glucosides devraient être testé pour augmenter le taux de détection.

Dans l'industrie de l'aviation, la dermatite de contact allergique est plus commune que l'irritation à cause de l'exposition répandue à des résines et matériaux corrosifs hautement allergènes. Les réactions croisées ne sont pas automatiques et plusieurs patients réagissent seulement aux produits provenant du milieu de travail. De nombreux cas auraient échappé à la détection si nous n'avions pas testé ces produits directement.

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First, I would like to greatly thank my thesis supervisor and mentor Dr. Denis Sasseville for accompanying, guiding and supervising me through my projects and thesis. I would also like to acknowledge my thesis committee (Dr. Ivan Litvinov, Dr. Linda Moreau and Dr. Suhad Ali) for their contributions and important comments on how I might improve my work. I also want to thank everyone who has supported me through this great journey at McGill University. The Bombardier Aerospace project was supported by a research grant from the Canadian Dermatology Foundation. I have no conflict of interest or other source of financing to declare.

Preface and contribution of authors

Over the past 2 years, I led the project on Alkyl Glucosides and Bombardier Aerospace under the supervision of Dr. Denis Sasseville. I reviewed the literature and extracted and analysed the data. I led the redaction of 3 published articles and composed the final thesis. Dr. Maïsa Alfala and Dr. Marie-Christine Ferrier Le Bouedec were co-authors for our articles on alkyl glucosides. Dr. Le Bouedec contributed to the French case report in chapter 1. Dr. Sasseville recruited the patient cohorts over the years at the McGill University Health Center contact dermatitis clinic. He guided and helped me to build a structure for our retrospective studies. He also participated in correcting my articles.

Introduction

Contact dermatitis is a frequent cause for dermatology consultation. The two major forms are irritant and allergic. They affect quality of life and lead to decreased productivity when work-related. Allergic contact dermatitis can occur in all ages and sexes. Prevalence of allergens and irritants vary according to regions, patterns of usage and specific occupations (work area, hobbies, etc.). For example, preservative use in cosmetic products are based on government legislation and some agents may be banned in certain countries. Irritant contact dermatitis is usually the most common occupational skin disease accounting for 70-80% of work-related skin disorders but this tendency is reversed in the aircraft industry.[1] Occupational skin diseases are not reportable; and this makes health department data an unreliable source for monitoring disease burden. According to a National Health Interview Survey in the US, manufacturing is one of the industries with the highest incidence of occupational dermatoses.[3] Population awareness and prevention methods are essential to decrease the incidence of occupational dermatoses.

Elicitation of allergic contact dermatitis is a well-studied and complex phenomenon. This type of cutaneous allergy requires previous epicutaneous sensitization in a naïve individual. Upon epicutaneous application of a new hapten, or incomplete antigen, antigen-presenting cells (APCs) will take it up and bind it to self-proteins, where it becomes a full antigen. APCs then travel to regional lymph nodes to present the antigen to T lymphocytes. Rare T cells capable of recognizing the full antigen then undergo clonal expansion and divide into memory and effector T cells that

are released in the circulation. . Upon re-exposure, the memory T lymphocytes will be able to recognise the specific antigen and trigger an eczematous reaction at the site of contact through secretion of pro-inflammatory cytokines. Irritant contact dermatitis is a multifactorial non-immunologically-mediated direct cytotoxic reaction, determined by the irritating properties of a substance that leads to epidermal barrier disruption and eczematous reaction. It is a dose-dependent reaction and also related to exposure parameters such as concentration, temperature, time, pH, duration of contact and occlusion. Irritation can be chemically induced, mechanical or photoinduced.

Differentiating between allergy and irritation is not always feasible because the two forms of dermatitis can be clinically indistinguishable, especially their chronic variants. The two conditions both present as eczematous reactions. Patch testing is the most commonly used and available test to diagnose allergic contact dermatitis and differentiate it from other forms of eczematous processes. Haptens used for patch testing differ from one country to another. Large patch testing centers use a wide array of commercially available series. The standard series developed by the North American Contact Dermatitis Group (NACDG) arises from the NACDG's research to monitor trends in allergic contact dermatitis throughout the USA and Canada. It is constantly being updated and adapted by adding new emerging haptens and removing others that have decreased in clinical importance. New molecules that eventually end up being allergenic are constantly being introduced by modern industries, including industries such as aircraft manufacturing and cosmetic production. The former affect only those working in the industry, whereas the latter affects the general public.

Chapter 1: Alkyl glucosides in contact dermatitis

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IA. Introduction

Alkyl glucosides are the products of condensation of glucose and a fatty alcohol. Their use began in the 1960's as non-ionic surfactants in rinse-off products such as shampoos, soaps, hair dyes and mousses, but they were eventually replaced by newer surfactants. The late 1990's saw a revival of popularity for alkyl glucosides because of their low potential for irritation and their ecological characteristics, as these surfactants are manufactured from renewable sources. The cosmetic industry has since used them increasingly, not only in rinse-off, but also in leave-on products such as sunscreens, deodorants and antiseptics. Beginning in the early 2000's, several case reports described allergic contact dermatitis from alkyl glucosides in different cosmetic and cleansing products.[2,4] At the same time, decyl glucoside, an important member of the alkyl glucoside family, was also found to be a "hidden allergen" in the new sunscreen ingredient Tinosorb® M.[2] When patch tested, alkyl glucosides occasionally induce mild irritation, therefore strong positive reactions probably reflect actual sensitization.[3]

Chemistry and metabolism

Alkyl glucosides are part of a family of organic molecules of vegetal origin composed of 19 different members. In 1893, ethyl glucoside, the shortest and simplest alkyl glucoside, was first synthesized.[5] Chemically, alkyl glucosides are produced by the condensation of a sugar, usually a cyclic form of glucose (D-glucopyranose), with a fatty alcohol composed of a linear side chain ranging from 2 to 22 carbons (Fig. 1).

Alcoholysis of glucose under acidic conditions is the preferred method of synthesis.[5] The anomeric hydroxyl group of the glucose moiety is the site of linkage with the fatty alcohol. The reaction conditions can cause the condensation of two or more glucose molecules at either of their hydroxyl groups in a repeating sequence, forming alkyl polyglucosides. These compounds are still called alkyl glucosides, regardless of their number of glucose molecules. Alkyl glucosides are chemically stable; they do not contain chemically reactive sites or polarized structures.[6]

Fatty alcohol is extracted from palm, coconut or rapeseed oil and glucose can be obtained from corn, wheat starch and potato. The average number of carbon atoms composing the side chain of the alcohol determines the name of the alkyl glucoside. For example, decyl glucoside has an average of 10 carbons on its side chain. Other members of the alkyl glucoside family include butyl, caprylyl, undecyl, myristyl, hexadecyl, octadecyl, and arachidyl glucosides, caprylyl/capryl glucoside, C10-16, C12-18, C12-20, C20-22 alkyl glucosides, branched isostearyl glucoside, and octyldodecyl glucoside.[5]

The likely first step in the metabolism of alkyl glucosides is cleavage by the human skin enzyme glucoside hydrolase, leading to release of the respective fatty alcohols and glucose.[5] According to an *in vitro* absorption assay on human skin sample with 10% caprylyl/capryl glucoside, transdermal absorption was less than 0.01%.[5]

Function and Safety of use

After a thorough review of toxicological data, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that the 19 alkyl glucosides are safe to use.[5] Most of the alkyl glucosides are primarily used as mild surfactants in cosmetics and cleansing products for human skin. They can also sometimes function as emulsion stabilizers in sunscreens, skin and hair cleansing agents and humectants.[5] They can be found in certain baby products such as wipes and cleansers.

Alkyl glucosides have been shown to be superior surfactants compared to “classic” polyethoxylated surfactants such as polysorbates. They are not susceptible to oxidation at room temperature and they are used in lower concentration leading to a lower skin irritancy potential. The lipophilic hydroxyl groups and the hydrophilic hydrocarbon chains help keep the molecule at the water-oil interface.[6] Nowadays, decyl glucoside is the most commonly used alkyl glucoside. In 2011, according to information from the Voluntary Cosmetic Registration Program (VCRP) database, decyl glucoside was reported to be an ingredient in 492 cosmetic formulations, mainly rinse-off products.[5] Cetearyl glucoside, lauryl glucoside and coco-glucoside are also frequently used. Cetearyl glucoside is probably the most commonly used glucoside in leave-on products other than sunscreens.[5,7] The concentration of use varies but is higher in rinse-off products. Lauryl glucoside has the highest concentration of use in leave-on products at 8% in a hair color spray and 5% in a skin product, while decyl glucoside can be present at a concentration of 33% in rinse-off products.[5]

Some recent publications suggested that certain alkyl glucosides could potentially be absorption enhancers. Tirumalasetty et al. showed that caprylyl and decyl glucosides could enhance the absorption of insulin *in vivo* through mucous membrane.[8] Aguirre and colleagues found that ingestion of coco-glucoside could enhance the intestinal permeation of calcitonin and sugar in rats.[9] The CIR Expert Panel expressed concern that the transdermal absorption of some cosmetic ingredients could lead to untoward effects.[5]

Cutaneous adverse effects

Irritation

Alkyl glucoside did not cause significant irritant contact dermatitis in clinical studies. An epicutaneous patch test with a 2% concentration and a soap chamber test at a concentration of 1% with lauryl, decyl and coco glucosides as well as an occlusive patch test with decyl glucoside 0.5% showed only a slight irritation potential.[5] Furthermore, patch testing with a 10% aqueous solution of decyl glucoside did not cause irritant reactions in 100 volunteers.[10] Lauryl glucoside has a pH of 11.5 to 12.5. Shanmugam et al[10] recently proposed that lack of correction of pH by suppliers of commercial allergens could render their preparation irritant.

Allergic contact dermatitis

Alkyl glucosides in sunscreen, cosmetics and cleansing products can sensitize by an as yet undetermined mechanism. Decyl glucoside, lauryl glucoside, cetearyl glucoside, and coco glucoside are responsible for most cases. The length of the alcohol chain does not affect the sensitizing potential.

A comparative study used 3 protocols to assess the skin sensitizing potential of 8 related alkyl glucosides. In the local lymph node assay, only C12-C18 glucoside, C4 glucoside, and C18 branched glucoside were mild sensitizers. The authors could not demonstrate sensitization by using the human insult repeated patch test protocol or the guinea pig maximization test.[11]

IB. Methods

Systematic review of literature

We systematically searched Pubmed for reported cases and case series of allergic contact dermatitis to alkyl glycosides.[1-10] We also reviewed bibliographies to identify additional publications. Inclusion was restricted to confirmed cases of allergic contact dermatitis with positive patch testing. In the literature, 13 articles met our inclusion criteria. Those included 25 case reports and 1 case series of 30 patients. We excluded 2 case reports (Shanmugam) because positive patch testing for alkyl glucosides was not clinically relevant. The 2 authors (C. Loranger and D. Sasseville) independently evaluated the eligibility of all studies. We then categorized the data according to type of products having caused allergic contact dermatitis: 1) Leave-on products; and 2) Rinse-off products to compare clinical presentation and culprit allergens.

We also searched for the most recent data of the North American Contact Dermatitis Group and Groupe d'Études et de Recherches en dermato-Allergologie (GERDA) to look at the rate of sensitization to decyl glucoside and lauryl glucoside respectively, over the last 8 years.

Data extraction, Inclusion and exclusion criteria

The following information was sough from each case report: author identification, year of publication, age and sex of patient, clinical presentation, relation of allergy to work, patch testing methods and culprit allergens.

For our MUHC database, we underwent data collection starting from 2009 and we continued extraction until June 2016. We included all patient tested with confirmed sensitization to decyl glycoside and/or lauryl glycoside. We looked at initial and final patch test reading results (i.e. 48 and 96 hours) to determine sensitization status of patients. We extracted data by reviewing all patient charts in the MUHC contact dermatitis clinic computer database. Over the last 7 years, the same dermatologist in charge of the McGill contact dermatitis clinic has evaluated each patient included in the MUCH database and has recorded demographics, clinical characteristics and patch test results in a standardized manner, minimizing inter-individual errors and increasing study reliability. A standard patch test protocol was employed and informed consent was obtained before using patch testing to try to confirm the molecules responsible for the dermatitis of each patient. Data was organized and compiled in an Excel document. Each patient was assigned a number and corresponding data arranged in chronological order according to the initial date of visit at the MUHC contact dermatitis clinic. We included patient's demographic characteristics (age, sex, history of atopy and occupation) plus clinical presentation and location of dermatitis at the time of initial medical visit. We took note of patients with cross sensitization to lauryl and decyl glucoside. Any missing information was reported as such on our excel document and

tables. Rates of cutaneous sensitization to lauryl and decyl glucoside over the last 7 years at the MUCH clinic were calculated after our data extraction was completed in July 2016.

IC. Results

Case reports and case series

Goossens et al. are credited with reporting the first 2 cases of sensitization to alkyl glucosides in cosmetic and cleansing products.[4] Since then, additional publications have described further cases of allergic contact dermatitis.[2,4,12-25] A retrospective study by Gijbels et al., who reviewed 19 years of data, counted 30 cases of contact allergy to different alkyl glucosides (Table 1).[12]

Analysis of available data has shown similarities between cases. When patch tested, the majority of patients react to multiple alkyl glucosides and females are more commonly sensitized. The median age of patients is 49.6 years. Sensitization can occur in an occupational setting, but the majority of cases are not work-related. Workers in contact with cosmetic or cleansing products like hairdressers, housekeepers, and nurses have been sensitized. Conditions such as atopic eczema and occupational irritation may enhance the penetration of glucosides by altering the epidermal barrier.[5] Hands, face, neck and scalp are commonly affected by exposure to shampoos, sunscreens and liquid soaps. Non-exposed sites, such as breast, abdomen, genitals and folds have been involved from use of antiseptics, skin cleansers and deodorant wipes. In most cases, strict avoidance of the culprit products and treatment with topical corticosteroids have

led to resolution of the dermatitis. More severe cases requiring treatment with systemic corticosteroids have occurred following exposure to decyl glucoside in Tinosorb® M sunscreens.[13,15]

Cosmetic Rinse-off products

Among the rinse-off products, shampoos are the most common cause of contact dermatitis from alkyl glucosides, with around 16 reported cases.[2,4,12] Shampoos often contain a mixture of different alkyl glucosides and their exact composition is not always clear. Some publications report allergic contact dermatitis from liquid, gel or cream formulations of hand and body soaps . The molecules most commonly implicated include decyl glucoside, coco-glucoside, lauryl glucoside and cetearyl glucoside. Because preservatives, fragrances and other allergens or irritants are present in shampoos and cosmetics, it is important to test a patient's personal products and their individual ingredients.

Cosmetic Leave-on products

SUNSCREENS

The sunscreen ingredient Tinosorb® M was introduced in the European, Asian and Australian markets in the early 2000's. It is not used in the United States because it has not yet been approved by the Food and Drug Administration. Tinosorb® M is composed of the new broad-spectrum UV filter methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT, also known as bisoctrizole) (50%) solubilized with decyl glucoside (7.5%), propylene glycol (0.4%), xanthan gum (0.2%) and water (ad 100%). [26]

Compared with other sunscreen preparations, Tinosorb® M offers the advantages of being photostable and protecting the skin by three different mechanisms, absorbing UV radiation like an organic filter and reflecting and scattering light as a physical sunblock.[6] The role of decyl glucoside is to facilitate dispersion of the UV filter micro particles in an aqueous phase. Unfortunately, while decyl glucoside is present in the final preparation, its name does not appear on the ingredient label of some sunscreens, where it therefore represents a “hidden allergen”.

Blondeel reported the first case of allergic contact dermatitis to Tinosorb® M in 2003 and several cases have since been published.[2,12-20] Between 2009 and 2012, Pereira and colleagues collated the largest case series: 92 patients were photopatch tested and 87 patients were patch tested with a cosmetics series that included Tinosorb® M, Tinosorb® S and lauryl glucoside.[17] In total, 5 of the 179 tested patients had positive reaction to Tinosorb® M and to lauryl glucoside, for a positivity rate of 2.8%. Tinosorb® S, a chemically unrelated UV filter has not been shown to cause allergic contact dermatitis. Interestingly, it does not need decyl glucoside as a stabilizer.

MBBT, used as a synonym for Tinosorb® M in previous studies, may have been falsely reported as the sensitizing agent.[18-19] In fact, pure MBBT was unavailable for testing until January 2014 in the European Photopatch Extended (EPE) series.[20] Previous tests labelled “MBBT” were in fact performed with a mixture of decyl glucoside and pure MBBT. This confounding factor illustrates the importance of testing with individual allergens and to correctly label material used for patch testing because of

hidden ingredients. To our knowledge, decyl glucoside appears to be the main sensitizer in Tinosorb® M.

ANTISEPTIC LOTION, DEODORANT AND HAIR MOUSSE

Goossens et al. published the first case report of allergic contact dermatitis on the hands from an antiseptic lotion containing coco-glucoside and lauryl glucoside.[4] Later, contact allergy from decyl glucoside, involving different parts of the body, was reported in a patient who used a chlorexidine-based antiseptic gel, and two patients exposed to a moisturizing lotion.[21,22] The two patients described by Krehic and colleagues reacted positively to lauryl glucoside on initial patch testing and to decyl glucoside more than to chlorexidine when patch tested to the product ingredients provided by the manufacturer.[21] Gijbels et al. described a case of contact dermatitis to deodorant wipes containing an unspecified mixture of alkyl glucosides. The dermatitis involved the ears, face and inguinal folds and patch tests were positive for coco glucoside and decyl glucoside.[12]

North American Contact Dermatitis Group (NACDG)

In 2009, decyl glucoside 5% in petrolatum was introduced in the NACDG standard series. The results of the 14 members of the group are compiled, tabulated and published after each cycle of 2 years. During the period 2009-10 patch testing with decyl glucoside was positive in 1.5% of 4302 patients thus tested, with a global relevance rate of 83.3% and 34.8% if only cases of definite and probable relevance are considered.

[25] The rate of positive reactions between 2011 and 2012 was established at 1.56% (66 positive cases out of 4231 tested patients) and around 50% of cases were considered relevant (4.5% definite, 15.2% probable and 27.3% possible).[28] During the 2013 to 2014 cycle, 4859 patients were tested, of which 88 (1.7%) had positive reactions to decyl glucoside.[29] The rate of global relevance was 88.3% (5.9% definite, 27.1% probable and 55.3% possible). There is therefore a slight but steady increase in the number of positive reactions detected over the years.

McGill University Health Centre database

The NACDG standard series is used at the McGill University Health Centre. Between January 2009 and June 2016, 3095 patients were patch tested. A total of 20 (0.65%) patients were found to be sensitized to decyl glucoside. During the same period, among the 3095 patch tested patients, 1628 were also tested to lauryl glucoside in a comprehensive cosmetics & vehicles series. A total of 15 (0.92%) of the latter patients gave a positive reaction to lauryl glucoside, 6 of whom were also allergic to decyl glucoside. Interestingly, 9 patients reacted to lauryl glucoside alone. Patient's demographics and results of testing appear in Table 2 and Table 3. The positivity rate was low in the first years, but has steadily increased between 2014-2016, when patch testing was positive in 1.37% of 437 patients in 2014, 1.47% of 409 patients in 2015 and 2.2% of 227 patients tested in the first six months of 2016. Most of the patients thus far detected were women (73%) with an atopic background (86%). The average age of the patients was 47.7 years (median 47 years), and the dermatitis most commonly affected the hands and the face, in accordance with previous reports. Only one case could be attributed to an occupational exposure.

Groupe d'Etudes et de Recherches en Dermato-Allergologie (GERDA)

Between 2005 and 2007, decyl glucoside 2% in water, provided by the manufacturer of a sunscreen that contained Tinosorb® M, was added to the patch testing battery used by the members of the group in France, Belgium and Switzerland, and gave positive reactions in 0.5% of tested patients. It was rapidly replaced in 2008 by lauryl glucoside 5% in vaseline, which is more easily obtained from suppliers of patch testing allergens. Since 2012, the positivity rate for lauryl glucoside has always been above1.5% (2% in 2012, 1.59% in 2013 and 2.59% in 2014).[30] These numbers were deemed considerable by the members of the GERDA. They concluded that this alkyl glucoside should remain in the baseline patch testing series, as it is a common emerging allergen.

At a recent meeting of the GERDA, Dr. Marie-Christine Ferrier-Le Bouedec presented the following case: A 32-year-old nurse aide with a background of atopic dermatitis, asthma and allergic rhinitis was seen in 2014 with a chronic dermatitis unresponsive to topical corticosteroids. The lesions involved the fingers, the dorsum and the palm of both hands, with extension to the forearms. She was patch tested in June 2015 with the European baseline series supplemented with a preservative series, her own topical products, nitrile gloves and products from the workplace. At the 72-hour reading, the only relevant positive reaction (2+) was to a hand cold cream that the patient had been using on a daily basis for a number of months. Her lesions cleared when she stopped using this moisturizer.

In December 2015, additional patch tests were conducted with the 17 ingredients of the cold cream, with 2+ reactions at 48 and 96 hours to a single compound called Glucolipide, tested at a concentration of 3% (Fig. 2). It is a mixture of arachidyl alcohol 55%, arachidyl glucoside 15% and behenyl alcohol 30%. Further tests at concentrations of 1% and 3% of a mixture of arachidyl alcohol and behenyl alcohol, as well as behenyl alcohol alone, were negative, suggesting that arachidyl glucoside was the actual sensitizer. The patient did not react to lauryl glucoside 5% nor to decyl glucoside 5%. Semi-open tests with shampoos containing coco-glucoside were negative, and also a test under occlusion with a cream containing xylityl glucoside. However, 2+ reactions were elicited with creams containing cetearyl glucoside and octyldodecylxyloside (Fig. 3). The ingredients of the latter products were not tested separately, but the pattern of reactivity again suggests that glucosides and xyloside are the culprits that cross-react with arachidyl glucoside.

Glucolipide (trade name Montanov™ 202, SEPPIC, Puteaux, France) is an emulsifier of vegetal origin, synthesized from rapeseed fatty alcohols and wheat glucose. Arachidyl glucoside (CAS 100231-68-3) is produced during the manufacturing process and is not available as a separate ingredient. Despite its ominous name, it is not derived from peanuts (*Arachis hypogaea*). It can be found in shampoos, conditioners, creams and sunscreens. We included Dr. Ferrier-Lebouedec's case in our published review article on allergic contact dermatitis to alkyl glucosides, and we believe that this case may be the first report of allergic contact dermatitis to arachidyl glucoside.

ID. Discussion and Conclusion

Screening and patch testing

Leave-on products can be tested undiluted under occlusion, while undiluted rinse-off products should be tested with the semi-open technique. Comprehensive baseline and cosmetic series should be used. It is essential to obtain from the manufacturer and to test the individual ingredients of any product that causes an allergic patch test reaction.

The optimal patch test concentration for the detection of allergy to glucosides is still not established. As of this writing, two major suppliers (AllergEAZE, SmartPractice, Phoenix, USA and Chemotechnique Diagnostics, Vellinge, Sweden) commercialize decyl glucoside at a concentration of 5% in petrolatum, but many cosmetic series have not yet introduced it or other alkyl glucosides. The molecule most frequently used for patch testing is lauryl glycoside 3% in petrolatum because it has been commercialized for a longer period of time. Lauryl glycoside seems to be a good marker of sensitization to the alkyl glucoside family but cases may be missed because it does not automatically cross react with other alkyl glucosides. Patients who react to Tinosorb® M should be tested to decyl glucoside as recommended by the NACDG and other authors of relevant case reports.

Cross-reactions

Reactions to multiple structurally related alkyl glucosides appear to be frequent, but not systematic, among patch tested patient, and are seen mainly between decyl glucoside, lauryl glucoside, coco glucoside and cetearyl glucoside. Thus, sensitization seems to be a group allergy with possible cross-reactivity, probably related to the similar structure of glucosides. It is well known, however, that the industrial manufacturing process results in blends of different alkyl glucosides[22] and patch test reactions to different glucosides may therefore represent concomitant reactions. A recent study, which aimed to identify possible allergenic impurities in commercial samples of alkyl glucosides, found that isobornyl acrylate (Fig. 4) may possibly be a cause of sensitization to many alkyl glucosides, but this finding needs confirmation by further patch tests in patients sensitized to alkyl glucosides.[7] Isobornyl acrylate is used as plasticizer in various plastic materials and could be leached out of the container by the surfactant properties of alkyl glucosides. The presence of isobornyl acrylate was not verified in the Glucolipide mixture that sensitized the arachidyl-allergic patient, but the manufacturer of the cold cream receives it from his supplier in polyethylene bags that likely do not contain this plasticizer.

Wilkinson and Powis published a case of allergic contact dermatitis to octyldodecyl xyloside, a constituent of a cosmetic serum. This new allergen is closely related to alkyl glucosides. Structurally, xylose replaces glucose and the aglycone moiety is an alcohol with a double side chain of 12 and 8 carbons instead of the fatty alcohol single side chain in alkyl glucosides.[31] No patch test was done to verify concomitant sensitization to alkyl glucosides. Interestingly, our patient displayed a strong positive patch test reaction to a cream containing this newer surfactant.

Blondeel raised the hypothesis of potential cross reactivity between decyl glucoside and methyl glucose dioleate. He described a patient sensitized to decyl glucoside in a sunscreen who also reacted to Nizoral shampoo, which contains methyl glucose dioleate.[2] Unfortunately, the patient refused further patch testing to identify the culprit sensitizer.

Conclusion

Alkyl glucosides are stable molecules made by condensation of glucose and a fatty alcohol. Their range of usage is limited to cosmetic and cleansing materials. Decyl glucoside was also recently introduced as a stabilizer in the sunscreen agent Tinosorb® M. Given the increasing number of publications, it seems that the sensitizing potential of alkyl glucosides is important and higher than expected. It may be underestimated because of the absence of systematic patch testing in many cosmetic series. Alkyl glucosides should be included in all patch test cosmetic series and, more specifically, decyl glucoside should be tested if allergy to Tinosorb® M is suspected. Because they do not automatically cross-react, it is recommended to test multiple alkyl glucosides to increase the rate of detection. Avoidance of all cosmetic products containing alkyl glucosides and sunscreens containing Tinosorb® M is recommended in sensitized patients, as cross-reactions are common among tested patients.

IE. Tables and figures

Author, year	Age and gender	Clinical picture	Exposure	History	Work-related	Patch test concentrations and reactions
Goossens, 2003 Belgium	55-year old male	Recurrent papular and erythemato-squamous lesions on the face, neck, forearms, wrists and dorsa of the hands.	Shampoo and shower gel (rinse-off)	No atopy	Yes	Lauryl glucoside 53% aq semi-open test (+++), 5%, 10% pet (++) and 12% aqua (++) Coco-glucoside 35% aq, 5%, 10% pet (++)
Goossens, 2003 Belgium	46-year old female	Severe erythema, scaling and fissuring on both hands, accompanied by paronychia	Antiseptic body lotion (leave-on)	Atopic eczema	No	Lauryl glucoside 5% pet. (++) Coco-glucoside 5% pet. (+)
Le Coz, 2003 France	29-year old female	Acute eczema at site of umbilical piercing	Chlorhexidine digluconate antiseptic gel (leave-on)	No atopy	No	Decyl glucoside 0.55% aq (++) Chlorhexidine (-)
Blondeel, 2003 Belgium	53- year old female	Aggravation of atopic eczema on UV-exposed skin and scalp	Sunscreen (leave-on)	Atopic eczema	No	Decyl glucoside 5%, 10% aq (++) Possibe reaction, but not tested: Methylglucose dioleate
Blondeel, 2003 Belgium	52- year old female	Eczematous lesions on scalp and trunk	Shampoo (Rinse-off)	Occupational hand dermatitis	No	Decyl glucoside 10% aq. (++)
Blondeel, 2003 Belgium	Young female	Eczematous lesions on hands	Shampoo (Rinse-off)	Hand eczema	No	Lauryl glucoside 5% pet (+) Coco-glucoside 5% pet (+) Decyl glucoside 5% pet (+)
Blondeel, 2003 Belgium	16-year old female	Painful fissuring on the fingers	Shampoo and hair dye (Rinse-off)	Occupational irritation	Yes	Lauryl glucoside 5% pet (+) Coco-glucoside 5% pet (++) Decyl glucoside 10% pet (+) Cetearyl glucoside 5% pet (++)
Giordano-Labadie, 2005 France	36- year old female	Pruritic erythematous and edematous eruption on face	Sunscreen spray (leave-on)	No atopy	No	Tinosorb® M (++) Decyl glucoside 5% (-), 10% pet (+)
Horn, 2005 UK	25- year old female	Eczematous lesions on upper chest, arms, neck, face, and scalp	Hair mousse (leave-on)	No atopy	No	Decyl glucoside 2% aq (++)
Conzalez-Pérez, 2007, Spain	54- year old female	Persistent facial dermatitis involving forehead and cheeks	Sunscreen (Avene 20) (Leave-on)	Not mentioned	No	"MBBT" (not pure) 2% pet (?)

Andersen, 2006 Denmark	67-year-old male	Sudden exacerbation of widespread vesicular dermatitis related to sun exposure on trunk and extremities	Sunscreen (leave-on)	Atopic eczema	No	Tinosorb® M 6% aq (++) Decyl glucoside 0.5-5% aq (+) Coco-glucoside 2% aq (positive, strength of reaction not mentioned)
Krehic, 2009 France	86-year old female	Acute eczema affecting the sub-mammary area and lateral sides of the neck	Chlorhexidine digluconate antiseptic lotion (leave-on)	No atopy or eczema	No	Decyl glucoside 1% pet (++), 3% pet (+++) Chlorexidine digluconate 0.5% aq (++) Lauryl glucoside (+++)
Krehic, 2009 France	80-year-old male	Acute lower leg eczema	Chlorhexidine digluconate antiseptic lotion (leave-on)	No atopy or eczema	No	Decyl glucoside 1%pet (++), 3% pet (+++) Chlorexidine digluconate 0.5% aq (+/?) Lauryl glucoside (++)
Andrade, 2010 Portugal	66 year-old male	Pruritic erythematous eruption on face and neck	Sunscreen (Avène) (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (++) Decyl glucoside 5% pet (++) No further aggravation after UV
O'Connell, 2011 UK	75-year-old male	Eczematous eruption, site undisclosed	Sunscreen (leave-on)	No atopy or eczema	No	Tinosorb® M 10% pet (+) Lauryl glucoside (-)
O'Connell, 2011 UK	85-year-old female	Eczematous lesions largely distributed on the face, neck, arms.	Sunscreen (leave-on)	Not mentioned	No	Lauryl glucoside 3% pet (+) Tinosorb® M 10% pet (+)
Pereira, 2013 Portugal	66-year-old male	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (++) Decyl glucoside 5% pet (++)
Pereira, 2013 Portugal	52-year-old female	Eczematous lesions on eyelids and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (+) Lauryl glucoside 3% pet (+)
Pereira, 2013 Portugal	64-year-old female	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (+) Lauryl glucoside 3% pet (+)
Pereira, 2013 Portugal	64- year old male	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (++) Lauryl glucoside 3% (+++)
Pereira, 2013 Portugal	39;- year old female	Eczematous lesions on eyelids	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 10% pet (++) Lauryl glucoside 3% pet (+++)

Gijbels, 2014 Belgium	24 females and 6 males aged 7-77 years	Eczematous lesions depend on the product; hands are affected with soaps while scalp and sometimes face, back, chest, and shoulders are affected with shampoos	Shampoos (12/30), skin cleansers (12/30) (rinse-off), sunscreens (5/30), skin-care (4/30), and deodorant (1/30) (leave-on)	15/30 had history of atopy	Yes in 4/30	One or more alkyl glucosides (cetearyl, coco-, decyl, and lauryl glucoside) 26/30 were polysensitized
de Groot, 2014 Netherlands	56- year old female	Itchy, red and burning eruption on face and neck	Sunscreen (leave-on)	Not mentioned	No	Tinosorb® M 8.1% aq (+)
Liuti, 2015 Spain	83-year old male	Severe eczematous patches on forehead, cheeks and upper chest	Sunscreen (leave-on)	Actinic keratoses	No	Decyl glucoside 1%, 3%, 5%, 10% pet & aq (positive, strength not specified) Tinosorb® M 10% pet (+) Lauryl glucoside 3% pet (++) "MBBT" EPE series (+) *(not pure MBBT)* Pure MBBT 10% pet. (-)

Table 1: Summary of reported cases of glucoside-induced allergic contact dermatitis

No	Sex	Age	Atopy	Site	Source	Polysen-sitized	Decyl glucoside		Lauryl glucoside	
							48 hrs	96 hrs	48 hrs	96 hrs
1	F	49	E, A, R	Face	Face cream	Yes	+	+	+	+
2	F	66	R	Face, eyelids	Facial cosmetics	Yes	0	++	0	+
3	F	71	R	Generalized	Moisturizers	Yes	+	+	+	+
4	M	42	E, R	Face, arms, axillae	Deodorants, shaving cream	Yes	?	+	NT	NT
5	M	50	E, R	Hands	Moisturizers	Yes	+	++	NT	NT
6	F	47	E, R	Hands	Hand creams	Yes	?	+	0	0
7	M	20	E, A, R	Face, eyelids	Face cream	Yes	0	+	0	+
8	F	37	E	Face	Facial cosmetics	Yes	0	+	0	0
9	F	51	E, R	Hands	Hand creams	Yes	+	+	0	+
10	F	45	E, A, R	Hands, generalized	Hand creams, moisturizers	Yes	?	+	0	0
11	F	35	E, R	Generalized	Moisturizers	Yes	0	+	0	0
12	M	16	E	Sun exposed	Sunscreens	Yes	0	++	NT	NT
13	M	29	E	Hands	Hand creams	No	+	+	NT	NT
14	F	42	A, R	Face, eyelids	Facial cosmetics	Yes	0	+	0	0
15	F	32	A	Hands	Hand creams	Yes	+	+	+	+
16	F	41	E, R	Face, trunk, arms	Moisturizers, sunscreens	No	+	+	0	0
17	F	62	E. A, R	Perianal, face, neck	Wet wipes, moisturizers	Yes	0	+	0	0
18	F	52	None	Face	Facial cleansers	No	0	+	0	0
19	M	51	R	Hands	Moisturizers	Yes	?	+	0	0
20	F	41	E, A, R	Face, arms	Moistrurizers, shampoos	Yes	0	+	0	0
21	M	43	R	Scalp, abdomen, knees	Shampoos, moisturizers	Yes	0	0	0	+
22	F	35	A	Scalp, face	Hair dye	Yes	0	0	0	++
23	F	60	None	Scalp, face, neck	Hair dye	Yes	0	0	0	+
24	F	82	None	Leg ulcer	Moisturizers	Yes	0	0	0	+
25	F	65	E	Generalized	Moisturizers	Yes	0	0	?	+
26	F	45	E	Hands	Hand creams	Yes	0	0	0	+
27	F	54	E, A, R	Chest, arms	Moisturizers	Yes	0	0	?	+
28	M	72	None	Leg ulcer	Moisturizers	Yes	0	0	+	+
29	F	49	E	Neck	Moisturizers	Yes	0	0	+	+

F: Female, M: Male, E: Eczema, A: Asthma, R: Rhinitis, NT: Not tested

Table 2. Characteristics of MUHC patients with positive reactions to glucosides

Characteristics	All cases (n=29) Tested to Decyl glucoside (3095) Tested to Lauryl glucoside (1628)
Age, mean	47.7
Sex, n (%) Female Male	 21 **(72,4%)** 8 (27,6%)
Clinical presentation, n (%) Face, scalp, neck or sun exposed Legs ulcer Hand dermatitis Generalized dermatitis Trunk (abdomen, proximal extremities)	 15 **(51,7%)** 2 (6,9%) 7 (24,1%) 4 (13,8%) 4 (13,8%)
Atopy, n (%) (Rhinitis, Eczema or Asthma)	25 **(86,2%)**
Type of product Rinse-off (shampoos, soap) Shampoos Soap and skin cleanser Shaving cream Leave-on Moisturizers Hand creams Sunscreen Deodorants Facial cosmetics and cream Wet wipes Hair dye	 2 1 1 **13** 6 2 1 4 1 2
Positivity rate Decyl glucoside Lauryl glucoside Both (cross reactivity)	 20/3095 (0.64%) 15/1628 (0.92%) 5/29 (17.2%)

Comment: All the 29 cases were patch tested to decyl glucoside but 25 were tested simultaneously to lauryl glucoside.

Table 3. Clinical and demographic characteristics of MUCH patients with positive reaction to glucosides.

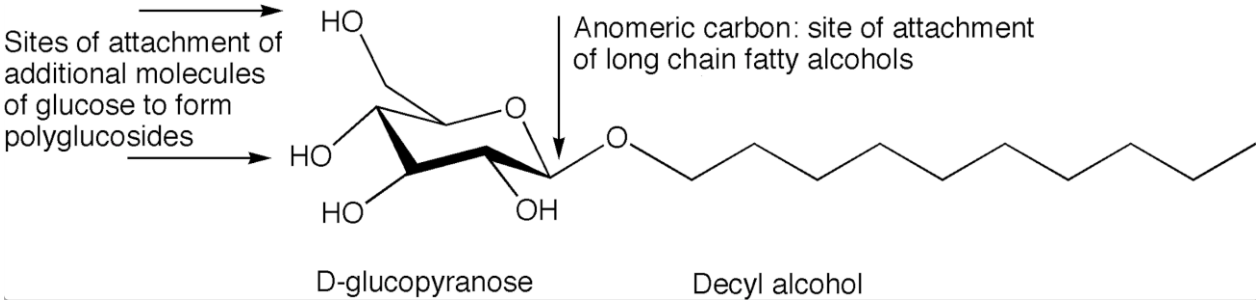

Figure 1. Chemical structure of decyl glucoside.

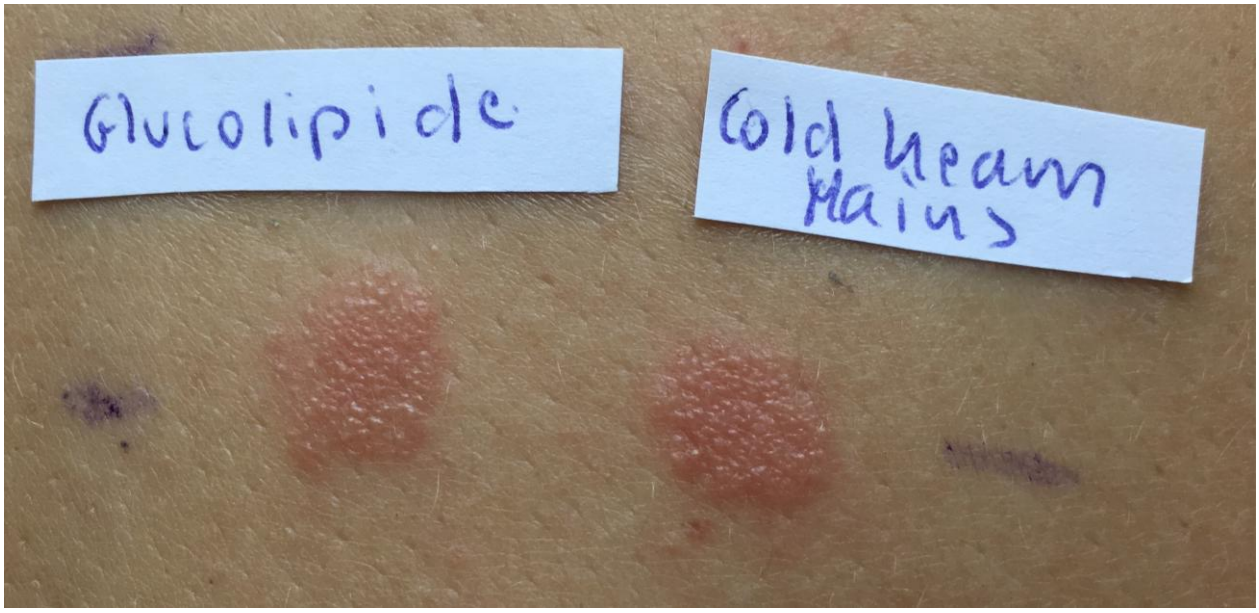

Figure 2. Positive patch test to glucolipide and cold hand cream

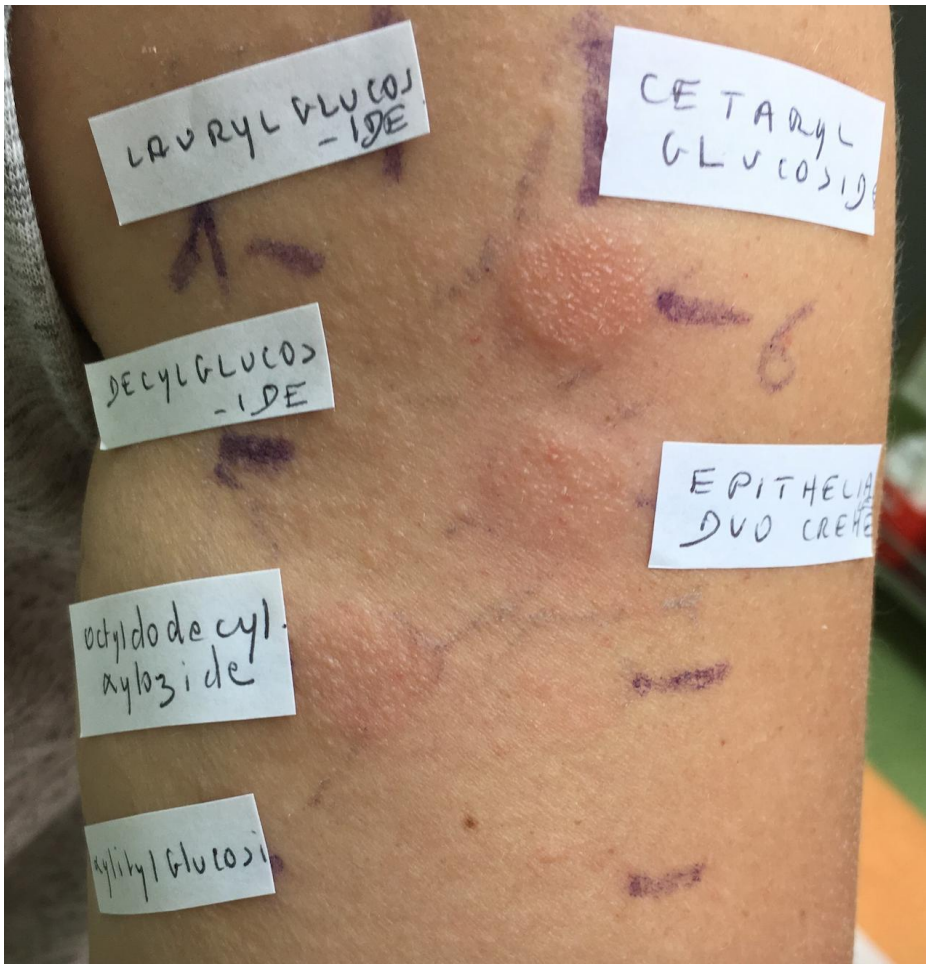

Figure 3. Repeat patch test with positive reaction to various glucosides.

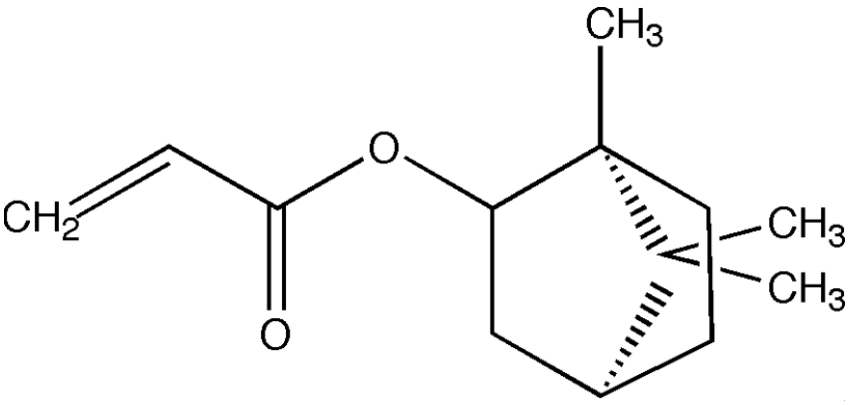

Figure 4. Chemical structure of isobornyl acrylate.

Chapter 2: Contact dermatitis in Bombardier Aircraft Industry

A modified, shorter version of this paper has been submitted to Dermatitis.

2A. Introduction

In the 1980s and 1990s, European and American authors have studied occupational contact dermatitis in the aircraft industry. These publications have reported cutaneous sensitization of workers to different products. Castelain et al. described fingertip and subungual dermatitis as a highly characteristic clinical presentation of allergic contact dermatitis in aircraft factory workers sensitized to resins and sealants.[32] They also observed a longitudinal reduction in the number of cases of allergic contact dermatitis between the years 1955-1965 and 1980-1991 due to improvements in occupational hygiene and the generalized use of numerically-controlled machine tools. In 1999, Hackett reported that the most frequent positive patch test among aircraft workers was to epoxy resins.[33] These thermosetting polymers are commonly found in modern aircraft-building materials such as reinforced fabrics pre-impregnated with a resin system ("prepregs"), surface coatings and sealants. In Hackett's study, the principal source of epoxy-related allergic contact dermatitis was presumed to be sealants and prepregs. However, patients were not always tested with their own workplace materials to prove the association.[33]

In the last 25 years, the contact dermatitis clinic of the McGill University Health Centre has evaluated and patch tested more than three hundred workers from Bombardier Aerospace plants located around the Montreal area. This report provides the first study documenting occupational contact dermatitis in the Canadian aircraft

industry. Affected workers were patch tested with commercially available standard as well as glues and adhesives series. Unique additional information was derived from the use of tailor-made series composed of workplace products. The aim of this study was to define the patterns of occupational dermatitis in each category of workers, broaden knowledge about contact allergens in the modern aircraft industry, observe changes and progression of epidemiological data over years, and ultimately compare results with European and American studies done in the field.

Background

Bombardier is a Canadian industrial leader in aviation and rail transportation. Its entry into the aerospace market took place in 1986 after the acquisition of Canadair (Montreal). The purchases of Irish Short Brothers plc (Belfast) in 1989, American Learjet Corporation (Wichita) in 1990, and Canadian de Havilland (Toronto) in 1992 solidified its position. Through the years, Bombardier Aerospace has been constantly growing with a focus on developing high-performance aircrafts.

Bombardier designs and builds a wide variety of planes including business and commercial turboprop and jet aircraft, as well as amphibious water bombers, among others. Its main production consists of business and regional jet (RJ) airplanes, a niche where it holds the world's number one position. Its Montreal factories exclusively produced 50-70-seat turbojet planes until a few years ago. A new 110-160-seater aircraft is now in production.

The events of September 11, 2001 in the USA, a decrease in market activity, and later a worldwide slumping economy, have all negatively affected the production of aircraft, leading to repeated lay-offs in the industry. In the three factories operated by Bombardier Aerospace in the Montreal area, the total number of workers has recently decreased by half, from 15 000 to 7000.

Worker distribution and task description

From design and engineering to delivery to customers, building of modern airplanes involves multiple complex steps and requires the expertise of a wide array of suppliers, subcontractors and on-site professionals including machinists and metalworkers, assemblers and sealers, composite material technicians, electricians and electronics specialists, painters, jet engine mechanics, surface preparers, cabinet-makers and upholsterers.

With respect to the manufacture or aircraft, absolute precision required for handling and assembling parts, as well as the complexity of the mechanical, hydraulic and electronic systems, all limit the potential for automation of the corresponding industrial processes. Most of the work is done by hand with traditional techniques for cutting, molding, drilling and painting. Being directly exposed to multiple potentially sensitizing and irritating products at each level of assembly, workers are at high risk of developing occupational contact dermatitis.

Machinists and metalworkers work on the fabrication of metallic parts and are exposed to direct skin contact and aerosolized mists of petroleum-based or water-miscible cutting oils, solvents, degreasers, anticorrosive agents, aluminum and steel.

Assemblers and sealers are in charge of putting together the different parts of the plane. The wings containing the fuel tanks and the pressurized cabin need to be perfectly sealed. Sealants are applied to jointed surfaces and to each rivet, either by hand with a brush or from air-driven applicator guns (Fig. 1), and then smoothed evenly with a spatula and sometimes with bare fingers (Fig. 2). Solvents are used to clean surfaces, tools and hands. Assemblers are exposed to metallic parts that have been coated with chromate-containing primer paints, and they often must repair small dents or defects with resin-based putties.

Composite materials that are lightweight and resistant to chemical, mechanical or thermal stress are now used extensively in aircraft manufacturing. They are easy to mold into complex shapes such as nose cones, tail ends and winglets of aircraft. Beginning in the “clean room”, where temperature and humidity are strictly controlled, large sheets of prepregs are machine-cut to the exact shape of the part to be molded (Fig. 3). Composite material technicians then apply this resin-impregnated stratified material to a ”tool’ or cast. They sometimes have to heat the prepreg with a blow-drier in order to make it stick to the mold. The mold and its attached prepreg are then sealed in an airtight plastic bag to which a vacuum is applied to ensure complete adherence of the resin-based material to the mold and exclusion of residual air bubbles. The part is then placed in a large autoclave, where hardening takes place at various temperatures

depending on the material used and the desired characteristics of the finished product. Once curing is complete, parts are taken out of their protective plastic sheeting – this process is called “debagging” - and are then ready for finishing by deburring, drilling and sanding. Handling of the materials prior to hardening puts technicians at risk of direct or airborne contact dermatitis, particularly when heating prepregs with a blow dryer. Hardened parts are theoretically non-allergenic, but drilling and sanding operations create heat that depolymerizes the resin and generate a shower of irritant or allergenic particles.

Surface preparers are exposed to a large number of solvents and cleaning products over a wide range of pH. Interior finishers handle and transform plastics, adhesives, varnishes, fabrics, leather, rubber and exotic woods, again with potential risk of occupational dermatitis. Electricians, electronic systems specialists and jet engine mechanics are affected less often, while painters are usually well protected by their impermeable suits and airline respirators.

Composition of products

Workers at each level of airplane construction handle a wide variety of potentially allergenic and irritant chemicals and metals. Since the early 2000s, modern low weight and highly resistant composite materials have been increasingly introduced in the aeronautical industry to improve the performance of planes by reducing weight and enhancing fuel efficiency.

Metals

Aluminum and steel are the main structural metals composing the frame of the aircraft. Metalworkers and machinists who handle them may become sensitized to nickel and cobalt, and very rarely to aluminum. Dust and particles can cause mechanical irritation.

Solvents and degreasers

Formerly used toxic solvents such as 1,1,1-trichloroethane (chlorothene), methylene chloride and xylene have been phased out and replaced with safer products based on D-limonene, or with DS-108, a mixture of naphtha, propoxypropanol and ethylhydroxypropionate. Acetone and methyl ethyl ketone are still in use. Furthermore, many of the resins and coating products used in the aircraft industry contain small amounts of xylene or toluene.

Anticorrosion agents

Metal parts must be protected from corrosion. Parts made of aluminum and other non-ferrous alloys are dipped in Alodine®. This clear liquid is based on chromic acid and acts as a protective film that, in addition to its anticorrosion properties, increases the adherence of paints on the treated parts. Mastinox 6856K is a corrosion inhibitor that contains strontium and barium chromates, therefore also based on the same hexavalent chromium conversion coating reaction as Alodine®. The green primer used as an undercoat on most metallic surfaces is another corrosion inhibitor that contains strontium chromate and cobalt phosphate.

Cutting oils

Machining metal on a lathe or by extrusion generates high temperatures that can damage the parts or the tool. This heat must be dissipated with a cooling fluid. Pure petroleum products, or “neat oils” were formerly used for that purpose, but are nowadays replaced by “severely hydrotreated” petroleum distillates that are miscible in water. To prevent microbial degradation, they commonly contain biocides that include formaldehyde releasers, particularly hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine (Grotan® BK), or iodopropynyl butylcarbamate and isothiazolinones such as methylchloroisothiazolinone (MCIT), methylisothiazolinone (MIT), 1,2-benzisothizolin-3-one (BIT) and 2-n-octyl-4-isothiazolin-3-one (OIT).

Sealants and coatings

Certain sealants are applied on every surface of the plane and are required for sealing fuel tanks and pressurized cabins. They are composed of a polysulfide polymer, manganese dioxide and terphenyl (PPG Aerospace Pro-Seal 870-B2 and PR-1750-B2, Flamemaster CS 5500) or a mixture of polysulfide and epoxy resins (PPG Aerospace PR-1422). Accelerators contain magnesium, calcium or barium chromates.

Other sealants are applied on rivets to increase resistance and prevent premature wearing. The sealants used in aeronautic industry are standard epoxy resins such as diglycidyl ether of bisphenol A and bisphenol F (DGEBA and DGEBF), as found in the paste adhesive Henkel Loctite Hysol EA-9309.3-NA used to bond aluminum and honeycomb core structural material. Other coatings and putties contain epoxy derivatives, modified by bromination (Huntsman Epocast 8623) or based on 4-glycidyloxy-N,N’-diglycidylaniline (GDOGA), also known as triglycidyl-p-aminophenol

(TGPAP), which confer more mechanical resistance to the polymer than bisphenol-A diglycidyl ether (Henkel Loctite Hysol EA-934-NA “liquid shim” among others). Some products are mixes of modified epoxys with phenolic (Novolac) resins, such as Henkel Loctite Hysol EA-956 or EA-934-NA**.** Accelerators are conventional aliphatic amines such as diethylenetriamine (DETA), triethylentetramine (TETA) or polyoxypropylene diamine. The two parts are now pre-mixed in a cartridge and kept refrigerated to prevent premature polymerization.

Pre-impregnated stratified materials (Prepregs)

These composite materials are composed of a flexible support of graphite, Kevlar®, fiberglass, carbon or aluminum, which is pre-impregnated with a semi-solid resin. Rolls of prepregs are conserved in a cold room to avoid polymerization of the resin. Both surfaces of the stratified materials are isolated with a thin plastic layer that will be removed before use. The composition of the resin is not fully known because manufacturers protect it as a trade secret. The pioneering work of Burrows[34] and Mathias[35] first identified the main sensitizers in prepregs, later confirmed in the Bruze study.[36] Subsequently, Kanerva was able to report quantitative data on the content of prepregs after using gas and liquid chromatographic methods.[37] The known ingredients are tetrabromobisphenol-A diglycidyl ether (Br-DGEBA), tetra-4,4’-methylenediamine (TGMDA), triglycidyl-para-aminophenol (TGPAP) as well as proprietary epoxy-phenolic resins.

2B. Methods

Systematic review of literature

We conducted a complete systematic review of the literature on occupational contact dermatitis in the aerospace industry using the PubMed database.[32-41] We looked for epidemiological data on work-related allergens, incidence of occupational irritant and allergic contact dermatitis in the aerospace industry, patch-testing methods and characteristics of sensitized patients from previous studies done around the world. We also examined the methods of data collection used by other studies of interest, sample size, patch test series used, etc.

Data collection and analysis

Our study was a retrospective study of occupational contact dermatitis in workers from Bombardier Aerospace in the greater Montreal area. The study covered a 25-year period from September 1990 to December 2015. Each patient was initially referred by the company health and security personnel, and subsequently questioned and examined at the McGill University Health Centre contact dermatitis clinic during a preliminary visit. Demographic characteristics including age, personal or family history of atopy, description of work, years of employment and a detailed description of dermatitis were recorded. Patch testing was performed during three subsequent visits over a 5-day period. Readings were done at day (D)2 and D4. After obtaining informed consent, each patient was patch tested with a the North American standard series (Chemotechnique Diagnostics, Vellinge, Sweden) for patient seen between 1990 and 2000, with the North American Contact Dermatitis Group (NACDG) standard series (Chemotechnique Diagnostics) for patient seen from 2000 to 2010, or with the NACDG standard series

from AllergEAZE (SmartPractice, Calgary, Canada), for all subsequent patients. Haptens were applied using finn Chambers (SmartPractice, Phoenix, AZ, USA). The Glues and adhesives series (Chemotechnique Diagnostics) was applied using IQ-ultra chambers (Chemotechnique Diagnostics). Most workers were also tested with their own workplace material, namely a personalized “Bombardier series” (Table 1) composed of 15 modified epoxy, polysulfide and phenolic resins tested on IQ-ultra chambers, and a composite materials series comprising ten 1x1 cm squares of various undiluted prepregs (Table 2) applied under Scanpor® tape (Norgesplaster AS, Vennesla, Norway). Patch test results and demographic information extracted from the clinic database were organized and compiled in an Excel spreadsheet. Identified allergens were ascribed to the following categories: standard series, glues series, Bombardier series, prepregs series, and others. Beginning in 1993, all workers referred for assessment of occupational contact dermatitis were tested with the standard, glues and Bombardier series. In addition, as of the year 2000, composite materials technicians were also tested with the customized prepregs series.

During the study period, at the request of the employer, investigators and additional members of the contact dermatitis clinic team visited the main Bombardier Aerospace plants to: a) observe the high-risk tasks and identify potentially hazardous materials, b) train the health and safety personnel in recognizing and preventing occupational contact dermatitis, and c) shoot a video to emphasize to the workforce the proper use of personal protective equipment.

2C. Results

Demographics

The present study extends over a 25-year period, during which 305 affected workers were evaluated. One patient was excluded because he did not book a follow up appointment for his patch test. Eight patients were seen for a second patch test between 8 months and 3 years after the first session. The first case of occupational dermatitis in the aircraft industry was seen at the MUHC contact dermatitis clinic in 1990, four years after Bombardier acquired Canadair and began production of the Canadair 450 water bomber and the commercial CRJ regional jet.

Before 1999, the number of patients was relatively low and constant with an average of three patients per year. In 1999, after Bombardier launched the Bombardier Continental business jet, later renamed Challenger 300, the number of cases started to increase dramatically to reach a peak in 2001 with 45 patients. (Fig. 4). By 2002, Bombardier Aerospace was producing a complete range of commercial airplanes with its CRJ series, plus business jets with its Global Express, Learjet 40 and 45XR aircraft. In 2005, the number of cases began to decrease and is now stable with approximately 5 to 10 cases per year.

The age distribution of workers affected with occupational dermatoses ranged from 19 to 64 years with a mean age of 37 years at the time of patch testing. The mean age of those patients diagnosed with allergic contact dermatitis is similar at 36 years. Seventy-three percent of workers referred for patch testing were males, paralleling the sex representation of workers at Bombardier Aerospace (Table 3). However, among

patch tested female workers, 58% had a final diagnosis of allergic contact dermatitis compared to 47% of males. Atopy, defined as a personal history of eczema, asthma or allergic rhinitis, was found in 30% of the cases. By comparison, during the peak years 2000 to 2002, atopy was present in 47% of all other patients tested in our clinic.

The time of onset of work-related dermatoses varied greatly among patients, from less than one year to more than 25 years after the beginning of employment. However, among patients with ACD, 49% developed sensitization within the first 3 years of employment (Table 4). This was especially true in the late 1990s and early 2000s when there was massive hiring of younger, inexperienced workers.

Analysis of the distribution of cases between specific categories of workers revealed that more than 50% of those referred for evaluation were assemblers or sealers, around 25% were composite material technicians, 5% were machinists and the remaining 20% were other professionals such as painters, electricians, cabinet makers, etc. The composite material technicians represents the group with the highest proportion of allergic contact dermatitis (79%) while machinist and other types of workers had the lowest rate (20%) (Fig. 5). Machinists and other workers such as painters, electricians and cabinetmakers demonstrated a higher incidence of ICD (60% and 50%) while the incidence was lowest for composite material technicians (17%). In our cohort of patients, the overall prevalence of ACD (51%) was higher than ICD (32%).

Clinical presentation

Not surprisingly, the hands were involved in the majority of cases. A fissured and scaly dermatitis affecting the tip of the first three fingers was commonly seen in sensitized workers (Fig. 6). Involvement of the dorsal hand was occasionally found in composite materials technicians who smooth out prepregs over molds with the back of their bare hands. The second most common site of involvement was the inner forearms of assemblers and sealers who often worked in short sleeves without protective equipment. The face and other exposed areas were commonly affected from airborne exposure or secondary contact by contaminated hands.

Fourteen workers were referred to our clinic because of repeated episodes of transient widespread, pruritic erythema and wheals that would fade within minutes to hours. Most of these workers claimed that these lesions would only occur while they were at work. None of the patients had lesions at the time of examination, but photos taken by some of them clearly showed urticaria. These patients were given a presumptive diagnosis of contact urticaria even though in some cases the lesions did not always first appear on exposed areas.

Patch test results

Overall, after patch testing, 152 patients (50%) were found sensitized to their workplace products (Table 4). Ninety-six workers (32%) were diagnosed with occupational irritant contact dermatitis and 56 (18%) with another type of dermatitis. Among those, 14 (4.5%) suffered from occupational urticaria, while 42 (13.5%) had non-occupational allergic contact dermatitis, atopic dermatitis, seborrheic dermatitis or

asteatotic and dyshidrotic eczemas. Allergy was more common than irritation due to the strong sensitizing potential of epoxy resins and polysulfide or phenolic resins in sealants and stratified materials. The distribution of the dermatitis was consistent with an airborne pattern in approximately 38% of allergic contact dermatitis patients and in 18 % of those diagnosed with irritant contact dermatitis.

Among the 152 workers with occupational sensitization, 54 (33.5%) had positive reactions to DGEBA epoxy resin from the standard series, 9 reacted to phenyl or cresyl glycidyl ether, 6 to DGEBF epoxy resin and 3 to cycloaliphatic epoxy. As mentioned above, resins used in the aeronautic industry are not always derived from DGEBA.

Polysulfide- (Thiokol), phenolic- and modified epoxy resin-based sealants and putties like Pro-Seal 870, PR-1422 and EA-934-NA were responsible for positive reactions in 87 (57.2%) of subjects. However, only 43 (28.3%) of those workers also reacted to epoxy resins present in the commercially available standard and glues series. Given that the individual ingredients of these products were not separately tested, the specific allergens for those patients who reacted only to workplace products still remain undetermined. There were four cases of concomitant reactions with aliphatic amines, used as epoxy resin hardeners.

Composite prepregs mounted on graphite, Kevlar® and fiberglass caused positive reactions in 77 (50.6%) of subjects, not specifically composite materials technicians. Only 32 (21%) of patients had concomitant reactions with one of the epoxy resins from the commercially available standard and glues series. The prepregs were tested “as is”

and we cannot therefore ascribe the workers' sensitization to a specific ingredient such as TGPAP or TGMDA.

Salts of hexavalent chromiumare ubiquitously present in the workplace as corrosion inhibiting agents. Allergic sensitization to this class of compounds was demonstrated in 20 patients through positive patch test reactions to potassium dichromate from the standard series. Nickel allergy was found in 28 patients but was not commonly considered relevant to work exposure. Cobalt and formaldehyde-releasing biocides caused relevant but rare reactions.

2D. Discussion and Conclusion

Allergic contact dermatitis

This study shows that allergic contact dermatitis is a common problem in the Canadian aircraft industry, with 152 workers affected out of 304 who were patch tested. In contrast to the findings of some earlier publications[32,33,36], ACD was more common than ICD in our large cohort. Various hypotheses can be proposed to explain this difference in relative prevalence of ICD versus ACD. First, there could have been an underestimation of ACD in earlier publications if subjects were not tested with their workplace materials. On the other hand, some studies were published before prepregs, now recognized as an important cause of ACD, became widely used. In our study population, a glance at the distribution of cases of ACD through the years reveals an increase in the number of sensitized workers that coincides with the introduction of the "new composite materials" in the early 2000s. Fortunately, the pioneering work of

Mathias, Burrows, Bruze and Kanerva has shed light on the main allergenic components of these products.[34-37]

Metals

Unsurprisingly, chromates were an important cause of sensitization as 20 workers presented with positive patch test reactions to potassium dichromate. Contact allergy to potassium dichromate in the aircraft industry was first described by Hall in 1944.[38] Chromic acid and salts of hexavalent chromiumare ubiquitous in the aircraft industry, found either in corrosion inhibitors, metalworking fluids, primers or epoxy coatings and putties.[33, 36, 38, 39] Nickel allergy was seen in 28 (18.4%) of patch-tested patients, a sensitization rate also found in the overall population of patients referred for patch testing and not always relevant to occupation. Positive reactions to cobalt were deemed relevant in 9 cases and were attributed to resin systems.

Epoxy resin systems

Epoxy resin systems contain potential allergens such as hardeners, monomer resins and reactive diluents. The most common allergen in sensitized workers was DGEBA-derived epoxy resin with 54 cases. This is not surprising because DGEBA is currently the most important sensitizer in epoxy resin systems.[40] Workers handling sealants, putties, surface-coating primers and paints, as well as prepregs undergo widespread exposure to sensitizing epoxy resins at multiple stages of production. Epoxy resins based on bisphenol F are also commonly used in the aircraft industry. We thus began screening with DGEBF epoxy resin, 0.25% pet. in January 2003. All patients with positive reactions to DGEBF also reacted to DGEBA and to their workplace products.

These simultaneous reactions may represent concomitant reactions due to exposure to both types of resins or true cross-reactions, as already reported by other groups of investigators.[41, 42] Contact allergy to cycloaliphatic epoxy resin was uncommon with only 3 patch test positive cases. By comparison with the 4 cases (9%) reported in Hackett's study[33], sensitization to phenyl and cresyl glycidyl ether reactive diluents were roughly similar in our cohort with 9 cases (6%). Aliphatic amines hardeners were responsible for ACD in only 6 (4%) of our patients compared to 4 (9%) in Hackett's study.[33]

Aniline epoxy resins

Sensitization to TGPAP and TGMDA from resin-based composite materials has been previously described.[34-37, 40, 42-44] A review of material safety data sheets enabled us to verify the presence of those allergens in the composition of most prepregs used at Bombardier Aerospace factories. These compounds are expensive, unstable and must be bought from suppliers of chemical products, as they are absent from commercially available patch test series, hence our decision to test the prepregs themselves. Burrows et al. have shown in their publication that testing composite materials "as is" can be a sensitive and reliable alternative[34], while Mathias warns about the risk of actively sensitizing workers tested with undiluted prepregs.[35] None of our patients reported a delayed reaction that would suggest active sensitization. In our study population, 76 workers showed positive patch test reactions to one or more prepreg, while only 32 (21%) had concomitant reactions to the regular DGEBA epoxy resin of the NACDG standard series. Therefore, the allergic sensitization to modified epoxies would have remained undetected in 44 cases. This is additional proof that commercially available DGEBA epoxy resin from the standard series, and even other epoxies from the glues

and plastics series, are inadequate to detect all cases of sensitization because TGPAP and TGMDA do not cross react with them.[40]

Bombardier series

Given the large number of sealants, primers, putties and surface-coating products used in the aircraft industry and the impossibility of obtaining individual ingredients, we elected to patch test with a representative number of the most commonly used products. We asked the employer to provide us with a selection of unmixed part A and part B of each product. After careful review of the material safety data sheets, each sample was prepared at a suitable concentration by dilution in petrolatum. This personalized series was then used to test most workers referred to our clinic with a suspicion of occupational contact dermatitis. The detailed composition of this series is shown in Table 1. Interestingly, 89 patients had positive reactions to components of this series but only 43 (28.3%) had concomitant reactions to epoxies from the standard or glues series. Similarly, allergic contact dermatitis from polysulfide-containing sealants has been described.[35] Our series contained three such sealants, ProSeal 870, CS 5500 and PR 1422, the latter also containing DGEBA epoxy resin. Twenty patients reacted only to these three products. Even though in each case the specific allergen could not be determined, at least the use of our personalized “Bombardier series” significantly helped identify more cases of ACD, thus facilitating avoidance of specific workplace products, and preventing relapse of incapacitating dermatitis.

Clinical presentation

Overall, we have observed that the time of onset of sensitization is unpredictable. It can occur after as short a time as two weeks or as long as 25 years of exposure. Older

and more experienced employees are unfortunately not at a lower risk of sensitization. Women were shown to have a higher rate of sensitization than men in our study. Because of the slenderness of their hands and fingers, women have the ability and dexterity to work in restricted and closed spaces. Thus, they are commonly assigned work at higher risk of sensitization such as assembling or laying of prepregs, which is mostly done in confined spaces often without wearing gloves for increased dexterity.

As expected, the clinical presentation of our workers with occupational allergic contact dermatitis is similar to that described by previous authors.[32, 33, 36] Hands, forearms and face are the most commonly affected body sites, in descending order. We have also noted the characteristic fingertip dermatitis associated with allergy to epoxy resin systems, as reported in previous publications.[32, 33] Interestingly, airborne exposure to allergens was responsible for dermatitis in one third of our cases. Composite materials technicians who used air driers to heat prepregs often developed facial dermatitis, at times with associated eyelid edema. Some of the most severely allergic patients would develop facial eczematous lesions within a few hours if they had simply walked through the workstation for a few minutes.

Occupational urticaria

As mentioned above, 14 workers with presumed contact urticaria presented with rapid onset of urticarial lesions occurring only at work. Two cases were confirmed by positive patch tests with early readings after 30, 60 and 90 minutes. The first patient reacted to Dinitrol® AV 15, an anticorrosive fluid containing hydrotreated naphtha and

aliphatic mineral spirits, and the second patient reacted to DGEBA epoxy resin and to cresyl and phenyl glycidyl ethers.[46] Acute reactions were previously reported with phenyl glycidyl ether.[33] The other suspected cases could not be confirmed by patch testing. Some cases of generalised urticaria could have been secondary to inhalation of volatile compounds. It is difficult to prove a causal relationship between work exposure and contact urticaria by patch testing. It is useless when sensitization occurs by inhalation, and considering that even specific inhalation challenges often fail to identify the culprit. We relied on a good history of urticaria occurring exclusively upon exposure in the workplace to make a provisional diagnosis.

Irritant contact dermatitis

We found irritant contact dermatitis to be common among the Bombardier workers with 96 out of 304 cases (32%). Hand dermatitis is the usual presentation. Machinists, electricians, painters and cabinet-makers are mainly affected from exposure to coolants, solvents, paints, glues and woods. Airborne irritant contact dermatitis with facial involvement was also present in 55 cases (18 %). Carbon fibers from uncured composite material are a possible cause of airborne irritation.[33] Also, hard particles from grinding, sanding, or drilling cured composites and metal can cause irritation on exposed skin.

Prevention methods

Over the years, implementation of effective prevention measures has been instrumental in reducing the number of cases of occupational dermatoses at Bombardier. In the early 2000s, a fair number of assemblers became sensitized because they were allowed to mix their own resin-based products from tiny plastic cups, with resultant spillage and contamination of the entire workstation. The task of mixing resins and hardeners was later assigned to a single experienced technician working in a specially dedicated work area. But the assemblers were still provided the mixtures in inadequate containers, and continued to become sensitized. It was only towards the end of the decade (i.e. 2010) that two-part resin-based materials became available in pre-mixed cartridges that decreased the risk of skin contamination.

The employer, through its occupational health and safety team, had always recommended that workers use protective equipment such as gloves, sleeves, aprons and masks and had made them readily available. However, workers and their unions were initially reluctant to use them, considering such equipment as bulky, hot, and not adapted to tasks requiring precision and manual dexterity. In the first half of the 2000 decade, when Bombardier Aerospace was expanding, sensitized workers could easily be re-assigned to a new workstation which avoided exposure to their allergens. Eventually, however, the number of available positions dwindled and affected workers had no other option than to leave the workforce. The labor unions finally recognized the importance of prevention and requested that preventive measures be better implemented and that workers be instructed in the correct use of personal protective equipment (Fig. 7). This led to a few workplace visits by members of our group to review prevention strategies with the employer's health and safety personnel, and the

production of an instructional video for the workforce. We believe that these measures have helped to reduce the number of cases of occupational allergic and irritant contact dermatitis in this specific work environment. However, a recent visit has allowed us to realize that a fair number of assemblers and composite materials technicians are still working without gloves and in short sleeves (Fig. 4).

Limitations of the study

Although our study remains one of the largest ever published about occupational dermatoses in the aircraft industry, we are conscious of its inherent limitations. The actual number of cases of allergic contact dermatitis may still be underestimated. The Bombardier Series was not available and not systematically tested until 1993. It was only at the beginning of the year 2000 that we tested our first patient with prepregs (Kevlar® and graphite). It is probable that some cases of allergic sensitization to prepregs prior to 2000 may have gone undetected. In those early years, we may have missed some cases of allergic contact dermatitis because of incomplete patch testing. The fact that we have not tested TGPAP and TGMDA or any of the individual components of the workplace materials is another limitation of our study. We are therefore unable to quantify the number of cases caused by each of those sensitizers.

Conclusion

This is the first Canadian study to look at allergic contact dermatitis in the aircraft industry. The workers of this specific trade are particularly at risk of occupational

dermatoses. In this particular milieu, which uses sophisticated, highly sensitizing building materials that cannot be replaced, allergic contact dermatitis is more prevalent than irritant contact dermatitis. Commercial allergens are largely insufficient to detect sensitization. More than 50% of patients with allergy to epoxy resins would have been missed had they not been tested to workplace products. Polysensitization is common, and allergy to chromates is not rare as demonstrated by Handley and Burrows.[39] Educating the employees as to the importance of wearing protective clothing can clearly make a positive impact to reduce the number of cases of occupational dermatoses and should remain an essential part of prevention strategies. The constant evolution in the types of materials used by the aerospace industry paves the way for the emergence of new allergens. This is another reason why it is essential to keep patch testing workers suspected of occupational contact dermatitis with their own workplace products.

2E. Tables and figures

Table 1. Products tested in the "Bombardier Series" with their respective concentrations. The number of tested products was always limited to 15 per patient, but the composition of the series varied over the 25 years of the study period. Pet: petrolatum.

Product	Main components according to MSDS
Pro-Seal 870 B2 Part A (25% & 2.5% Pet)	Manganese Dioxide 30-60% Hydrogenated Terphenyls 30-60% Magnesium Chromate 10-30% 1,3-Diphenylguanidine 1.8%
Pro-Seal 870 B2 Part B (50% pet)	Liquid Polysulfide Polymer 30-60% Modified Polysulfide Polymer 1-10%
EA 934 NA "Liquid Shim" Part A (1% pet)	GDODGA (also known as TGPAP) 30-60% Phenol Formaldehyde, Glycidyl Ether 10-30%
EA 934 NA "Liquid Shim" Part B (1% pet)	Diethylenetriamine 10-30% Triethylenetetramine 1-5%
PR 1422 B2 Part A (5% & 1% pet)	N,N-Dimethylacetamide 15-40% Calcium dichromate 10-30%
PR 1422 B2 Part B (50% & 5% pet)	Modified Polysulfide Polymer 1-5% Bisphenol A Diglycidyl Ether 0.5-1.5%
CS 5500 Part A (100%)	Liquid Polysulfide Polymer <71% Phenolic Formaldehyde Polymer <5%
CS 5500 Part B (10% pet)	Manganese Dioxide <65% Hydrogenated Terphenyl <50% 1,3 Diphenylguanidine <3%
7009 Scotch Weld Core Splice Part A (1% pet)	Maleic Anhydride (Myrcene adduct) 1-10% Maleic Anhydride (Cymene adduct) 20-30% Hexahydrophthalic Anhydride 28-32%
7009 Scotch Weld Core Splice Part B (1% pet)	4-Glycidyloxy-N,N-diglycidylaniline (GDODGA or TGPAP) 60-65%
EA 9309.3 Part A (1% pet)	Epoxy Resin 60-100% Modified Epoxy Resin 1-5%
EA 9309.3 Part B (2% pet)	Polyglycol Diamine 60-100%

	Diethylenetriamine 1-5% Substituted Piperazine 10-30%
EA 956 Part A	Triglycidyl-p-aminophenol (TGPAP) 30-60% Epoxy Resin 30-60%
Scotch Weld EC 3501 Part A (2% pet)	Mercaptan 40-60% Polyamide Resin 5-15% Triethylenetetramine 0.1-1.5% 2,4,6-Tris(dimethylaminomethyl)phenol 1-5%
Scotch Weld EC 3501 Part B (2% pet)	Bisphenol A Diglycidyl Ether 40-70%
Epocast 50-A1 Part A (1% pet)	Bisphenol A Diglycidyl Ether 30-50% 1,4-Butanediol Diglycidyl Ether 1-3% Bisphenol A Epoxy Resin 7-13% Dibromo Cresyl Glycidyl Ether 3-7%
Epocast 50-A1 Part B (1% pet)	Bisphenol A Epoxy Resin 30-60% Novolac Resin Glycidyl Ether 30-60%
Scotch Weld EC 2216 Part A (2% pet)	Polymer Diamine 70-90% 4,7,10-Trioxatridecane-1,3-diamine 10-30%
Scotch Weld EC 2216 Part B (1.5% pet)	Bisphenol A Diglycidyl Ether 70-80%
Eccobond CT 5047-2 Part A (5% pet)	Bisphenol A Diglycidyl Ether 10-20% Trimethylolpropane Triglycidyl ether 1-10%
Eccobond CT 5047-2 Part B(1.5% pet)	Propoxylated Polyethylene Polyamine 60-100% Polyethylene Polyamine 1-5%
Permabond HM 128 (1% pet)	Polyglycol Dimethacrylate 30-60% Hydroxyalkyl Methacrylate 10-30% Cumene Hydroperoxide 1-5%

GDODGA: 4-Glycidyloxy-N,N-diglycidylaniline; TGPAP: Triglycidyl-p-aminophenol; Pet: petrolatum

Table 2: Composition of the "Prepreg Series"

Prepreg	Main components according to MSDS
BAMS 5553-01 TY Copper Mesh	Proprietary Epoxy Resin (±70%)
MXM 7701 Kevlar Low Temp	Aromatic Glycidyl Polyether Epoxy Phenolic Resin #2 Modified Epoxy Resin
Cycom 5208 Fiberglass High Temp	Aniline Derivative Aromatic Glycidyl Derivative #2 Modified Epoxy Phenolic Resin
Cycom 799H Fiberglass, Phenolic	Phenolic Resin 30-60%
Cycom 5276 Graphite High Temp	Aromatic Glycidyl 3-7% Modified Epoxy Resin 5-10%
FM 300-2 High Temp Adhesive Film	Epoxy Resin
Scotch-Weld CMS 551-10 Surface Film	Epoxy Resin Liquid 10-30% Phenol Aldehyde Epoxy Resin 30-60% Phenyl Glycidyl Derivative 10-30%
CMS 551-09 Supported Adhesive Film	Aniline Derivative 3-7% Epoxy Phenolic Resin #2 3-7% Aromatic Glycidyl Derivative #2 10-30% Modified Polyhalogenated Aromatic ..Glycidyl Ether 40-70% Halogenated Aromatic Epoxy Resin 1-5%
Metlbond 1113 Adhesive Film	Resorcinol Diglycidyl Ether 4-5% Epoxy Phenolic Resin #1 40-70% Epoxy Phenolic Resin #2 10-30%
Cycom 306 Finishing Film	Bisphenol A 2-22% Aromatic Glycidyl Polyether 10-30% Epoxy Phenolic Resin #1 1-5%

Table 3. MOAHLFA index of aircraft industry workers with occupational dermatoses

MOAHLFA	N	%
Male	222	73
Occupational	262	86
Atopy	90	30
Hands	190	62
Legs	9	3
Face	84	28
Age >40 years	120	39

Table 4. Demographics and characteristics of 152 aircraft industry workers with allergic contact dermatitis and their positive patch test reactions.

Characteristics		**Positive reactions** N	(%)
Sex	Female	48	(31.6)
	Male	104	(68.4)
Years of Employment	Unknown	16	(10.5)
	<1 year	15	(9.9)
	1-3 years	60	(39.5)
	4-10 years	34	(22.4)
	>10 years	27	(17.8)
Type of work	Assembler/Sealer	75	(49.3)
	Composite materials technician	65	(42.7)
	Machinist	4	(2.6)
	Other (mechanic, painter, cabinetmaker)	8	(5.3)

Tested series	Allergens		
NA (1990-2000)	Potassium dichromate	20	(13.2)
NACDG (2000-15)	Nickel sulfate	28	(18.4)
Standard series	Cobalt chloride	9	(5.9)
	DGEBA epoxy resin	54	(33.5)
	Thiuram mix	2	(1.3)
	Diphenylguanidine	1	(0.7)
Glues & Plastics	DGEBF epoxy resin	6	(3.9)
	Cycloaliphatic epoxy resin	3	(2)
	Phenyl & cresyl glycidyl ether	9	(5.9)
	EDA, DETA, TETA	5	(3.3)
	Hexamethylene triamine	1	(0.7)
	Diaminodiphenyl methane	3	(2)
	Toluene diisocyanate	1	(0.7)
	Phenol formaldehyde resin (Novolac)	2	(1.3)
	4-tert-Butylphenol formaldehyde resin	2	(1.3)
	Tosylamide formaldehyde resin	1	(0.7)
	Ethylhexyl acrylate	1	(0.7)
Cooling oils	2-n-Octyl-4-isothiazolin-3-one	3	(1.3)
Tailor-made (1993-2015)	Polysulfide, phenolic, modified epoxy and their amine catalysts (Proseal 870, PR 1422, EA-934-NA, etc.)	89	(58.5)
	Concomitant reaction with DGEBA epoxy	43	(28.3)
	Concomitant reaction with EDA, DETA,TETA	4	(2.6)
Prepregs	Kevlar, Graphite, Fiberglass with resin based on TGPAP or TGMDA	76	(50)
	Concomitant reaction with DGEBA epoxy	32	(21)

NA: North American; NACDG: North American Contact Dermatitis Group; DGEBA: diglycidyl ether of bisphenol A; DGEBF: diglycidyl ether of bisphenol F; EDA: ethylenediamine; DETA: diethylenetriamine; TETA: triethylenetetramine; TGPAP: triglycidyl-p-aminophenol; TGMDA: tetra-4,4'-methylenediamine; pet: petrolatum

Figure 1. Sealer with airgun

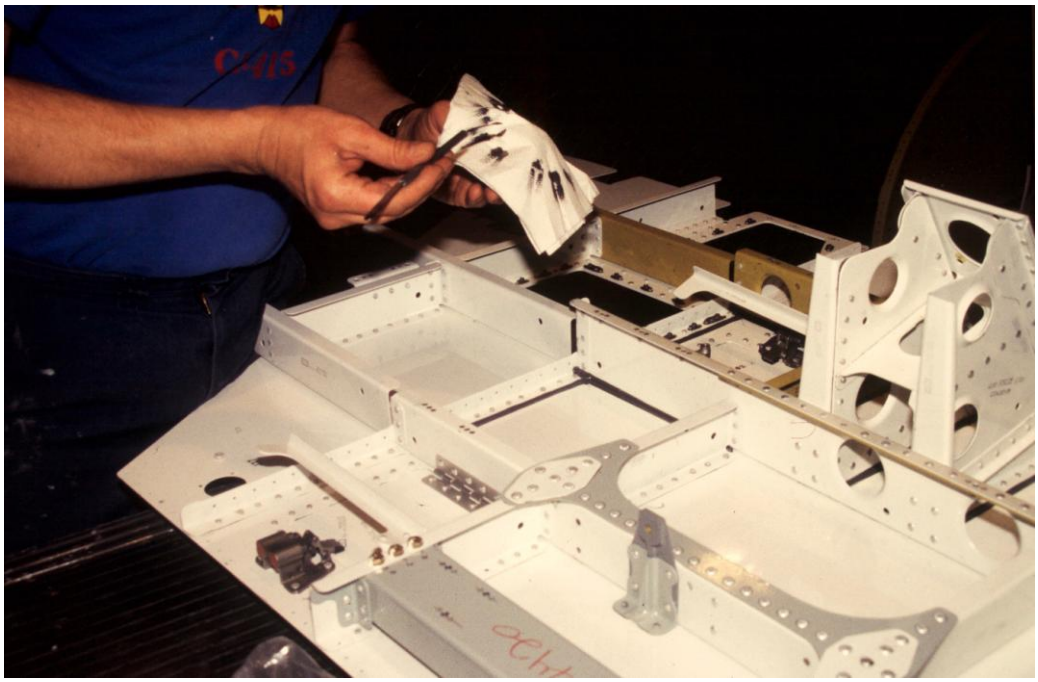

Figure 2. Sealer with spatula

Figure 3. Prepregs on tool

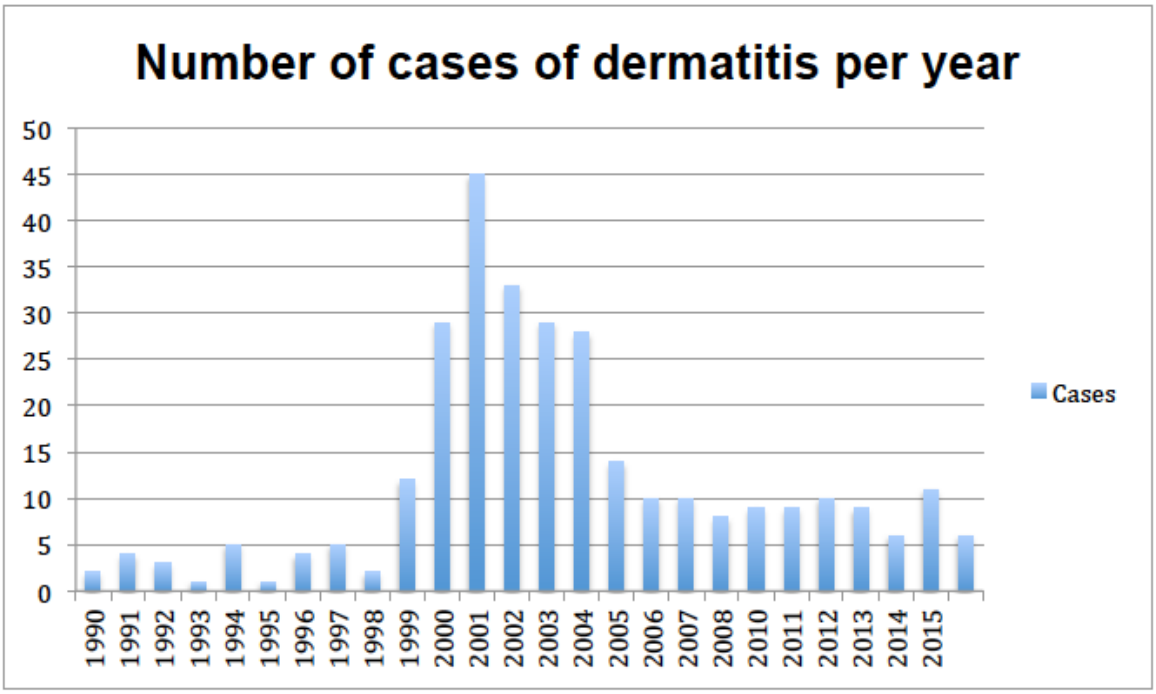

Figure 4. Number of cases of dermatitis per year

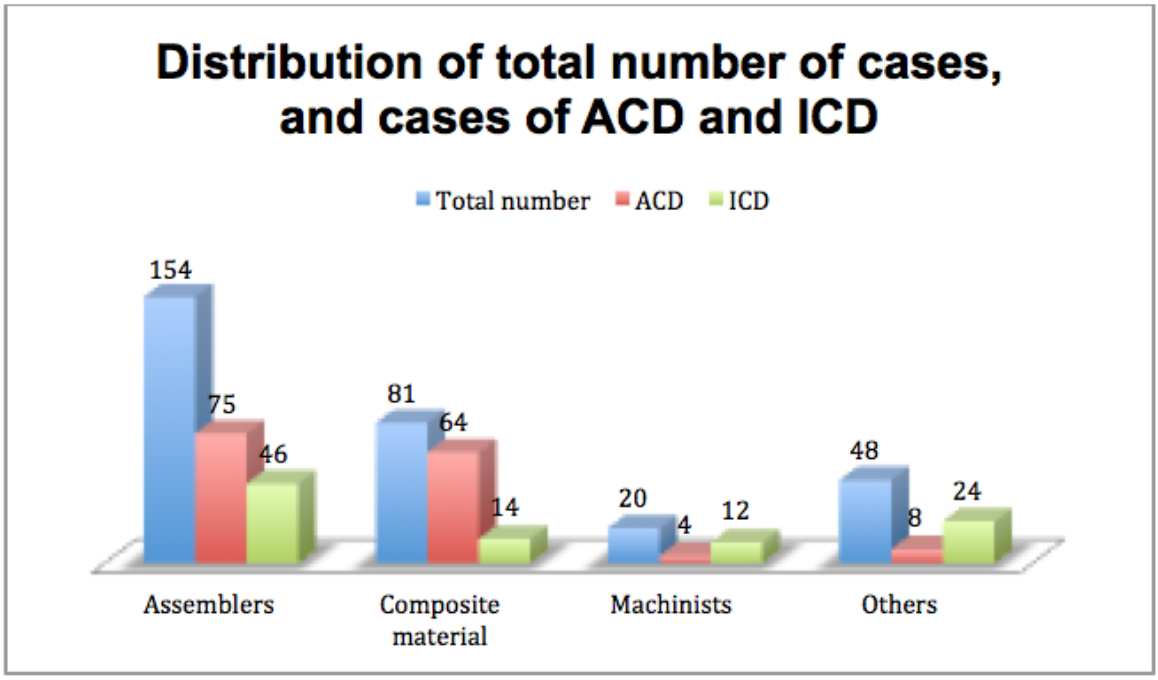

Fig 5. Distribution of total number of cases, and cases of ACD and ICD (Blue total cases, red ACD, green ICD)

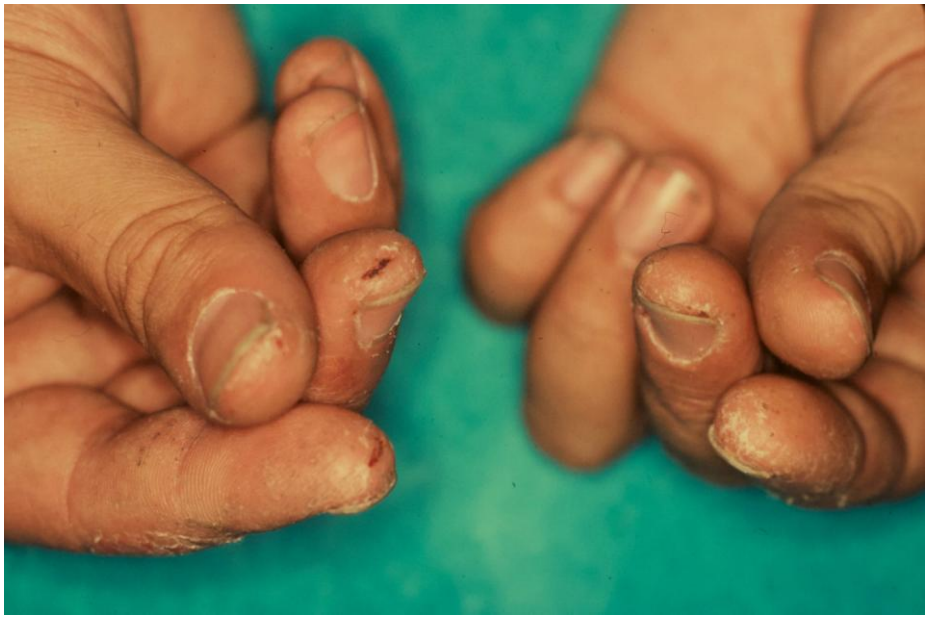

Figure 6. Example of hand dermatitis

Figure 7. Example of protective equipment

Summary and future perspectives

This masters thesis in experimental medicine seeks to expand our knowledge of contact dermatitis arising from exposure to sensitizing chemicals used in either the cosmetic industry or the aircraft manufacturing industry. The thesis analyses, reports on, and comments on some major types of contact dermatitis found in those industries. The science of patch testing has greatly improved in the past few decades, and we are now able to diagnose with more sensitivity and specificity the cause of allergic contact dermatitis for referred patients. This has been achieved mainly by using expanded specialised hapten series, and by testing patients with their own products. Our work confirms that it is essential to test patients with their own materials in certain situations where contact dermatitis is suspected because not all allergens are available from commercial patch test supply companies. Material safety data sheet are often not sufficiently comprehensive, but they remain one important guide to finding a culprit allergen.

In chapter 1, the structure, function, uses, and methods for patch testing with alkyl glucosides are described in detail. A complete review of the literature regarding allergic contact dermatitis to the most important alkyl glycosides is provided. We also summarize and analyse our experience at the McGill University Health Centre with patch testing alkyl glucosides. Our research specifically highlights that alkyl glucosides are new important sensitizers in the cosmetics industry and that testing different members of the family should be routinely performed because the molecules do not always cross-react.

Recent publications have raised awareness regarding the presence of decyl glucoside as a hidden ingredient in Tinosorb® M sun blocking agent, as it is present at low concentrations and it is not listed as an active ingredient. Dermatologists in the field have to be vigilant with this matter. We also report the first case of sensitivity to arachidyl glucoside in a 32-year-old nurse, who reacted to her hand cold cream, and who subsequently reacted to a cream containing octodecylxyloside suggesting probable cross-reactivity.

In chapter 2, we provide the first study on occupational contact dermatitis in the Canadian aircraft Industry. We demonstrate that allergic contact dermatitis is more common than irritant dermatitis in this setting. We report that the most common allergens found in this particular industry are epoxys and chromates. Modified epoxy resin systems found in prepregs are unique sensitizers as DGEBA from commercial hapten series and modified epoxy resins do not necessarily cross react. The profile of the patients affected and the characteristic clinical presentations of their dermatitis are described and discussed. Adapting patch testing was essential to correctly diagnose ACD in these subjects, and testing workplace materials was essential. In the setting of occupational contact dermatitis, it can be informative to visit the workplace environment to observe personal protective measures, and how products are handled by workers. In addition to worker and supervisor awareness, simple preventive measures can definitively help to decrease the number of cases of contact dermatitis.

Further studies might focus on:

- Optimal hapten concentration and vehicles for the most important alkyl glucosides (decyl glucoside and lauryl glucoside);
- Clarification of the cross-reactivity between alkyl glucoside and octodecylxyloside by testing each ingredient separately
- Better characterization of the sensitizing potential of tetra-4,4'-methylenediamine (TGMDA) vs. triglycidyl-para-aminophenol (TGPAP);
- A better delineation of cross reactivity between the commercially available epoxy resin diglycidyl ether of bisphenol A (DGEBA) and modified epoxy resin or epoxy derivatives found in prepregs and sealants

It is crucial for dermatologists specialised in contact dermatitis to stay up to date with new emerging allergens because industries are continuously developing, manufacturing and commercialising new products and many of these will contain new potent sensitizers.

Finally, note that the 2 published studies on alkyl glucosides (discussed in chapter 1) are included in the appendix, as well as the submitted manuscript draft on contact dermatitis in Bombardier aircraft industry (discussed in chapter 2).

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Appendix 1

Alkyl glucosides: Contact allergen of the Year

Appendix 2

A review of alkyl glucosides in contact dermatitis

Appendix 3

Occupational contact dermatitis in the Canadian aircraft industry: A 25-year retrospective study

Alkyl Glucosides

Maisa Alfalah, MD,* Camille Loranger, MD,† and Denis Sasseville, MD, FRCPC†

Alkyl glucosides are surfactants synthesized through the condensation of long-chain fatty alcohols and glucose, extracted from vegetal, renewable sources. Although available for more than 4 decades, they have been rediscovered in recent years because of their eco-friendly character. They are used in various leave-on and rinse-off cosmetics and are considered of low irritancy and allergenicity. However, since the early 2000s, cases of allergic contact dermatitis to this family of molecules have been repeatedly reported. Decyl glucoside was found to be a "hidden" allergen in the sunscreen ingredient Tinosorb M and is likely responsible for most allergic contact dermatitis reported to this compound. Members of the North American Contact Dermatitis Group have seen a steady increase of the rate of sensitization to decyl glucoside. Cross-reactions with other glucosides are common but not automatic; thus, patch testing multiple compounds is recommended.

Considered eco-friendly because of their complete biodegradation, alkyl glucosides are plant-derived, nonionic surfactants. They are produced by the reaction of glucose with fatty alcohols, mainly extracted from palm or coconut oil.[1,2] Glucosides have emulsifying, cleansing, and foaming properties. Alkyl glucosides include a number of chemically related compounds, such as decyl, lauryl, cetearyl, and coco glucoside, and are closely related to other surfactants, such as methyl glucose dioleate.[3] They are widely used in a variety of household products including cosmetic, skin care, hair dyes, cleansing, fragrance, and tanning formulations.[1] They have been used for more than 4 decades in rinse-off products such as shampoos. However, they were eventually replaced by other surfactants before making a comeback in the 1990s. Because they are considered nonirritant or weakly irritant compounds,[4] they are extensively used nowadays in both rinse-off and leave-on cosmetics.[3,5]

GLUCOSIDES AS UNEXPECTED ALLERGENS

The allergenic properties of glucosides have only been identified since 2003, when Goossens et al[6] described 2 cases of contact allergy to lauryl glucoside and coco glucoside. Their observation was soon followed by 2 reports describing 5 patients with contact allergy to decyl glucoside.[3,5] Several additional case reports and series have since clearly established the allergenicity of glucosides in various cosmetic and cleansing products.[2,7–13] Some of these reports have revealed the "hidden" presence of decyl glucoside as a stabilizing agent for the microparticles of the sunscreen ingredient Tinosorb M.[3,6,8–12] A comparative study using the murine local lymph node assay assessed the skin-sensitizing potential of 8 glucosides of different alkyl chain length and branching and showed that 3 of the 8 tested glucosides may be classified as potential sensitizers.[4] However, in the same study, the repeated insult patch test protocol failed to demonstrate a sensitizing potential for all tested glucosides.[4]

EPIDEMIOLOGY AND CLINICAL PICTURE

The prevalence of glucoside-induced allergic contact dermatitis is probably underestimated,[9] because of the lack of large well-designed studies and lack of multiple glucosides in most cosmetic patch test series. Members of the North American Contact Dermatitis Group patch test approximately 2400 patients per year. They added decyl glucoside 5% in petrolatum to their standard series in 2009 and have since noted a small but constant increase in the rate of positive reactions to this surfactant, from 1.5% in 2019–2010 to 1.7% in 2013–2014.[14]

During the last 12 years, approximately 20 patients with allergic contact dermatitis from different glucosides have been described in 10 case reports and case series.[2,3,5–12] In addition, another 30 patients with allergic contact dermatitis from 1 or more alkyl glucosides were recently described in a retrospective study that reviewed records for 19 years.[13] Of 50 patients, 37 (74%) were females, probably because of their higher use of cosmetics. The patients' ages ranged from 7 to 86 years, with the average age of 49.6 years. The most frequently implicated cosmetic products were sunscreens (n = 16, 32%), shampoos (n = 16, 32%), skin-cleansing products (n = 15, 30%), facial and body lotions and creams (n = 5, 10%), and hair care products such as dyes and mousses (n = 4, 8%). At least 20 patients (40%) had a history of atopy, and 6 patients

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(12%) had occupational exposure to implicated products. It is believed that impaired skin barrier enhances the penetration of rinse-off products that contain glucosides.[2,3]

The clinical picture varied according to the area targeted by the responsible products. For sunscreens, eczema was largely distributed on the face and to a lesser extent on the neck, arms, and upper chest. With shampoos, dermatitis was mostly localized on the scalp, more obviously along the frontal hairline and occipitonuchal area, and less so on the face and trunk. In occupational exposures, eczematous plaques affected mainly the hands because of contact with shampoos or hair care products by hairdressers and application of antiseptic agents or creams by nurses. Patients had positive reactions to 1 or more alkyl glucoside (decyl, lauryl, coco, and cetearyl glucosides). However, because of testing inconsistency between published reports, it is difficult to determine which glucoside is most often associated with contact allergy.

CROSS-REACTIONS OF GLUCOSIDES

Most patients simultaneously tested to several glucosides had multiple positive reactions.[3,6,8,13] Glucosides often present as mixtures of various alkyl chain lengths, some of them being impurities that persist during their industrial production.[9] Therefore, the simultaneous positive patch test reactions to several derivatives may represent concomitant reactions instead of cross-reactions.[8,10] In addition, most patients who reacted to 1 or more glucoside derivatives also had positive reactions to other surfactants and nonrelated chemicals.[3,13] This polysensitization may be explained by increased transcutaneous penetration facilitated by barrier disruption and inflammation.[13]

PATCH TESTING

Currently, glucosides are rarely included in cosmetic patch test series.[9] The European photopatch test baseline series recommends testing decyl glucoside when investigating reactions to methylene bisbenzotriazolyl tetramethylbutylphenol (Tinosorb M).[15] The optimal concentration and vehicle for glucosides as patch test allergens are not yet established. However, it was suggested that decyl glucoside in a 10% aqueous solution would detect definite allergic reactions without inducing irritation.[3,5] Because these surfactants rarely exist in a pure form, it would be interesting to know the exact chemical composition of the commercially available glucoside allergens.[3] In addition, patch testing should ideally be performed not only with the suspected products but also with their separate ingredients.[11]

CONCLUSIONS AND RECOMMENDATIONS

Glucoside-induced allergic contact dermatitis is not an infrequent problem and is probably underestimated. The increasing number of reported cases may represent more awareness of a situation that has long been missed but may also be due to the increased use of these mild surfactants in a variety of household products. They should be recognized as emergent allergens, and we strongly urge patch testers to include various glucosides in their cosmetic series.

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Alkyl Glucosides in Contact Dermatitis

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Ecologically sound because they are synthesized from natural and renewable sources, the mild surfactants alkyl glucosides are being rediscovered by the cosmetic industry. They are currently found in rinse-off products such as shampoos, liquid cleansers, and shower gels, but also in leave-on products that include moisturizers, deodorants, and sunscreens. During the past 15 years, numerous cases of allergic contact dermatitis have been published, mostly to lauryl and decyl glucosides, and these compounds are considered emergent allergens. Interestingly, the sunscreen Tinosorb M contains decyl glucoside as a *hidden* allergen, and most cases of allergic contact dermatitis reported to this sunscreen ingredient are probably due to sensitization to decyl glucoside. This article will review the chemistry of alkyl glucosides, their sources of exposure, as well as their cutaneous adverse effects reported in the literature and encountered in various patch testing centers.

Alkyl glucosides are the products of condensation of glucose and a fatty alcohol. Their use began in the 1960s as nonionic surfactants in rinse-off products such as shampoos, soaps, hair dyes, and mousses, but they were eventually replaced by newer surfactants. The late 1990s saw a revival of popularity for alkyl glucosides because of their low potential for irritation and their ecological characteristics because these surfactants are manufactured from renewable sources. The cosmetic industry has since used them increasingly not only in rinse-off but also in leave-on products such as sunscreens, deodorants, and antiseptics. Beginning in the early 2000s, several case reports described allergic contact dermatitis from alkyl glucosides in different cosmetic and cleansing products.[1,2] At the same time, decyl glucoside, an important member of the alkyl glucoside family, was also found to be a *hidden allergen* in the new sunscreen ingredient Tinosorb M (BASF, Monheim, Germany).[2] When patch tested, alkyl glucosides occasionally induce mild irritation, therefore, strong positive reactions probably reflect actual sensitization.[3]

This article will describe the basic chemistry and cutaneous adverse effects of alkyl glucosides, review the literature and the results of patch testing in our and other centers, and provide recommendations for patch testing and prevention.

CHEMISTRY AND METABOLISM

Alkyl glucosides are part of a family of organic molecules of vegetal origin composed of 19 different members. In 1893, ethyl glucoside, the shortest and simplest alkyl glucoside, was first synthesized.[3] Chemically, alkyl glucosides are produced by the condensation of a sugar, usually a cyclic form of glucose (D-glucopyranose), with a fatty alcohol composed of a linear side chain ranging from 2 to 22 carbons (Fig. 1). Alcoholysis of glucose under acidic conditions is the preferred method of synthesis.[3] The anomeric hydroxyl group of the glucose moiety is the site of linkage with the fatty alcohol. The reaction conditions can cause the condensation of 2 or more glucose molecules at either of their hydroxyl groups in a repeating sequence, forming alkyl polyglucosides. These compounds are still called alkyl glucosides, regardless of their number of glucose molecules. Alkyl glucosides are chemically stable; they do not contain chemically reactive sites or polarized structures.[4]

Fatty alcohol is extracted from palm, coconut, or rapeseed oil, and glucose can be obtained from corn, wheat starch, and potato. The average number of carbon atoms composing the side chain of the alcohol determines the name of the alkyl glucoside. For example, decyl glucoside has an average of 10 carbons on its side chain. Other members of the alkyl glucoside family include butyl, caprylyl, undecyl, myristyl, hexadecyl, octadecyl, arachidyl glucosides, caprylyl/capryl glucoside, C10-16, C12-18, C12-20, C20-22 alkyl glucosides, branched isostearyl glucoside, and octyldodecyl glucoside.[3]

The likely first step in the metabolism of alkyl glucosides is cleavage by the human skin enzyme glucoside hydrolase, leading to

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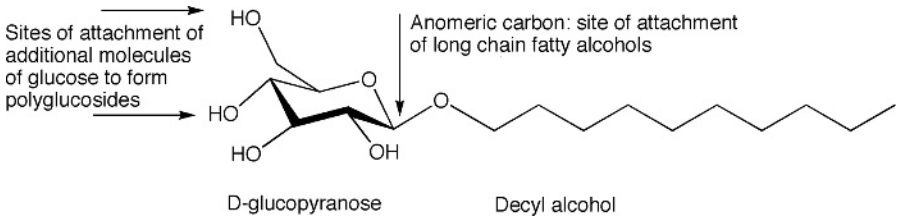

Figure 1. Chemical structure of decyl glucoside.

release of the respective fatty alcohols and glucose.[3] According to an in vitro absorption assay on human skin sample with 10% caprylyl/capryl glucoside, transdermal absorption was less than 0.01%.[3]

FUNCTION AND SAFETY OF USE

After a thorough review of toxicological data, the Cosmetic Ingredient Review Expert Panel concluded that the 19 alkyl glucosides are safe to use.[3] Most of the alkyl glucosides are primarily used as mild surfactants in cosmetics and cleansing products for human skin. They can also sometimes function as emulsion stabilizers in sunscreens, skin and hair cleansing agents, and humectants.[3] They can be found in certain baby products such as wipes and cleansers.

Alkyl glucosides have been shown to be superior surfactants compared with *classic* polyethoxylated surfactants such as polysorbates. They are not susceptible to oxidation at room temperature and they are used in lower concentration leading to lower skin irritancy potential. The lipophilic hydroxyl groups and the hydrophilic hydrocarbon chains help keep the molecule at the water-oil interface.[4] Nowadays, decyl glucoside is the most commonly used alkyl glucoside. In 2011, according to information from the Voluntary Cosmetic Registration Program database, decyl glucoside was reported to be an ingredient in 492 cosmetic formulations, mainly rinse-off products.[3] Cetearyl glucoside, lauryl glucoside, and coco glucoside are also frequently used. Cetearyl glucoside is probably the most commonly used glucoside in leave-on products other than sunscreens.[3,5] The concentration of use varies but is higher in rinse-off products. Lauryl glucoside has the highest concentration of use in leave-on products at 8% in a hair color spray and 5% in a skin product, whereas decyl glucoside can be present at a concentration of 33% in rinse-off products.[3]

Some recent publications suggested that certain alkyl glucosides could potentially be absorption enhancers. Tirumalasetty et al[6] showed that caprylyl and decyl glucosides could enhance the absorption of insulin in vivo through mucous membrane. Aguirre et al[7] found that ingestion of coco glucoside could enhance the intestinal permeation of calcitonin and sugar in rats. The Cosmetic Ingredient Review Expert Panel expressed concern that the transdermal absorption of some cosmetic ingredients could lead to untoward effects.[3]

CUTANEOUS ADVERSE EFFECTS

Irritation

Alkyl glycosides did not cause significant irritant contact dermatitis in clinical studies. An epicutaneous patch test with a 2% concentration and a soap chamber test at a concentration of 1% with decyl, lauryl, and coco glucosides as well as an occlusive patch test with decyl glucoside 0.5% showed only a slight irritant potential.[3] Furthermore, patch testing with a 10% aqueous solution of decyl glucoside did not cause irritant reactions in 100 volunteers.[8] Lauryl glucoside has a pH of 11.5 to 12.5. Shanmugam et al[8] recently proposed that lack of correction of pH by suppliers of commercial allergens could render their preparations irritant.

Allergic Contact Dermatitis

Alkyl glucosides in sunscreens, cosmetics, and cleansing products can sensitize by an as yet undetermined mechanism. Decyl glucoside, lauryl glucoside, cetearyl glucoside, and coco glucoside are responsible for most cases. The length of the alcohol chain does not affect the sensitizing potential.

A comparative study used 3 protocols to assess the skin sensitizing potential of 8 related alkyl glucosides. In the local lymph node assay, only C12-C18 glucoside, C4 glucoside, and C18 branched glucoside were mild sensitizers. The authors could not demonstrate sensitization by using the human insult repeated patch test protocol or the guinea pig maximization test.[9]

Case Reports and Case Series

Goossens et al[1] are credited with reporting the first 2 cases of sensitization to alkyl glucosides in cosmetic and cleansing products. Since then, additional publications have described further cases of allergic contact dermatitis.[1,2,10–23] A retrospective study by Gijbels et al,[10] who reviewed 19 years of data, counted 30 cases of contact allergy to different alkyl glucosides (Table 1).

Analyses of available data have shown similarities between cases. When patch tested, the majority of patients react to multiple alkyl glucosides and women are more commonly sensitized. The median age of patients is 49.6 years. Sensitization can occur in an occupational setting but the majority of cases are not work related. Workers in contact with cosmetic or cleansing products like hairdressers, housekeepers, and nurses have been sensitized. Conditions such as atopic eczema and occupational irritation may enhance the penetration of glucosides by altering the epidermal barrier.[3] Hands, face, neck, and scalp are commonly affected by exposure to shampoos, sunscreens, and liquid soaps. Nonexposed sites, such as breast, abdomen, genitals, and folds have been involved from use of antiseptics, skin cleansers, and deodorant wipes. In most cases, strict avoidance of the culprit products and treatment with topical

TABLE 1. Summary of Reported Cases of Glucoside-Induced Allergic Contact Dermatitis

Author, Year	Age and Sex	Clinical Picture	Exposure	History	Work-Related	Patch Test Concentrations and Reactions
Goossens, 2003 Belgium	55-year-old man	Recurrent papular and erythemato-squamous lesions on the face, neck, forearms, wrists, and dorsa of the hands.	Shampoo and shower gel (rinse-off)	No atopy	Yes	Lauryl glucoside 53% aq semiopen test (+++), 5%, 10% pet (++), and 12% aqua (++) coco glucoside 35% aq, 5%, 10% pet (++)
Goossens, 2003 Belgium	46-year-old woman	Severe erythema, scaling, and fissuring on both hands, accompanied by paronychia	Antiseptic body lotion (leave-on)	Atopic eczema	No	Lauryl glucoside 5% pet. (++) coco glucoside 5% pet. (+)
Le Coz, 2003 France	29-year-old woman	Acute eczema at site of umbilical piercing	Chlorhexidine digluconate antiseptic gel (leave-on)	No atopy	No	Decyl glucoside 0.55% aq (++) chlorhexidine (−)
Blondeel, 2003 Belgium	53-year-old woman	Aggravation of atopic eczema on UV-exposed skin and scalp	Sunscreen (leave-on)	Atopic eczema	No	Decyl glucoside 5%, 10% aq (++) possible reaction, but not tested: methylglucose dioleate
Blondeel, 2003 Belgium	52-year-old woman	Eczematous lesions on scalp and trunk	Shampoo (rinse-off)	Occupational hand dermatitis	No	Decyl glucoside 10% aq. (++)
Blondeel, 2003 Belgium	Young woman	Eczematous lesions on hands	Shampoo (rinse-off)	Hand eczema	No	Lauryl glucoside 5% pet (+) coco glucoside 5% pet (+) decyl glucoside 5% pet (+)
Blondeel, 2003 Belgium	16-year-old woman	Painful fissuring on the fingers	Shampoo and hair dye (rinse-off)	Occupational irritation	Yes	Lauryl glucoside 5% pet (+) coco glucoside 5% pet (++) decyl glucoside 10% pet (+) cetearyl glucoside 5% pet (++)
Giordano-Labadie, 2005 France	36-year-old woman	Pruritic erythematous and edematous eruption on face	Sunscreen spray (leave-on)	No atopy	No	Tinosorb M (++) decyl glucoside 5% (−), 10% pet (+)
Horn, 2005 UK	25-year-old woman	Eczematous lesions on upper chest, arms, neck, face, and scalp	Hair mousse (leave-on)	No atopy	No	Decyl glucoside 2% aq (++)
Gonzalez-Pérez, 2007, Spain	54-year-old woman	Persistent facial dermatitis involving forehead and cheeks	Sunscreen (Avene 20) (leave-on)	Not mentioned	No	MBBT (not pure) 2% pet (?)
Andersen, 2006 Denmark	67-year-old man	Sudden exacerbation of widespread vesicular dermatitis related to sun exposure on trunk and extremities	Sunscreen (leave-on)	Atopic eczema	No	Tinosorb M 6% aq (++) decyl glucoside 0.5%-5% aq (+) coco glucoside 2% aq (positive, strength of reaction not mentioned)

(continued on next page)

TABLE 1. *(Continued)*

Author, Year	Age and Sex	Clinical Picture	Exposure	History	Work-Related	Patch Test Concentrations and Reactions
Krehic, 2009 France	86-year-old woman	Acute eczema affecting the submammary area and lateral sides of the neck	Chlorhexidine digluconate antiseptic lotion (leave-on)	No atopy or eczema	No	Decyl glucoside 1% pet (++), 3% pet (+++) chlorexidine digluconate 0.5% aq (++) lauryl glucoside (+++)
Krehic, 2009 France	80-year-old man	Acute lower leg eczema	Chlorhexidine digluconate antiseptic lotion (leave-on)	No atopy or eczema	No	Decyl glucoside 1%pet (++), 3% pet (+++) chlorexidine digluconate 0.5% aq (+/?) Lauryl glucoside (++)
Andrade, 2010 Portugal	66-year-old man	Pruritic erythematous eruption on face and neck	Sunscreen (Avène) (leave-on)	Not mentioned	No	Tinosorb M 10% pet (++) decyl glucoside 5% pet (++) no further aggravation after UV
O' Connell, 2011 UK	75-year-old man	Eczematous eruption, site undisclosed	Sunscreen (leave-on)	No atopy or eczema	No	Tinosorb M 10% pet (+) lauryl glucoside (−)
O' Connell, 2011 UK	85-year-old woman	Eczematous lesions largely distributed on the face, neck, arms.	Sunscreen (leave-on)	Not mentioned	No	Lauryl glucoside 3% pet (+) Tinosorb M 10% pet (+)
Pereira, 2013 Portugal	66-year-old man	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 10% pet (++) decyl glucoside 5% pet (++)
Pereira, 2013 Portugal	52-year-old woman	Eczematous lesions on eyelids and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 10% pet (+) lauryl glucoside 3% pet (+)
Pereira, 2013 Portugal	64-year-old woman	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 10% pet (+) lauryl glucoside 3% pet (+)
Pereira, 2013 Portugal	64-year-old man	Eczematous lesions on face and anterior cervical region	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 10% pet (++) lauryl glucoside 3% (+++)
Pereira, 2013 Portugal	39-year-old woman	Eczematous lesions on eyelids	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 10% pet (++) lauryl glucoside 3% pet (+++)
Gijbels, 2014 Belgium	24 women and 6 men aged 7–77 y	Eczematous lesions depend on the product; hands are affected with soaps whereas scalp and sometimes face, back, chest, and shoulders are affected with shampoos	Shampoos (12/30), skin cleansers (12/30) (rinse-off), sunscreens (5/30), skin care (4/30), and deodorant (1/30) (leave-on)	15/30 had history of atopy	Yes in 4/30	One or more alkyl glucosides (cetearyl, coco, decyl, and lauryl glucoside) 26/30 were polysensitized
de Groot, 2014 Netherlands	56-year-old woman	Itchy, red, and burning eruption on face and neck	Sunscreen (leave-on)	Not mentioned	No	Tinosorb M 8.1% aq (+)

Liuti, 2015 Spain	83-year-old man	Severe eczematous patches on forehead, cheeks, and upper chest	Sunscreen (leave-on)	Actinic keratoses	No	Decyl glucoside 1%, 3%, 5%, 10% pet & aq (positive, strength not specified) Tinosorb M 10% pet (+) lauryl glucoside 3% pet (++) MBBT EPE series (+) (not pure MBBT) pure MBBT 10% pet. (−)

corticosteroids has led to resolution of the dermatitis. More severe cases requiring treatment with systemic corticosteroids have occurred after exposure to decyl glucoside in Tinosorb M sunscreens.[11,12]

Cosmetic Rinse-Off Products

Among the rinse-off products, shampoos are the most common cause of contact dermatitis from alkyl glucosides, with approximately 16 reported cases.[1,2,10] Shampoos often contain a mixture of different alkyl glucosides and their exact composition is not always clear. Some publications report allergic contact dermatitis from liquid, gel, or cream formulations of hand and body soaps. The molecules most commonly implicated include decyl glucoside, coco glucoside, lauryl glucoside, and cetearyl glucoside. Because preservatives, fragrances, and other allergens or irritants are present in shampoos and cosmetics, it is important to test a patient's personal products and their individual ingredients.

Cosmetic Leave-On Products

Sunscreens

The sunscreen ingredient Tinosorb M was introduced in the European, Asian, and Australian markets in the early 2000s. It is not used in the United States because it has not yet been approved by the Food and Drug Administration. Tinosorb M is composed of the new broad-spectrum UV filter methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT, also known as bisoctrizole) (50%) solubilized with decyl glucoside (7.5%), propylene glycol (0.4%), xanthan gum (0.2%), and water (ad 100%).[24] Compared with other sunscreen preparations, Tinosorb M offers the advantages of being photostable and protecting the skin by 3 different mechanisms, absorbing UV radiation like an organic filter and reflecting and scattering light as a physical sunblock.[4] The role of decyl glucoside is to facilitate dispersion of the UV filter microparticles in an aqueous phase. Unfortunately, although decyl glucoside is present in the final preparation, its name does not appear on the ingredient label of some sunscreens, where it therefore represents a hidden allergen.

Blondeel reported the first case of allergic contact dermatitis to Tinosorb M in 2003, and several cases have since been published.[2,10–18] Between 2009 and 2012, Pereira et al[15] collated the largest case series: 92 patients were photopatch tested, and 87 patients were patch tested with a cosmetics series that included Tinosorb M, Tinosorb S, and lauryl glucoside. In total, 5 of the 179 tested patients had positive reaction to Tinosorb M and to lauryl glucoside, for a positivity rate of 2.8%. Tinosorb S, a chemically unrelated UV filter, has not been shown to cause allergic contact dermatitis. Interestingly, it does not need decyl glucoside as a stabilizer.

The MBBT, used as a synonym for Tinosorb M in previous studies, may have been falsely reported as the sensitizing agent.[17,18] In fact, pure MBBT was unavailable for testing until January 2014 in the European Photopatch Extended series.[18] Previous tests labeled "MBBT" were in fact performed with a mixture of decyl glucoside and pure MBBT. This confounding factor illustrates the importance of testing with individual allergens and to correctly

label material used for patch testing because of hidden ingredients. To our knowledge, decyl glucoside seems to be the main sensitizer in Tinosorb M.

Antiseptic Lotion, Deodorant, and Hair Mousse

Goossens et al[1] published the first case report of allergic contact dermatitis on the hands from an antiseptic lotion containing coco glucoside and lauryl glucoside. Later, contact allergy from decyl glucoside, involving different parts of the body, was reported in a patient who used a chlorexidine-based antiseptic gel and 2 patients exposed to a moisturizing lotion.[19,20] The 2 patients described by Krehic et al[19] reacted positively to lauryl glucoside on initial patch testing and to decyl glucoside more than to chlorexidine when patch tested to the product ingredients provided by the manufacturer. Gijbels et al[10] described a case of contact dermatitis to deodorant wipes containing an unspecified mixture of alkyl glucosides. The dermatitis involved the ears, face, and inguinal folds, and patch tests were positive for coco glucoside and decyl glucoside.[10]

North American Contact Dermatitis Group

In 2009, decyl glucoside 5% in petrolatum was introduced in the North American Contact Dermatitis Group (NACDG) standard series. The results of the 14 members of the group are compiled, tabulated, and published after each cycle of 2 years. During the period 2009–2010, patch testing with decyl glucoside was positive in 1.5% of 4302 patients thus tested, with a global relevance rate of 83.3% and 34.8% if only cases of definite and probable relevance are considered.[25] The rate of positive reactions between 2011 and 2012 was established at 1.56% (66 positive cases out of 4231 tested patients), and approximately 50% of cases were considered relevant (4.5% definite, 15.2% probable, and 27.3% possible).[26] During the 2013–2014 cycle, 4859 patients were tested, of which 88 (1.7%) had positive reactions to decyl glucoside.[27] The rate of global relevance was 88.3% (5.9% definite, 27.1% probable, and 55.3% possible). There is therefore a slight but steady increase in the number of positive reactions detected through the years.

McGill University Health Centre Database

The NACDG standard series is used at the McGill University Health Centre (MUHC). Between January 2009 and June 2016, 3095 patients were patch tested. A total of 20 (0.65%) patients were found to be sensitized to decyl glucoside. During the same period, among the 3095 patch tested patients, 1628 were also tested to lauryl glucoside in a comprehensive cosmetics and vehicles series. A total of 15 (0.92%) of the latter patients gave a positive reaction to lauryl glucoside, 6 of whom were also allergic to decyl glucoside. Interestingly, 9 patients reacted to lauryl glucoside alone. Patient demographics and results of testing appear in Tables 2 and 3. The positivity rate was low in the first years but has steadily increased between 2014 and 2016 when patch testing was positive in 1.37% of 437 patients in 2014, 1.47% of 409 patients in 2015, and 2.2% of 227 patients tested in the first 6 months of 2016. Most of the patients thus far detected were women (73%) with an atopic background (86%). The average age of the patients was 47.7 years (median, 47 years), and the dermatitis most commonly affected the hands and the face in accordance with previous reports. Only 1 case could be attributed to an occupational exposure.

Groupe d' Etudes et de Recherches en Dermato-Allergologie

Between 2005 and 2007, decyl glucoside 2% in water, provided by the manufacturer of a sunscreen that contained Tinosorb M, was added to the patch testing battery used by the members of the group in France, Belgium, and Switzerland and gave positive reactions in 0.5% of tested patients. It was rapidly replaced in 2008 by lauryl glucoside 5% in petrolatum, which is more easily obtained from suppliers of patch testing allergens. Since 2012, the positivity rate for lauryl glucoside has always been more than 1.5% (2% in 2012, 1.59% in 2013, and 2.59% in 2014).[28] These numbers were deemed considerable by the members of the Groupe d' Etudes et de Recherches en Dermato-Allergologie (GERDA). They concluded that this alkyl glucoside should remain in the baseline patch testing series because it is a common emerging allergen.

At a recent meeting of GERDA, one of the authors (M.C.F.L.) presented the following case: a 32-year-old nurse aide with a background of atopic dermatitis, asthma, and allergic rhinitis was seen in 2014 with chronic dermatitis unresponsive to topical corticosteroids. The lesions involved the fingers, the dorsum, and the palm of both hands, with extension to the forearms. She was patch tested in June 2015 with the European baseline series supplemented with a preservative series, her own topical products, nitrile gloves, and products from the workplace. At the 72-hour reading, the only relevant positive reaction (2+) was to a hand cold cream that the patient had been using on a daily basis for a number of months. Her lesions cleared when she stopped using this moisturizer.

In December 2015, additional patch tests were conducted with the 17 ingredients of the cold cream, with 2+ reactions at 48 and 96 hours to a single compound called glucolipide, tested at a concentration of 3% (Fig. 2). It is a mixture of arachidyl alcohol 55%, arachidyl glucoside 15%, and behenyl alcohol 30%. Further tests at concentrations of 1% and 3% of a mixture of arachidyl alcohol and behenyl alcohol, as well as behenyl alcohol alone, were negative, suggesting that arachidyl glucoside was the actual sensitizer. The patient did not react to lauryl glucoside 5% or to decyl glucoside 5%. Semiopen tests with shampoos containing coco glucoside were negative and so was a test under occlusion with a cream containing xylityl glucoside. However, 2+ reactions were elicited with creams containing cetearyl glucoside and octyldodecylxyloside (Fig. 3). The ingredients of the latter products were not tested separately, but the pattern of reactivity again suggests that glucosides and xyloside are the culprits that cross-react with arachidyl glucoside.

Glucolipide (Montanov 202; SEPPIC, Puteaux, France) is an emulsifier of vegetal origin, synthesized from rapeseed fatty alcohols

TABLE 2. Characteristics of MUHC Patients With Positive Reactions to Glucosides

No	Sex	Age	Atopy	Site	Source	Polysensitized	Decyl Glucoside		Lauryl Glucoside	
							48 h	96 h	48 h	96 h
1	F	49	E, A, R	Face	Face cream	Yes	+	+	+	+
2	F	66	R	Face, eyelids	Facial cosmetics	Yes	0	++	0	+
3	F	71	R	Generalized	Moisturizers	Yes	+	+	+	+
4	M	42	E, R	Face, arms, axillae	Deodorants, shaving cream	Yes	?	+	NT	NT
5	M	50	E, R	Hands	Moisturizers	Yes	+	++	NT	NT
6	F	47	E, R	Hands	Hand creams	Yes	?	+	0	0
7	M	20	E, A, R	Face, eyelids	Face cream	Yes	0	+	0	+
8	F	37	E	Face	Facial cosmetics	Yes	0	+	0	0
9	F	51	E, R	Hands	Hand creams	Yes	+	+	0	+
10	F	45	E, A, R	Hands, generalized	Hand creams, moisturizers	Yes	?	+	0	0
11	F	35	E, R	Generalized	Moisturizers	Yes	0	+	0	0
12	M	16	E	Sun exposed	Sunscreens	Yes	0	++	NT	NT
13	M	29	E	Hands	Hand creams	No	+	+	NT	NT
14	F	42	A, R	Face, eyelids	Facial cosmetics	Yes	0	+	0	0
15	F	32	A	Hands	Hand creams	Yes	+	+	+	+
16	F	41	E, R	Face, trunk, arms	Moisturizers, sunscreens	No	+	+	0	0
17	F	62	E, A, R	Perianal, face, neck	Wet wipes, moisturizers	Yes	0	+	0	0
18	F	52	None	Face	Facial cleansers	No	0	+	0	0
19	M	51	R	Hands	Moisturizers	Yes	?	+	0	0
20	F	41	E, A, R	Face, arms	Moisturizers, shampoos	Yes	0	+	0	0
21	M	43	R	Scalp, abdomen, knees	Shampoos, moisturizers	Yes	0	0	0	+
22	F	35	A	Scalp, face	Hair dye	Yes	0	0	0	++
23	F	60	None	Scalp, face, neck	Hair dye	Yes	0	0	0	+
24	F	82	None	Leg ulcer	Moisturizers	Yes	0	0	0	+
25	F	65	E	Generalized	Moisturizers	Yes	0	0	?	+
26	F	45	E	Hands	Hand creams	Yes	0	0	0	+
27	F	54	E, A, R	Chest, arms	Moisturizers	Yes	0	0	?	+
28	M	72	None	Leg ulcer	Moisturizers	Yes	0	0	+	+
29	F	49	E	Neck	Moisturizers	Yes	0	0	+	+

A indicates asthma; E, eczema; F, female; M, male; NT, not tested; and R, rhinitis.

and wheat glucose. Arachidyl glucoside (CAS 100231-68-3) is produced during the manufacturing process and is not available as a separate ingredient. Despite its ominous name, it is not derived from peanuts (*Arachis hypogaea*). It can be found in shampoos, conditioners, creams, and sunscreens. At the time of submission of this article, we believe that this case may be the first report of allergic contact dermatitis to arachidyl glucoside.

Screening and Patch Testing

Leave-on products can be tested undiluted under occlusion, whereas undiluted rinse-off products should be tested with the semiopen technique. Comprehensive baseline and cosmetic series should be used. It is essential to obtain from the manufacturer and to test the individual ingredients of any product that causes an allergic patch test reaction.

The optimal patch test concentration for the detection of allergy to glucosides is still not established. As of this writing, 2 major suppliers (AllergEAZE; SmartPractice, Phoenix, AZ and Chemotechnique Diagnostics, Vellinge, Sweden) commercialize decyl glucoside at a concentration of 5% in petrolatum, but many cosmetic series have not yet introduced it or other alkyl glucosides. The molecule most frequently used for patch testing is lauryl glycoside 3% in petrolatum because it has been commercialized for a longer period of time. Lauryl glycoside seems to be a good marker of sensitization to the alkyl glucoside family, but cases may be missed because it does not automatically cross-react with other alkyl glucosides. Patients who react to Tinosorb M should be tested to decyl glucoside as recommended by the NACDG and other authors of relevant case reports.

Cross-Reactions

Reactions to multiple structurally related alkyl glucosides seem to be frequent, but not systematic, among patch tested patients and are seen mainly between decyl glucoside, lauryl glucoside, coco glucoside, and cetearyl glucoside. Thus, sensitization seems to be a group allergy with possible cross-reactivity, probably related to the similar structure of glucosides. It is well known, however, that the industrial manufacturing process results in blends of different alkyl glucosides[20] and patch test reactions to different glucosides may

TABLE 3. Clinical and Demographic Characteristics of MUHC Patients With Positive Reaction to Glucosides

Characteristics	All Cases (n = 29) Tested to Decyl Glucoside (3095) Tested to Lauryl Glucoside (1628)
Age, mean, y	47.7
Sex, n (%)	
Female	21 (72.4)
Male	8 (27.6)
Clinical presentation, n (%)	
Face, scalp, neck, or sun-exposed	15 (51.7)
Leg ulcer	2 (6.9)
Hand dermatitis	7 (24.1)
Generalized dermatitis	4 (13.8)
Trunk (abdomen, proximal extremities)	4 (13.8)
Atopy, n (%) (rhinitis, eczema, or asthma)	25 (86.2)
Type of product	
Rinse-off (shampoos, soap)	
Shampoos	2
Soap and skin cleanser	1
Shaving cream	1
Leave-on	
Moisturizers	13
Hand creams	6
Sunscreen	2
Deodorants	1
Facial cosmetics and cream	4
Wet wipes	1
Hair dye	2
Positivity rate	
Decyl glucoside	20/3095 (0.64%)
Lauryl glucoside	15/1628 (0.92%)
Both (cross-reactivity)	5/29 (17.2%)

All the 29 cases were patch tested to decyl glucoside, but 25 were tested simultaneously to lauryl glucoside.

therefore represent concomitant reactions. A recent study, which aimed to identify possible allergenic impurities in commercial samples of alkyl glucosides, found that isobornyl acrylate (Fig. 4) may possibly be a cause of sensitization to many alkyl glucosides, but this finding needs confirmation by further patch tests in patients sensitized to alkyl glucosides.[5] Isobornyl acrylate is used as a plasticizer in various plastic materials and could be leached out of the container by the surfactant properties of alkyl glucosides. The presence of isobornyl acrylate was not verified in the glucolipide mixture that sensitized the arachidyl-allergic patient, but the manufacturer of the cold cream receives it from his supplier in polyethylene bags that likely do not contain this plasticizer.

Wilkinson and Powis[29] published a case of allergic contact dermatitis to octyldodecyl xyloside, a constituent of a cosmetic

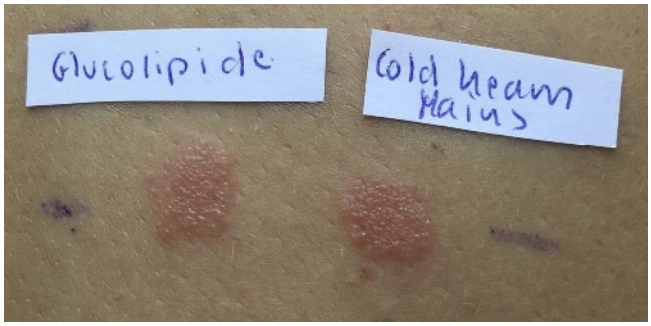

Figure 2. Positive patch tests to cold cream and glucolipide.

serum. This new allergen is closely related to alkyl glucosides. Structurally, xylose replaces glucose and the aglycone moiety is an alcohol with a double-side chain of 12 and 8 carbons instead of the fatty alcohol single-side chain in alkyl glucosides. No patch test was done to verify concomitant sensitization to alkyl glucosides. Interestingly, our patient displayed a strong positive patch test reaction to a cream containing this newer surfactant.

Blondeel[2] raised the hypothesis of potential cross-reactivity between decyl glucoside and methyl glucose dioleate. He described a patient sensitized to decyl glucoside in a sunscreen who also reacted to Nizoral (Janssen, Beerse, Belgium) shampoo, which contains methyl glucose dioleate. Unfortunately, the patient refused further patch testing to identify the culprit sensitizer.

CONCLUSIONS

Alkyl glucosides are stable molecules made by condensation of glucose and a fatty alcohol. Their range of usage is limited to cosmetic

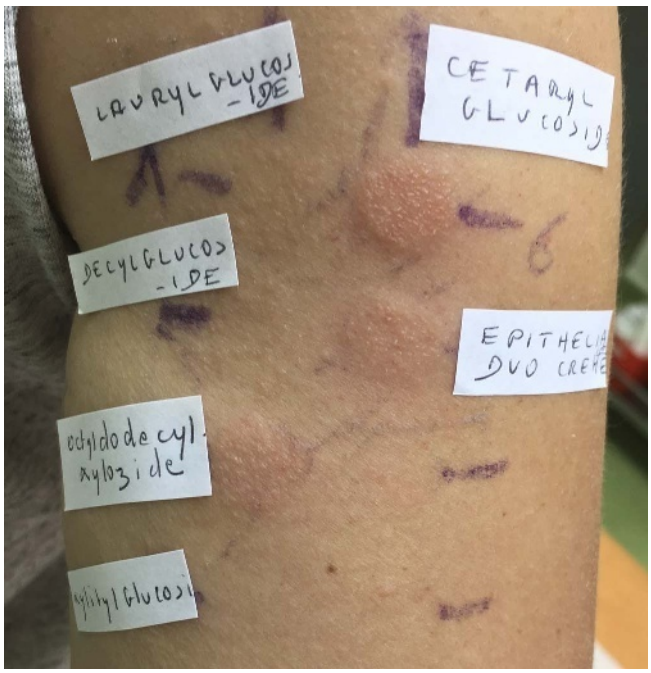

Figure 3. Repeat patch tests with positive reactions to various glucosides.

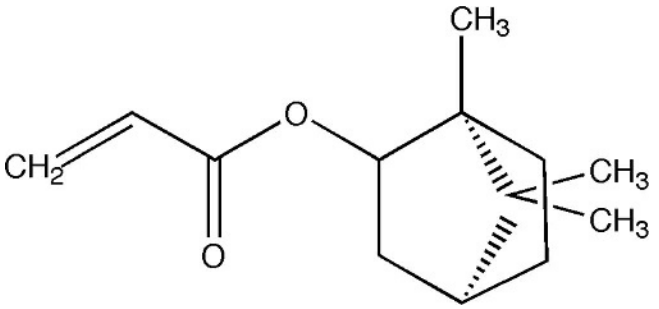

Figure 4. Chemical structure of isobornyl acrylate.

and cleansing materials. Decyl glucoside was also recently introduced as a stabilizer in the sunscreen agent Tinosorb M. Given the increasing number of publications, it seems that the sensitizing potential of alkyl glucosides is important and higher than expected. It may be underestimated because of the absence of systematic patch testing in many cosmetic series. Alkyl glucosides should be included in all patch test cosmetic series and, more specifically, decyl glucoside should be tested if allergy to Tinosorb M is suspected. Because they do not automatically cross-react, it is recommended to test multiple alkyl glucosides to increase the rate of detection. Avoidance of all cosmetic products containing alkyl glucosides and sunscreens containing Tinosorb M is recommended in sensitized patients because cross-reactions are common among tested patients.

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Dermatitis

Occupational contact dermatitis in the Canadian aircraft industry: a 25-year retrospective study

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Abstract:	Background. Aircraft building exposes workers to irritant and sensitizing products. Objectives. To study occupational dermatoses among aircraft workers over 25 years. Methods. The files of aerospace workers referred between 1990 and 2015 were extracted from the database of the McGill University Health Centre contact dermatitis clinic. These were subdivided according to demographics, type of work, patch testing results and final diagnosis. Results. Of 305 workers, 58% were 40 years old or less, one third were women. Onset of dermatitis varied from 2 months to 25 years, but 120 (39%) cases occurred during the first 3 years. 51% of the cases involved assemblers, and 27% composite materials technicians, over-represented as they constitute 10% of the workforce. Of the 305 workers, 152 suffered from allergic contact dermatitis (ACD) and 96 from irritant contact dermatitis (ICD). Of those with ACD, 124 reacted to epoxy-based workplace products, but only 48 had positive patch tests to commercially available epoxy allergens. Conclusion: More than 60% of the cases of epoxy allergy would have been missed without testing with workplace products.

Occupational contact dermatitis in the Canadian aircraft industry:

A 25-year retrospective study

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Occupational contact dermatitis in the Canadian aircraft industry: A 25-year retrospective study

In the 1980s and 1990s, European and American authors have studied occupational contact dermatitis in the aircraft industry.[1,2] Modern aircraft-building materials such as reinforced fabrics pre-impregnated with a resin system ("prepregs"), surface coatings and sealants contain potentially allergenic thermosetting polymers. Over a period of 25 years, the contact dermatitis clinic of the McGill University Health Centre has patch tested more than 300 aerospace workers. In this work, we aim to define the patterns of occupational dermatitis in each category of workers, broaden knowledge about contact allergens in the aircraft industry, observe changes and progression of cases over the years, and compare our results with those of previous publications.

Materials and Methods

This retrospective study covers a period from September 1990 to December 2015. Each patient, referred by the company health and security personnel, was questioned and examined at the McGill University Health Centre contact dermatitis clinic during a preliminary visit. Demographic characteristics including age, years of employment, personal or family history of atopy, description of work and of dermatitis were recorded. Patch testing was performed during three subsequent visits over 5 days. Allergens were applied at day (D) 0 and removed at D2. Readings were done at day D2 and D4 according to ICDRG criteria. Doubtful reactions were correlated with the

patient's history of exposure and rejected or included accordingly. Patients reporting late reactions were seen again and re-tested if necessary. After obtaining informed consent, each patient was patch tested with a North American standard series (Chemotechnique Diagnostics, Vellinge, Sweden) between 1990 and 2000, and then with the North American Contact Dermatitis Group (NACDG) standard series (Chemotechnique Diagnostics from 2000 to 2010, thereafter AllergEAZE, SmartPractice, Calgary, Canada), applied on Finn Chambers (SmartPractice, Phoenix, AZ, USA). The Glues and Adhesives series (Chemotechnique Diagnostics) was tested on IQ chambers (Chemotechnique Diagnostics). Most workers were also tested with workplace materials, included in a personalized "tailor-made series" (Table 1) composed of 15 modified epoxy, polysulfide and phenolic resins tested on IQ chambers. The employer provided unmixed part A and part B of each product. After careful review of the material safety data sheets, samples were mixed in petrolatum in serial dilutions so that their main component was at an acceptable concentration for patch testing. These preparations were tested on 6 controls and irritant concentrations were excluded. Also used was a composite materials series comprising ten 1x1 cm squares of various undiluted prepregs (Table 2) applied on Scanpor® tape (Norgesplaster AS, Vennesla, Norway). Beginning in 1993, all workers referred for assessment of occupational contact dermatitis were tested with the standard, glues, and tailor-made series. In addition, from the year 2000, composite materials technicians were also tested with the customized prepregs series. Machinists and metal workers were tested with the cooling oils and metals series. A few workers were tested with pieces of workplace gloves, solvents (including oxidized limonene) or barrier creams and industrial cleansers, the latter with the semi-open technique and after testing at least 6 controls. Patients for which contact urticaria was

suspected were submitted to open and closed patch tests, respectively on the inner forearm and on the upper back, with readings after 30, 60 and 90 minutes. The same procedure was repeated on at least 6 controls when workplace products were tested. No prick testing was done.

Results

Demographics

A total of 305 workers were evaluated. One was excluded because he was lost to follow-up. Eight patients were seen for a second patch test between 8 months to 3 years after the first session. Before 1999, the number of patients was relatively low and constant with an average of three patients per year. In 1999 the number of cases increased sharply to reach a peak in 2001 with 45 patients (Fig. 1). In 2005, the number of cases decreased and is now stable with approximately 5 to 10 cases per year.

The age distribution of workers ranged from 19 to 64 years with a mean of 37 years. Of those with allergic contact dermatitis (ACD) the mean age was similar at 36 years. Seventy-three percent of workers were males, paralleling the sex representation of workers in this industry. However, among patch tested female workers, 58% had a final diagnosis of allergic contact dermatitis compared to 47% of males. Atopy, defined as a personal history of eczema, asthma or allergic rhinitis, was found in 30% of the cases. Forty-six workers (15%) gave a history of past or present atopic dermatitis. Irritant contact dermatitis (ICD) affected 15 of these workers and worsened the atopic

eczema of 6 of them. By contrast, of 23 workers with ACD, 8 felt that it worsened their atopic dermatitis.

The time of onset of work-related dermatoses varied among patients from less than one year to more than 25 years after the beginning of employment. However, 49% of workers with ACD developed sensitization before 3 years of employment (Table 3).

More than 50% of affected workers were assemblers or sealers, around 25% were composite material technicians, 5% machinists and the remaining 20% were other professionals such as painters, electricians, cabinet makers, etc. The composite material technicians represent the group with the highest proportion of allergic contact dermatitis (79%) while machinist and other types of workers have the lowest rate (20%). Machinists and other workers have a higher incidence of ICD (60% and 50%) while the incidence is lowest for composite material technicians (17%). In our cohort, the overall prevalence of ACD (51%) was higher than ICD (32%).

Clinical presentation

The hands were most often involved. A fissured and scaly dermatitis affecting the tip of the first three fingers was commonly seen in sensitized workers (Fig. 2). Involvement of the dorsal hand was occasionally found in composite materials technicians who smooth out prepregs over molds with the back of their bare hand. The second most common site of involvement was the inner forearm of assemblers and

sealers who often worked in short sleeves without protective equipment. The face and other exposed areas were affected by airborne exposure or contaminated hands.

Fourteen workers were referred because of repeated episodes of transient widespread, pruritic erythema and wheals lasting minutes to hours. Most of these workers claimed that these lesions only occurred at work. None of the patients had lesions at the time of examination, but photos clearly showed urticaria. These patients were given a presumptive diagnosis of contact urticaria even though in some cases the lesions did not always first appear on exposed areas.

Patch testing

Overall, 152 (50%) patients were sensitized to workplace products (Tables 3 and 4). Ninety-six (32%) workers were diagnosed with occupational irritant contact dermatitis and 56 (18%) with another type of dermatitis. Among those, 14 (4.5%) suffered from occupational urticaria, while 42 (13.5%) had non-occupational allergic contact dermatitis, atopic dermatitis, seborrheic dermatitis or asteatotic and dyshidrotic eczemas. Allergy was more common than irritation due to the strong sensitizing potential of epoxy resins and polysulfide or phenolic resins in sealants and prepregs. The distribution of the dermatitis was consistent with an airborne pattern in 57 (37.5%) of allergic contact dermatitis patients and in 18% of those diagnosed with irritant contact dermatitis.

Among the 152 workers with occupational sensitization, 54 (35.5%) had positive reactions to DGEBA epoxy resin from the standard series, 9 reacted to phenyl or cresyl

glycidyl ether, 6 to DGEBF epoxy resin and 3 to cycloaliphatic epoxy from the glues and adhesives series. Polysulfide- (Thiokol), phenolic- and modified epoxy resin-based sealants and putties were responsible for positive reactions in 89 (58.5%) subjects. Given that the individual ingredients of these products were not separately tested, the specific allergens of those patients who reacted only to workplace products still remain undetermined. Prepregs caused positive reactions in 76 (50%) subjects, not exclusively composite materials technicians. The prepregs were tested “as is” and we cannot therefore ascribe the workers’ sensitization to a specific ingredient.

Allergic sensitization to hexavalent chromium was revealed in 20 patients through positive patch test reactions to potassium dichromate. Nickel allergy was found in 28 patients (19 women and 9 men) but was relevant to work exposure in only two cases, both assemblers. Cobalt and formaldehyde-releasing biocides caused relevant but rare reactions. All patients were tested with Finn Chambers, and none had multiple reactions suggestive of aluminium allergy. Machinists were tested to a metals series that contained aluminium 100% and aluminium (III) chloride hexahydrate (both from Chemotechnique). No reaction was seen.

Of the suspected cases of contact urticaria, only two had positive tests at the 30 and 60 minutes readings. The first patient reacted to Dinitrol® AV 15, an anticorrosive fluid containing hydrotreated naphtha and aliphatic mineral spirits, and the second patient reacted to DGEBA epoxy resin and to cresyl and phenyl glycidyl ethers.[3] Immediate reactions were previously reported with phenyl glycidyl ether.[2]

Discussion

Workers distribution and task description

Machinists and metalworkers are exposed to direct skin contact and aerosolized mists of petroleum-based or water-miscible cutting oils, solvents, degreasers, anticorrosive agents, aluminum and steel. Assemblers and sealers put together the different parts of the plane. Sealants are applied to jointed surfaces with a brush or air-driven applicator guns, and then smoothed with a spatula, at times with bare fingers. Solvents are used to clean surfaces, tools and hands. Assemblers are exposed to metallic parts coated with chromate-containing primer paints, and they often must repair small dents or defects with resin-based putties. Composite material technicians apply prepregs to a ”tool’ or cast. The part is heat-cured and finished by deburring, drilling and sanding. Handling of the materials prior to hardening puts technicians at risk of direct or airborne contact dermatitis, particularly when heating prepregs with a blow dryer. Hardened parts are theoretically non-allergenic, but drilling and sanding operations create heat that depolymerizes the resin, and generate a shower of irritant or allergenic particles. Surface preparers are exposed to solvents and cleaning products over a wide range of pH. Interior finishers handle and transform plastics, adhesives, varnishes, fabrics, leather, rubber and exotic woods. Electricians, electronic systems specialists and jet engine mechanics are affected less often, while painters are usually well protected by their impermeable suits and airline respirators.

Irritant contact dermatitis

ICD was common among the workers with 96 out of 304 cases (32%). Fifteen had a history of atopic dermatitis and 6 reported that it was worsened by ICD (40%). Hand dermatitis was the usual presentation. Machinists, electricians, painters and cabinet-makers were affected by exposure to coolants, solvents, paints, glues and woods. Airborne dermatitis with facial involvement was also present in 55 cases (18 %). Carbon fibers from uncured composite material were a possible cause of airborne irritation (2). Also, hard particles from grinding, sanding, or drilling cured composites and metal can cause irritation on exposed skin.

Allergic contact dermatitis

Allergic contact dermatitis is a common problem in the Canadian aircraft industry, with 152 out of 304 patch tested workers. Contrarily to the findings of some earlier publications,[1,2,4] ACD was more common than ICD in our cohort. Various hypotheses can be proposed to explain this difference. First, ACD may have been underestimated in earlier publications if subjects were not tested with their workplace materials. Second, some studies were published before prepregs, an important cause of ACD, became widely used. In our study population, the distribution of cases of ACD through the years reveals an increase in the number of sensitized workers that coincides with the introduction of these composite materials in the early 2000s.

Epoxy resin systems

The most common allergen in our sensitized workers was DGEBA-derived epoxy resin with 55 cases. This is not surprising because DGEBA is currently the most important sensitizer in epoxy resin systems.[5] Epoxy resins based on bisphenol F are also commonly used in the aircraft industry. We thus began screening with DGEBF epoxy resin 0.25% pet. in January 2003. All patients with positive reactions to DGEBF also reacted to DGEBA and to their workplace products. These simultaneous reactions may represent concomitant reactions or true cross-reactions.[6,7] Contact allergy to cycloaliphatic epoxy resin was uncommon with only 3 patch test positive cases. By comparison with the 4 cases in Hackett's study,[2] sensitization to phenyl and cresyl glycidyl ether reactive diluents was more common in our cohort with 9 cases (6%). Aliphatic amines hardeners were responsible for ACD in only 6 (4%) of our patients compared to 4 (9%) in Hackett's study.[2]

Aniline epoxy resins

Prepregs are made of a flexible support of graphite, Kevlar®, fiberglass, carbon or aluminum, pre-impregnated with a semi-solid resin. Burrows[4] and Mathias[8] had already identified the main sensitizers in prepregs, later confirmed in the Bruze study.[9] Subsequently, Kanerva reported quantitative data on the content of prepregs after using gas and liquid chromatography.[10] The known ingredients are tetrabromo-bisphenol-A diglycidyl ether (Br-DGEBA), tetra-4,4'-methylenediamine (TGMDA), triglycidyl-p-aminophenol (TGPAP) as well as proprietary epoxy-phenolic resins.

Sensitization to TGPAP and TGMDA from resin-based composite materials has been previously described.[4,7-12] These compounds are expensive, unstable and must be

bought from suppliers of chemical products, as they are absent from commercially available patch test series, hence our decision to test the prepregs themselves. Burrows et al. have shown in their publication that testing composite materials “as is” can be a sensitive and reliable alternative,[4] while Mathias warns about the risk of actively sensitizing workers tested with undiluted prepregs.[8] Two workers developed late reactions and were seen again: one patient who had a positive reaction on D4 to one prepreg reacted to three additional prepregs by D7. The second worker was negative on D4 but positive to EA-934-NA Part A by D9. None of our patients reported a delayed reaction beyond D9 that would suggest active sensitization. Seventy-six workers reacted to one or more prepregs, while only 32 (21%) had concomitant reactions to the regular DGEBA epoxy resin of the NACDG standard series. Therefore, allergic sensitization to aniline epoxies would have remained undetected in 44 cases. This shows that commercially available epoxy allergens are inadequate to detect all cases of sensitization because TGPAP and TGMDA do not cross react with them.[5]

Tailor-made aircraft series

Most aircraft coatings and putties contain standard epoxy resins such as diglycidyl ethers of bisphenol A and bisphenol F (DGEBA and DGEBF), and epoxy derivatives, modified by bromination or based on 4-glycidyloxy-N,N’-diglycidylaniline (GDOGA), also known as triglycidyl-p-aminophenol (TGPAP). Some products are mixes of modified epoxys with phenolic (Novolac) resins. Accelerators are conventional aliphatic amines such as diethylenetriamine (DETA), triethylenetetramine (TETA) or polyoxypropylene diamine. The two parts are now pre-mixed in a cartridge and kept refrigerated to prevent premature polymerization. Interestingly, 89 patients had positive

reactions to components of our tailor-made series but only 43 (28.3%) had concomitant reactions to epoxies from the standard or glues series. Allergic sensitization from catalysts were uncommon

All prepregs, and 10 of the compounds of the tailor-made series are epoxy-based (Tables 1 and 2). By combining the patch test results of the two series, 124 workers became sensitized to one or more epoxy-containing workplace products, 76 to prepregs, as already mentioned, and 48 to epoxy-based sealants and coatings. However, only 48 (38.7%) of these 124 patients showed concomitant reactions to any of the commercially available epoxy allergens. Therefore, 76 epoxy-allergic workers (61.3%) would have been missed if not tested with products from the workplace.

Sealants are composed of a polysulfide polymer, manganese dioxide and terphenyl, or a mixture of polysulfide and epoxy resins**.** Accelerators contain magnesium, calcium or barium chromates. ACD from polysulfide-containing sealants has been described.[13] Our series contained three such sealants. Twenty patients reacted only to these three products. Even though in each case the specific allergen could not be determined, at least the use of our personalized series significantly helped identify more cases of ACD and facilitate avoidance of specific workplace products.

Metals

Unsurprisingly, chromates were an important cause of sensitization as 20 workers presented with positive patch test reactions to potassium dichromate. In 1944, Hall first described contact allergy to potassium dichromate in the aircraft industry.[14] Chromic

acid and hexavalent chromium salts are ubiquitous, found in corrosion inhibitors, metalworking fluids, primers or epoxy coatings and putties.[2,4,14,15] Nickel allergy was seen in 28 (18.4%) patch-tested patients, a sensitization rate also found in the overall population of patients referred for patch testing (27% in women and 7% in men) and rarely relevant to occupation. Positive reactions to cobalt were deemed relevant in 9 cases and were attributed to resin systems.

Clinical presentation

The time of onset of sensitization was unpredictable. Older and more experienced employees were unfortunately not at a lower risk of sensitization. Women were shown to have higher rates of sensitization than men. Because of the slenderness of their hands and fingers, women have the dexterity required to work in restricted spaces. Thus, they are commonly assigned work at higher risk of sensitization such as laying of prepregs in confined spaces, often without gloves.

The clinical findings parallel previous authors' descriptions.[1,2,4] Hands, forearms and face were the most commonly affected sites, in descending order. We have also noted the characteristic fingertip dermatitis (Fig. 2) associated with allergy to epoxy resin systems.[1,2] Interestingly, airborne exposure to allergens was causative in 57 (37.5%) of our cases. Composite materials technicians who used driers to heat prepregs often developed facial dermatitis, at times with eyelid edema. Some of the most severely allergic patients would develop facial eczematous lesions within a few hours of walking through the workstation for a few minutes.

Urticaria

Fourteen workers with presumed contact urticaria presented with the rapid onset of urticarial lesions occurring within minutes or hours of beginning work. Two cases were confirmed by positive patch tests with early readings. The other suspected cases could not be confirmed by patch testing. Some cases of generalised urticaria could have been secondary to inhalation of volatile compounds rather than by skin contact. It is difficult to prove the causal relationship between work exposure and contact urticaria by patch testing. It is useless when sensitization occurs by inhalation, when even specific inhalation challenges may fail to identify the culprit. We relied on a good history of urticaria occurring exclusively upon exposure in the workplace, with negative findings such as dermographism or other physical urticaria, to make a provisional diagnosis of occupational urticaria.

Prevention methods

Over the years, implementation of effective prevention measures has reduced the number of cases of occupational dermatoses. In the early 2000s, a fair number of assemblers became sensitized because they were allowed to mix resin-based products in tiny plastic cups, with resultant spillage and contamination of the entire workstation. The task of mixing resins and hardeners was later assigned to a single experienced technician working in a specially dedicated work area. The assemblers were still served the mixture in inadequate containers and continued to become sensitized. It was only

towards the end of the last decade that two-part resin-based materials became available in pre-mixed, frozen cartridges that decreased the risk of skin contamination.

The employer had always recommended that workers use available protective equipment such as thick neoprene gloves, Tyvek® sleeves, aprons and masks. However, workers were initially reluctant to use them, considering such equipment as bulky, hot, and not adapted to tasks requiring precision and manual dexterity. The labor unions eventually recognized the importance of prevention and requested that preventive measures be more strictly implemented and that workers be instructed in the correct use of personal protective equipment (Fig 3.). These measures have helped to reduce the number of cases of occupational contact dermatitis in this work environment.

Limitations of the study

Although our study is one of the largest about occupational dermatoses in the aircraft industry, we are conscious of its inherent limitations. The actual number of allergic contact dermatitis cases may still be underestimated. The tailor-made series was not systematically tested until 1993. Only at the beginning of 2000 have we tested our first patient with prepregs (Kevlar® and graphite). It is probable that some cases of allergic sensitization to prepregs prior to 2000 may have been undetected. In those early years, we may have missed some cases of allergic contact dermatitis because of incomplete patch testing. The fact that we have not tested TGPAP and TGMDA or any of the individual components of the workplace materials is another limitation of our study. We are therefore unable to quantify the number of cases caused by each of those

sensitizers. The cases of urticaria claimed to occur only at work remain puzzling and unexplained for the most part except for two cases where patch tests were positive.

Conclusion

This is the first Canadian study to look at contact dermatitis in the aircraft industry. Workers are particularly at risk of occupational dermatoses. In this milieu allergic contact dermatitis is more prevalent than irritant contact dermatitis. Commercial allergens are largely insufficient to detect sensitization. More than 50% of patients with allergy to epoxy resins would have been missed without testing with workplace products. Polysensitization is common, and allergy to chromates is not rare. Educating the employees to the importance of protective equipment can clearly reduce the number of cases of occupational dermatoses and should remain an essential part of prevention strategies. The constant evolution in materials used by the aerospace industry paves the way for the emergence of new allergens. This is why it is essential to keep patch testing workers suspected of occupational contact dermatitis with their workplace products.

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Legends of figures.

Fig. 1. The number of cases of occupational dermatoses increased sharply during the first half of the 2000 decade, paralleling increased hiring and production.

Fig. 2. Characteristic scaly and fissured fingertip dermatitis in a worker sensitized to epoxy resins.

Fig. 3. An assembler wearing adequate protective equipment.

Figure 1.

Click here to download Figure Fig. 1. Cases per year.pdf

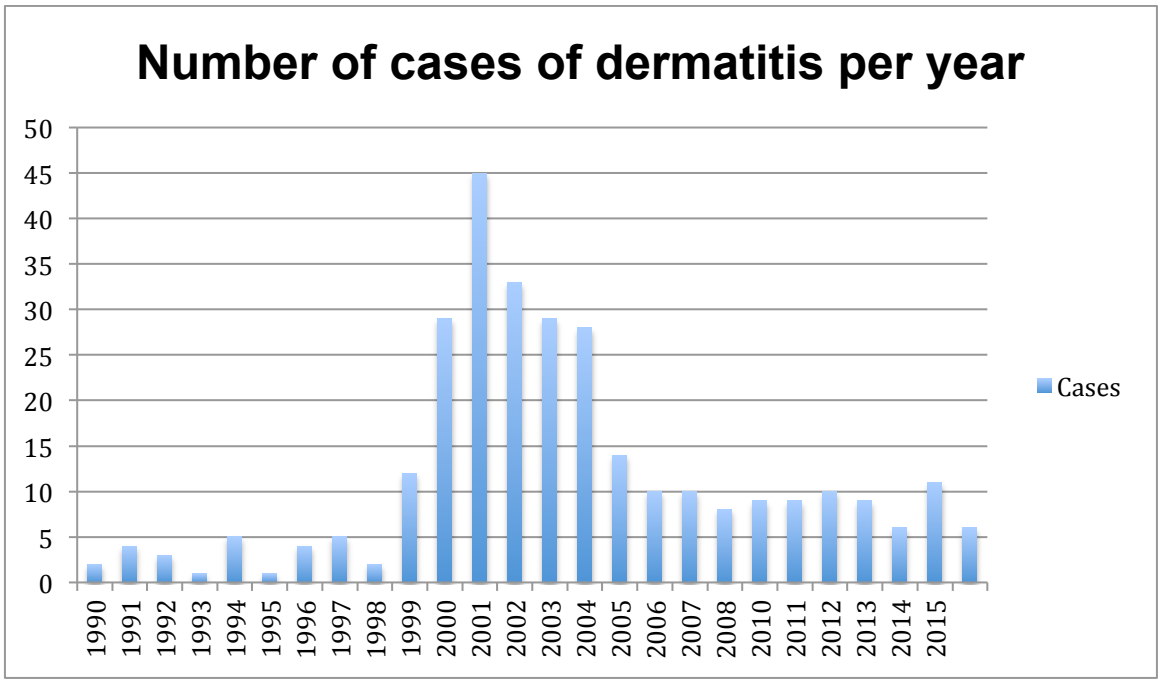

Figure 2.

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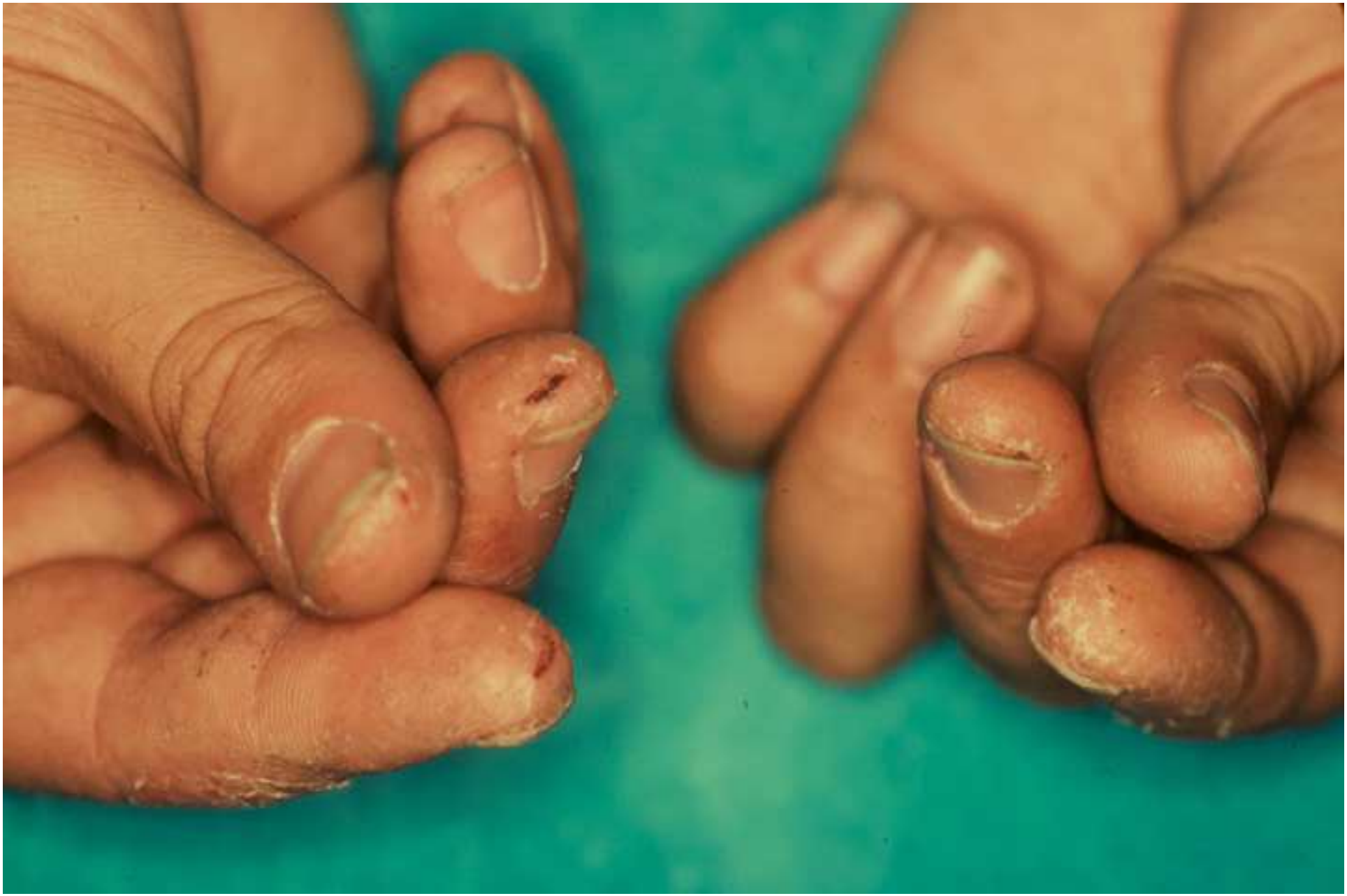

Figure 3.

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Table 1. Products tested in the "Tailor-made Series" with their respective concentrations. The number of tested products was always limited to 15 per patient, but the composition of the series varied over the 25 years of the study period.

Product	Main components according to MSDS
1. Pro-Seal 870 B2 Part A (25% pet) 2. Pro-Seal 870 B2 Part A (2.5% pet) (Similar composition for PR 1750 B1/2)	Manganese Dioxide 30-60% Hydrogenated Terphenyls 30-60% Magnesium Chromate 10-30% 1,3-Diphenylguanidine 1.8%
3. Pro-Seal 870 B2 Part B (50% pet) (Similar composition for PR 1750 B1/2)	Liquid Polysulfide Polymer 30-60% Modified Polysulfide Polymer 1-10%
4. EA 934 NA "Liquid Shim" Part A (1% pet)	GDODGA (also known as TGPAP) 30-60% Phenol Formaldehyde, Glycidyl Ether 10-30%
5. EA 934 NA "Liquid Shim" Part B (1% pet)	Diethylenetriamine 10-30% Triethylenetetramine 1-5%
6. PR 1422 B2 Part A (5% pet) 7. PR 1422 B2 Part A (1% pet)	N,N-Dimethylacetamide 15-40% Calcium dichromate 10-30%
8. PR 1422 B2 Part B (50% pet) 9. PR 1422 B2 Part B (5% pet)	Modified Polysulfide Polymer 1-5% Bisphenol A Diglycidyl Ether 0.5-1.5%
10. CS 5500 Part A (100%) 11. CS 5500 Part A (50% pet)	Liquid Polysulfide Polymer <71% Phenolic Formaldehyde Polymer <5%
12. CS 5500 Part B (10% pet)	Manganese Dioxide <65% Hydrogenated Terphenyl <50 1,3 Diphenylguanidine <3%
13. 7009 Scotch Weld Core Splice A (1% pet)	Maleic Anhydride (Myrcene adduct) 1-10% Maleic Anhydride (Cymene adduct) 20-30% Hexahydrophthalic Anhydride 28-32%
14. 7009 Scotch Weld Core Splice B (1% pet)	4-Glycidyloxy-N,N-diglycidylaniline (GDODGA or TGPAP) 60-65%
15. EA 9309.3 Part A (1% pet)	Epoxy Resin 60-100% Modified Epoxy Resin 1-5%
16. EA 9309.3 Part B (2% pet)	Polyglycol Diamine 60-100% Substituted Piperazine 10-30%
17. EA 956 Part A (1% pet)	Triglycidyl-p-aminophenol (TGPAP) 30-60% Epoxy Resin 30-60%

18. Scotch Weld EC 3501 Part A (2% pet)	Mercaptan 40-60% Polyamide Resin 5-15% Triethylenetetramine 0.1-1.5% 2,4,6-Tris(dimethylaminomethyl)phenol 1-5%
19. Scotch Weld EC 3501 Part B (2% pet)	Bisphenol A Diglycidyl Ether 40-70%
20. Epocast 50-A1 Part A (1% pet) (Similar to Epocast 8623)	Bisphenol A Diglycidyl Ether 30-50% 1,4-Butanediol Diglycidyl Ether 1-3% Bisphenol A Epoxy Resin 7-13% Dibromo Cresyl Glycidyl Ether 3-7%
21. Epocast 50-A1 Part B (1% pet)	Bisphenol A Epoxy Resin 30-60% Novolac Resin Glycidyl Ether 30-60%
22. Scotch Weld EC 2216 Part A (2% pet)	Polymer Diamine 70-90% 4,7,10-Trioxatridecane-1,3-diamine 10-30%
23. Scotch Weld EC 2216 Part B (1.5% pet)	Bisphenol A Diglycidyl Ether 70-80%
24. Eccobond CT 5047-2 Part A (5% pet)	Bisphenol A Diglycidyl Ether 10-20% Trimethylolpropane Triglycidyl ether 1-10%
25. Eccobond CT 5047-2 Part B (1.5% pet)	Propoxylated Polyethylene Polyamine 60-100% Polyethylene Polyamine 1-5%
26. Permabond HM 128 (1% pet)	Polyglycol Dimethacrylate 30-60% Hydroxyalkyl Methacrylate 10-30% Cumene Hydroperoxide 1-5%

GDODGA: 4-Glycidyloxy-N,N-diglycidylaniline; TGPAP: Triglycidyl-p-aminophenol; Pet: petrolatum

Table 2: Composition of the "Prepreg Series"

Prepreg	Main components according to MSDS
1. BAMS 5553-01 TY Copper Mesh	Proprietary Epoxy Resin (±70%)
2. MXM 7701 Kevlar Low Temp	Aromatic Glycidyl Polyether Epoxy Phenolic Resin #2 Modified Epoxy Resin
3. Cycom 5208 Fiberglass High Temp	Aniline Derivative Aromatic Glycidyl Derivative #2 Modified Epoxy Phenolic Resin
4. Cycom 799H Fiberglass, Phenolic	Phenolic Resin 30-60%
5. Cycom 5276 Graphite High Temp	Aromatic Glycidyl 3-7% Modified Epoxy Resin 5-10%
6. FM 300-2 High Temp Adhesive Film	Epoxy Resin
7. Scotch-Weld CMS 551-10 Surface Film	Epoxy Resin Liquid 10-30% Phenol Aldehyde Epoxy Resin 30-60% Phenyl Glycidyl Derivative 10-30%
8. CMS 551-09 Supported Adhesive Film	Aniline Derivative 3-7% Epoxy Phenolic Resin #2 3-7% Aromatic Glycidyl Derivative #2 10-30% Modified Polyhalogenated Aromatic Glycidyl Ether 40-70% Halogenated Aromatic Epoxy Resin 1-5%
9. Metlbond 1113 Adhesive Film	Resorcinol Diglycidyl Ether 4-5% Epoxy Phenolic Resin #1 40-70% Epoxy Phenolic Resin #2 10-30%
10. Cycom 306 Finishing Film	Bisphenol A 2-22% Aromatic Glycidyl Polyether 10-30% Epoxy Phenolic Resin #1 1-5%

Table 3. Demographics and characteristics of 152 aircraft industry workers with allergic contact dermatitis and their positive patch test reactions.

Characteristics		Positive reactions N	(%)
Sex	Female	48	(31.6)
	Male	104	(68.4)
Years of Employment	Unknown	16	(10.5)
	<1 year	15	(9.9)
	1-3 years	60	(39.5)
	4-10 years	34	(22.4)
	>10 years	27	(17.8)
Type of work	Assembler/Sealer	75	(49.3)
	Composite materials technician	65	(42.7)
	Machinist	4	(2.6)
	Other (mechanic, painter, cabinetmaker)	8	(5.3)
Tested series	**Allergens**		
NA (1990-2000)	Potassium dichromate 0.25% pet	20	(13.2)
NACDG (2000-15)	Nickel sulfate 2.5 % pet	28	(18.4)
Standard series	Cobalt chloride 1% pet	9	(5.9)
	DGEBA epoxy resin 1% pet	54	(33.5)
	Thiuram mix 1% pet	2	(1.3)
	Diphenylguanidine 1% pet	1	(0.7)
Glues & Plastics	DGEBF epoxy resin 0.25% pet	6	(3.9)
	Cycloaliphatic epoxy resin 0.5% pet	3	(2)
	Phenyl, Cresyl glycidyl ether 0.25% pet each	9	(5.9)
	EDA 1% pet, DETA 1% pet, TETA 0.5% pet	5	(3.3)
	Hexamethylene tetramine 2% pet	1	(0.7)
	Diaminodiphenyl methane 0.5% pet	3	(2)
	Toluene diisocyanate 2% pet	1	(0.7)
	Phenol formaldehyde resin (Novolac 5% pet)	2	(1.3)
	4-tert-Butylphenol formaldehyde resin 1% pet	2	(1.3)
	Tosylamide formaldehyde resin 10% pet	1	(0.7)
	2-Ethylhexyl acrylate 0.1% pet	1	(0.7)
Cooling oils	2-n-Octyl-4-isothiazolin-3-one 0.1% pet	3	(2)
Tailor-made	Polysulfide, phenolic, modified epoxy	89	(58.5)

(1993-2015)	and their amine catalysts (Proseal 870, PR 1422, EA-934-NA, etc.)		
	Concomitant reaction with DGEBA epoxy	43	(28.3)
	Concomitant reaction with EDA, DETA,TETA	4	(2.6)
Prepregs	Kevlar, Graphite, Fiberglass with resin based on TGPAP or TGMDA	76	(50)
	Concomitant reaction with DGEBA epoxy	32	(21)

NA: North American; NACDG: North American Contact Dermatitis Group; DGEBA: diglycidyl ether of bisphenol A; DGEBF: diglycidyl ether of bisphenol F; EDA: ethylenediamine; DETA: diethylenetriamine; TETA: triethylenetetramine; TGPAP: triglycidyl-p-aminophenol; TGMDA: tetra-4,4'-methylenediamine; pet: petrolatum

Table 4. Click here to download Table Table 4. 152 workers with ACD.docx

Table 4. Workers with allergic contact dermatitis. Demographics, type of work, results of patch tests, and distribution of dermatitis.

Name	Age	Gender		Type of work				Patch Test Series					Dermatitis	
		M	F	A	C	Ma	O	S	G	T	P	O	Location	Air
BD	30	X		X				Ep, Cr					Fingers	
BJ	35	X			X			Ep	DETA				Hands	
BL	29		X	X				Cr		4			Hands, face	X
FSA	51	X		X						4			Fingers	
HD	37	X		X				Ni, Co, Cr		2,3,7,9			Hands	
RR	26	X		X						2,3,9,			Hands	
BY	35	X				X		Ep					Hands	
LD	42		X	X				Cr		2,3,7,9			Hands, wrists	
CS	38	X		X						4			Hands, forearms	
LF	40	X		X				Ep	EDA, DETA	2,4,5			Hands, forearms, face	X
AN	33		X	X						4			Hands, forearms, face	X
LB	31	X		X						4			Hands, forearms	
CR	41	X				X		Coloph				OIT,CO	Hands, forearms	
LR	41	X		X				Cr		1,3,4,8			Hands, face	X
LN	26	X		X				Co, Cr, DPG					Hands	
MS	21	X		X				Ep		1,3,4,8,9			Hands	
VY	22	X		X				Ep		4			Hands, forearms	
RJF	22	X		X				Ep	PGE	1,4			Hands, forearms	
LT	25		X		X				PTBFR				Hands, forearms	
TC	39		X	X						1,4			Hands	
LB	30		X		X					4			Hands, forearms	
GA	36	X		X				Cr		1,2			Hands, forearms	
BM	43	X		X				Cr, Ep	PGE, CEp	1,4			Hands, forearms, back	
BS	29		X		X			Ni, Ep		4			Hands, abdomen	
MD	47		X		X			Co, Ni, Ep		1,4			Hands, wrists	
GJP	46	X		X				Cr, Ep		2,3,4,9			Hands	
CS	41		X		X						2,5		Hands, face	X
LL	39		X		X						2,5		Face	X
MR	34	X		X						1,2			Hands, forearms	
MAG	28		X	X				Ni, Ep		4			Hands, forearms, face	X

MR	51		X		X		Ni			5		Palms, fingertips	
CR	28	X			X		Cr, Ep			2,5		Forearms, face	X
LD	28	X		X			Ep	PGE, CEp	4			Forearms	
DG	40		X		X		Ep			2,5		Face	X
VM	23		X		X		Cr, Ep		2	2,5		Hands, forearms, neck, abdomen	
GL	29	X		X			Car, Thi					Hands	
HM	32		X	X			Ep, Quat		1,2,4			Hands, forearms, face	X
BL	42		X		X		Ep	TDI, EHA	2,4	2,5		Hands, face	X
SLN	30		X		X		Ni	PGE	4	2,5		Forearms, face	X
LP	40	X			X					2		Forearms, thighs	
LA	46	X		X			Ep		4			Hands	
JP	22	X		X					4			Forearms	
PM	37		X		X		Au, Co, Cr, Ni, Ep		2	2		Hands, face	X
SF	21	X		X			Cr		1,2			Hands	
GMP	28		X		X		Ep			2,5		Forearms, face	X
GC	39		X		X		Ep	PGE		2,5		Hands, forearms, face	X
TGC	27	X		X			Ep, For	TSFR, MDA, HMT				Hands, forearms	
HD	31	X		X			Cr, Ep		1,4			Hands, wrists, forearms	
LD	49		X		X		Ep		1,2,4	2,5		Hands, forearms	
SDJ	38	X			X		Ep			5		Face	X
CJ	22	X		X			Ep		4,7			Arms, face	X
GC	21	X			X		Ep		4	2,5		Hands, fingers	
BF	36	X			X					5		Forearms	
GG	56	X				X					CO	Hands, forearms	
LK	27		X	X			Ni	Nov	1,2			Hands, wrists	
BJF	43	X			X					2,5		Forearms, arms, face	X
GJ	47	X		X					4			Hands	
MJL	28	X		X			Co, Ep		1,2,3,6,7,8,9,10,11			Hands	
PG	43		X		X		Ni			2,5		Forearms, face	X
CR	51	X			X					5		Hands, forearms, face	X

AJ	34		X	X			Ep				Forearms	
CDT	34	X			X					2,5	Hands, forearms. legs	
LA	21		X	X			Co, Cr. EDA	MDA, IDA	1,2,3,5		Hands, forearms, face	X
KMN	21		X	X			Au, Ni		4	2,5	Forearms, arms	
CL	25	X		X			Ni		3,4,6,8,9,10,11		Fingers, forearms	
AS	37	X		X					4		Hands	
PA	54	X			X					2,5	Eyelids, face	X
RG	33	X		X					4		Hands	
DA	40	X		X					4		Hands, forearms	
LD	54		X		X				4	2,5	Fingers	
RA	29	X			X					2,5	Hands, forearms, thighs	
TM	41	X				X	Ep			2	Hands, forearms, face	X
EM	41	X		X					4	2,5	Face	X
PS	30	X		X			Ep, Car, Thi		4	2,5	Hands, forearms, face	X
MK	24		X		X		Ni			5	Hands	
LM	28		X	X			Cr		1,2,6		Hands	
BM	21	X		X					1		Dorsum of hands	
RA	21		X		X		Ni			5	Hands, forearms	
CCA	25	X		X			Cr		1,2,3,6,7,8,9		Hands, neck, folds	
LAJF	19	X		X			Ep	PGE	4		Forearms	
HM	45	X			X		Ep		4	2,5	Forearms, arms, thighs, legs	
BJF	43	X		X					3,8,9,10		Hands, fingers	
DM	31	X			X					2,5	Forearms, face	X
GLO	22	X			X		Ni, Ep			2,3,5,9	Hands, forearms	
MDA	31	X			X				4	5,9	Hands, forearms, arms	
BJ	44	X			X		Ep			1-10	Hands, forearms, face	X
JS	28	X		X						5,9	Hands, forearms, neck	
BS	37	X		X			Ep		1,4		Forearms, face, chest	X
RP	27	X		X					1		Face	X
LN	23		X	X					6,7		Hands	
CR	44	X			X					2,3,5,9	Forearms, face	X
SJD	37		X		X				4		Forearms, face	X
PP	27	X		X					4		Forearms	

PM	27		X		X				4	2,3,5,6,9	Hands, forearms, generalized	X
BM	32		X	X			Ni		3,4,,8,9,10,11		Hands, wrists, face, neck	X
GG	25	X			X		Ep	PGE	4	2,3,5,6,9	Forearms, face	X
CE	23		X		X		Co, Ni			9	R hand, abdomen	
DK	44	X			X					2,3,5	Face	X
SA	38	X		X						5,9	Hands, forearms	
MP	26	X		X						5,9	Hands, forearms, face, neck	X
LR	43	X			X					2,5,6,9	Face	X
HP	47	X		X			Ni, Ep	MDA	4		Forearms, face	X
BF	28	X		X					1,2,14		L hand	
BY	44	X			X				14		Hands (palms)	
GM	31	X				X			5,9	5	Arms	
GD	40		X	X					5,9		Forearms	
LLC	24	X		X					4,6,7		Forearms, arms	
GP	30	X		X					4		Hands, face, legs, abdomen	X
NC	40	X		X			Car, EDA	DETA	1	5,9	Hands, forearms	
RM	46		X		X				4	2,3,5,9	Hands, forearms	
PM	40		X	X						5,9	Wrists, arms	
BD	36	X			X					3,5,9	Hands, face	X
CJ	50	X			X					2,3,5,6,9	Generalized	
DM	60	X				X				5,9	Hands	
LM	29	X			X		Ni			5,9	Forearms, neck	X
RJ	44	X			X					2,5,9	Forearms, face	X
BA	32	X		X			Ep		4		Forearms	
AC	48	X		X					4		Hands, arms	
MMC	28		X			X	Ep				Forearms	
PS	35	X		X					3,8,9,10,11		Fingers	
HA	30		X		X		Ni		3	9	Face, neck, generalized	X
SN	54		X		X		Ep, For	DGEBF	4,15,17,19,20,23, 24	1-10	Forearms	
GJP	52	X		X			Cr, Ep		4,15,17,20		Fingers	
SLE	30	X				X	Ep	DGEBF,EA	2,4,8,9,11,13,15	1-10	Hands	

NM	47	X			X			Cr, Ep		4,5,17,20,21,23,24	1-10		Hands	
BN	30		X		X						9		Hands (palms)	
SS	20	X		X				Co, Cr, Ni					Hands	
BG	46	X			X			Ni			4,5		Hands, forearms	
LM	61	X		X					PFR-2,MP				Fingertips	
AN	24		X		X			Ep		4,15,17,19,20,23,24	1,2,4,5,6,7,8,9,10		Forearms, arms	
RE	40	X		X							4,5,7,8,9		Forearms	
CS	43	X		X							9		Forearms, arms, face	X
MY	50	X		X				Cr, EDA			4,5,9		R arm, face	X
GP	46	X		X						4				
SL	53		X				X	Ep		19,20,24			Hands, face, neck	X
CS	53	X			X			Ep	CEp, PGE CGE	4,15,17,19,20,24			Forearms	
PC	39		X	X							9		Forearms	
LPL	42	X			X						9		Forearms, face	X
GD	51	X			X						9		Hands, forearms	
BE	31	X			X			Ep		4,15,17,19,20,23,24	1,2,4,5,6,7,8,9,10		Hands, forearms, face	X
LR	52	X						PTBFR				SGG	Face	X
JAC	42		X			X					9		Hands	
SD	36	X				X		Ep	DGEBF	4,19,20,21	2,3,5,8,9		Hands, forearms, neck	X
BF	58	X				X		Ep	DGEBF	2,4,5,8,9,11	1,2,3,4,6,7,8		Forearms, face	X
SAJP	52	X				X					5,9		Face (eyelids)	X
TC	28	X					X				1,2,9		Hands, forearms, face	X
LM	25		X		X			Ep, Nov	DGEBF	4,15,17,19,20,22	2,3,5,6,8		Hands	
CP	44	X			X						9		Forearms, face	X
LG	40	X		X				Ep	DGEBF	2,4,5,8,9,11	1-10		Hands, forearms	
TC	24	X					X				1,2,9		Forearms, face, chest	X
LS	52		X		X						9		Hands, arms, face	X
CS	43	X		X						4,17			Face, abdomen	X
Total:		104	48	75	65	4	8	Total Epoxys: 55		89	76	3		57

Air: airborne distribution, M: male, F: female, A: assembler, C, composite materials technician, Ma: machinist, O: other, S: standard series, G: glues series, T: tailor-made series, P: prepregs series, Co: cobalt chloride, Cr: potassium dichromate Ni: nickel sulfate, Au: gold sodium thiosulfate, Coloph: colophonium, Ep: epoxy resin. DGEBF: diglycidyl ether of bisphenol F, CEp: cycloaliphatic epoxy resin, EA: epoxy acrylate, CGE: cresyl glycidyl ether, PGE: phenyl glycidyl ether, MDA: 4,4-diaminodiphenylmethane, DETA: diethylene triamine, EDA: ethylene diamine, HMT: hexamethylene tetramine, IDA: isophorone diamine, TDI: toluene diisocyanate, EHA: 2-ethylhexyl acrylate, DPG: diphenylguanidine, Car: carba mix, Thi: thiuram mix, For: formaldehyde, PTBFR: para-tertiary butylphenol formaldehyde resin, Quat: quaternium-15, TSFR: tosylamide formaldehyde resin, PFR-2: Phenol formaldehyde resin, Nov: Phenol formaldehyde resin (Novolac), MP: 2-monomethylol phenol. OIT: 2-n-octyl-4-isothiazolin-3-one, CO: Cutting oils 1%, 5%, 10%, 50% aqua, SGG: Scotch Grip Glue. Numbers in columns T and P correspond to those in Table 1 and Table 2, respectively.