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NICNAS

Final Report on Hazard Classification of Common Skin Sensitisers

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Background

In 2003, the Occupational Dermatology Research and Education Centre (ODREC) noted that many of the top 53 common sensitisers seen in the ODREC clinic and the 361 sensitisers included in commercial European patch testing kits (Chemotechnique Diagnostics) were not classified as sensitisers on the National Occupational Health and Safety Commission's (NOHSC) *List of Designated Hazardous Substances*. In response, NICNAS submitted a scoping paper to NOHSC including a screening of a preliminary list of the top 28 ODREC common sensitisers against the NICNAS *Australian Inventory of Chemical Substances*, the NOHSC *List of Designated Hazardous Substances* and the EC dangerous substances list – *Annex 1 of the 28th Adaptation to 67/548/EEC*. This scoping paper also included results of preliminary literature searches to determine the likely resource requirements for classifying sensitiser chemicals currently missing from the NOHSC list.

On the basis of this initial paper, the NOHSC Chemical Standards Sub Committee at its meeting of 1 July 2003 invited NICNAS to submit a proposal to examine all top 53 ODREC common sensitisers to determine their status with respect to NOHSC hazard classification and, for chemicals currently missing from the NOHSC Hazardous Substances List and the EC Annex 1, to obtain data and classify these against the criteria for sensitisation in the NOHSC *Approved Criteria for the Classification of Hazardous Substances* (1999) (NOHSC Approved Criteria).

Of these ODREC common sensitiser chemicals, NICNAS identified a total of 20 individual chemicals that were currently not classified as sensitisers. For these chemicals, NICNAS proposed and in November 2003 NOHSC agreed to NICNAS assessing and classifying these chemicals against the NOHSC Approved Criteria for sensitsation. Specifically, the project proposal included the following actions:

1. Release of a notice under section 48 of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cmwlth) calling for unpublished sensitisation data and any associated adverse incidents during use of these chemicals;
2. Conduct of literature surveys and compilation of sensitisation data;
3. Classification of these chemicals against the Approved Criteria for sensitisation and submission of results to NOHSC for adoption to the List of Designated Hazardous Substances.

Project Results

Correction of the Chemical Identity of N-Cyclohexylbenzothiazyl Sulphenamide and Cl+Me-Isothiazolinone (Kathon CG)

Further checking of the chemicals to be assessed and classified revealed 2 cases of incorrect identity based on initial information from the Chemotechnique Diagnostics catalogue. For N-Cyclohexylbenzothiazyl sulphenamide, the CAS number was incorrectly listed in the catalogue as 3081-14-9. The correct CAS number was found to be 95-33-0. This chemical is listed in the EC under Annex 1 of the 28th Adaptation to 67/548/EEC.

For the second chemical with the synonyms of Cl+Me-isothiazolinone (Kathon CG), chemical identity information was not available from the catalogue. From an initial search of the CAS National Chemical Inventories (NCI), the chemical was identified as 3(2H)-Isothiazolone, 2-(chloromethyl)-, CAS 21277-94-1. However, a subsequent literature search and information requested from Chemotechnique Diagnostics indicated that this chemical is actually a mixture of two chemicals, 3(2H)-Isothiazolone, 5-chloro-2-methyl- (CAS 26172-55-4) and 3-Isothiazolone, 2-methyl- (CAS 2682-20-4). From a search of the NCI, this mixture itself was found to possess its own chemical identity of 5-Chloro-2-methyl-3(2H)-isothiazolone, mixt. with 2-methyl-3(2H)-isothiazolone, CAS 55965-84-9. Under this chemical identity, this mixture was found to be already listed in the EC under Annex 1 of the 28th Adaptation to 67/548/EEC.

As the scope of this current project only extended to assessing chemicals currently not listed on either the NOHSC *List of Designated Hazardous Substances* or the EC dangerous substances list – *Annex 1 of the 28th Adaptation to 67/548/EEC*, these two chemicals, N-Cyclohexylbenzothiazyl sulphenamide and Cl+Me-isothiazolinone (Kathon CG), were not assessed as part of this present project.

Results from the Call for Information on Sensitiser Chemicals

A notice calling for information was included in the *Chemical Gazette* of November, 2003. The notice requested unpublished sensitisation toxicity data and information on any adverse incidents regarding sensitisation by skin contact for 20 sensitiser chemicals. The Gazette Notice is attached (see Appendix).

Written responses were received from two companies. Rohm and Haas Australia Pty Ltd. requested clarification of the scope of assessment for Cl+Me-isothiazolinone and noted concerns with the very low concentration cutoff for Cl+Me-isothiazolinone of 0.0015% to be adopted in the EC. NICNAS clarified with Rohm and Haas that Cl+Me-isothiazolinone (Kathon) was not assessed as part of this project. The assessment of chemicals already listed on either the NOHSC List of Designated Hazardous Substances or the EC Annex 1, as well as the nomination of concentration cutoffs for those chemicals for which hazard classification is appropriate are outside the scope of the present project brief.

Subsequent to the call for information, two of the original 20 chemicals - amerchol and wool alcohols (lanolin) were found not to be separate chemicals. They were thus regarded as the one chemical for assessment and classification.

Literature Reviews – Comparisons of Animal and Human Data to the NOHSC Approved Criteria

Data searching was conducted using the US National Library of Medicine database ChemIDplus, the web portal Chemfinder, the International Programme on Chemical Safety INCHEM database, review databases of the American Conference of Governmental Industrial Hygienists (ACGIH), the US Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, online reports of the US National Toxicology Programme (NTP), Cosmetic Ingredient Reviews, Chemical Information System (CIS), the US/Canadian NIOSHTIC with OSHLINE databases, the European Chemicals Review web portal, the Canadian Centre for Occupational Health and Safety (CCOHS) web information service, the Chemical Abstracts Service SCIFINDER system and the bibliographic databases OSHROM, TOMES CPS System, TOXLINE with PUBMED, Current Contents and the Australian Medical Index. The bibliographic databases enabled searching for keywords such as the common names and terms relating to sensitisation in all the major scientific journals including the allergy journal Contact Dermatitis. Lastly, searches were also conducted using the web search engine GOOGLE.

Literature reviews revealed varying amounts and types of information for each of the chemicals. Human data were found for all chemicals in the form of individual case reports showing reactions to particular chemicals. For many, larger surveys or reviews of human patch test results for defined patient populations presenting to dermatology clinics were additionally available. Animal studies were also found for the majority of chemicals. Studies of structure-activity modelling for sensitisation for particular chemicals were also obtained but these were rare.

Animal data were examined with particular emphasis. The NOHSC Approved Criteria notes that hazard classification with the risk phrase R43 is appropriate on the basis of practical experience of skin sensitisation in a substantial number of persons or on the basis of positive animal tests. Regarding animal tests, NOHSC Approved Criteria 4.71 notes that the criteria are met on the basis of animal studies if ≥ 30% and ≥ 15% of animals show positive reactions in adjuvant and non-adjuvant type test methods respectively. OECD Test Guideline 406, adopted in 1992, outlines approved methods for conducting adjuvant and non-adjuvant tests. A more recent OECD Test Guideline 429 outlines sensitisation testing using the local lymph node assay. Therefore, given these specific, quantifiable criteria and the availability of OECD Test Guidelines for both adjuvant and non-adjuvant skin sensitisation tests in animals, the results from such animal studies were given particular scrutiny and priority when classifying against the NOHSC Approved Criteria. Guidance on interpretation of animal studies themselves was obtained from ECETOX (2000) *Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment. Monograph No. 29*. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

In a minority of instances, few or only poor quality animal data were found. In these cases, human patch test datasets and/or individual case reports were the only information available on which the skin sensitisation potential of the chemical could be evaluated. No OECD Guidelines exist for skin sensitisation testing in humans and so in the absence of animal data, each of the human patch test surveys and case reports was evaluated on individual merit. The quality of each study was determined by considering the adequacy of identification of the chemical to be tested, documentation of study methodology and any quality control of patch test readings. In many cases, the evaluation of patch test results were conducted at established dermatological clinics to international standards or guidelines eg. International Contact Dermatitis Research Group (ICDRG) recommendations. Where stated, the institution conducting the study, the standards with which the data were evaluated, the severity of reactions and the prevalence of reaction amongst the test populations were noted.

An important criterion in the NOHSC Approved Criteria for hazard classification on the basis of human data is the prevalence of reactions associated with an individual chemical. This is embodied in Approved Criteria 4.6.6 which states the requirement of "*practical experience showing that the substances are capable of inducing sensitisation by skin contact in a substantial number of persons*". Practical experience is also defined as positive data normally in more than one dermatological clinic. For each of the chemicals then, assessment of the sensitisation potential on the basis of human data included not just the consideration of the percentage of the test population showing positive reactions in patch testing, the robustness of the reactions and where they were obtained, but a judgment also as to how representative the test or sample population is to any wider population with potential exposure to the chemical. Even though some studies document a significant percentage of the test population with positive reactions, the representativeness of these test populations to the wider population with potential exposure are sometimes questionable due to admission of patients into the study on the basis of strictly defined, pre-existing allergic or irritant conditions. As expected, few studies were found where the induction of sensitisation with appropriate controls groups was attempted in naïve human subjects. In order then to compare human data to the Approved Criteria, each chemical report in this project considered the prevalence of reactions from human surveys and case reports in the light of potential exposure of the general population to the chemical as estimated from general use information from the surveys themselves or, where noted, from central information sources such as the US National Library of Medicine Hazardous Substances Data Bank (HSDB). In this manner, an assessment was made as to whether the data obtained from defined patient populations represented evidence of skin sensitisation in a substantial number of persons. General guidance on the interpretation of human data was obtained from ECETOX (2002) *Use of Human Data in Hazard Classification for Irritation and Sensitisation. Monograph No. 32*. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

As well as hazard classifications of individual chemicals, concentration cutoffs for classification of mixtures were also derived. Unfortunately, the majority of the information for sensitisation was sourced from diagnostic human patch tests where, in the cases of positive results, exposure data and, in particular, the concentration of chemical responsible for the initial induction of sensitisation was not known. Also, animal test data where available did not always include concentrations for induction

and challenge. Moreover, even where the common guinea pig maximisation test was available, inferring a concentration cutoff for humans from such a test alone was not possible as the use of adjuvant, intradermal as well as topical injections during induction provides worst-case conditions that precludes direct extrapolation of induction doses to humans. Given these difficulties, no data for any classified chemical suggested deviation from the default concentration cutoff for sensitisation in the NOHSC Approved Criteria of ≥ 1%.

Occupational Database Case Entries of Reactions from Specific Chemicals

NICNAS also obtained information on cases of allergic reactions as recorded in occupational dermatological databases. Data were obtained from the Occupational Dermatology Research and Education Centre (ODREC) in Melbourne and also from the Centre for Occupational and Environmental Health, University of Manchester. This latter institution maintains two separate occupational health databases, the EPIDERM occupational skin surveillance database and the more general Occupational Physicians Reporting Activity (OPRA) database. For each chemical, the numbers of case entries in each database are provided in the project summaries.

These database entries are a source of information from which the prevalence of reactions to particular chemicals can be inferred. However, the entries themselves cannot be examined and so their relevance to sensitisation potential according to the NOHSC Approved Criteria cannot be confirmed. In this respect, they are presented for information only. They are of only limited value to hazard classification.

Summary of Final Classification of Assessed Chemicals

Table 1 summarises classification recommendations for 19 assessed chemicals. The common names for the chemicals are those in general use such as in the Chemotechnique Diagnostics Patch Test catalogue.

Hazard classification according to the NOHSC Approved Criteria on the basis of assessment of the single endpoint of skin sensitisation is recommended for 9 chemicals. On the basis of meeting the NOHSC Approved Criteria for skin sensitisation, the risk phrase R43 and hazard category Irritant (Xi) are appropriate for these chemicals.

An additional chemical, cobalt chloride hexahydrate, also meets the NOHSC Approved Criteria for skin sensitisation. However, on the basis of listing of the anhydrous form in the European Union (EU) Annex 1 of the 28th Adaptation to 67/548/EEC, hazard classification on the basis of both skin and respiratory sensitisation is recommended. For this chemical, the risk phrases R42/43 and hazard categories Harmful (Xn) and Irritant (Xi) are appropriate.

As noted previously, two chemicals, N-Cyclohexylbenzothiazyl sulphenamide and Cl+Me-isothiazolinone (Kathon CG) were found already listed in the European Union (EU) Annex 1 of the 28th Adaptation to 67/548/EEC. These were not assessed.

For 7 chemicals, data available for the assessment did not meet the NOHSC Approved Criteria at this time. Lastly, for 2 chemicals, coconut diethanolamide and phenol formaldehyde resin, data were insufficient for classification against the NOHSC Approved Criteria.

Table 1. Summary of Classification Recommendations

Common Name(s)	AICS Chemical Name	CAS #	Recommended for Hazard Classification (R43)
Glyceryl monothioglycolate (GMTG)	Acetic acid, mercapto-, monoester with 1,2,3-propanetriol	30618-84-9	Yes
Cobalt(II) chloride, hexahydrate	Cobalt(II) chloride, hexahydrate	7791-13-1	Yes (and R42) Anhydrous form currently listed in EU Annex 1, Directive 67/548/EEC
Diazolidinyl urea; (Germall II)	Urea, N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis(hydroxymethyl)-	78491-02-8	Yes
Dowicil 200	3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride, (Z)-	51229-78-8	Yes
Imidazolidinyl urea; (Germall 115)	Urea, N,N''-methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-	39236-46-9	Yes
Cl+Me-isothiazolinone; (Kathon CG)	Mixture of 3(2H)-Isothiazolone, 5-chloro-2-methyl- & 3-Isothiazolone, 2-methyl-	55965-84-9	Currently listed in Annex 1, Directive 67/548/EEC
2-Nitro-4-phenylenediamine	1,4-Benzenediamine, 2-nitro-	5307-14-2	Yes

Abietic acid	1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4a-dimethyl-7-(1-methylethyl)-, [1R-(1a,4ab,4ba,10aa)]-	514-10-3	Yes
N-Cyclohexyl-2-benzothiazolesulfenamide	2-Benzothiazolesulfenamide, N-cyclohexyl-	95-33-0	Currently listed in Annex 1, Directive 67/548/EEC
Zinc dimethyldithiocarbamate (Ziram)	Zinc, bis(dimethylcarbamodithioato-S,S')-, (T-4)-	137-30-4	Yes
Wool alcohols	Alcohols, lanolin	8027-33-6	No
Coconut diethanolamide (Coco. DEA)	Amides, coco, N,N-bis(hydroxyethyl)	68603-42-9	No
Basic Red 46	C.I. Basic Red 46	12221-69-1	No
Benzalkonium chloride	Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides	8001-54-5	No
Phenol formaldehyde resin (P-F-R-2)	Phenol, polymer with formaldehyde	9003-35-4	No
Toluenesulfonamide formaldehyde resin	Benzenesulfonamide, 4-methyl-, polymer with formaldehyde	25035-71-6	No
4-tert-Butylphenol formaldehyde resin (PTBP)	Formaldehyde, polymer with 4-(1,1-dimethylethyl)phenol	25085-50-1	No
Sodium metabisulfite	Disulfurous acid, disodium salt	7681-57-4	No
Triethyleneglycol dimethacrylate	2-Propenoic acid, 2-methyl-, 1,2-ethanediylbis(oxy-2,1-ethanediyl) ester	109-16-0	No

Glyceryl monothioglycolate (GMTG)

Chemical Identification

Chemical Name:	Acetic acid, mercapto-, monoester with 1,2,3-propanetriol
CAS #	30618-84-9
Synonyms:	Glycerin monothioglycolate; glycerol monomercaptoacetate; glyceryl monothioglycolate; GMTG
Use:	Used in acid permanent wave products (i.e. hair products). Also as a cosmetic ingredient (Adams & Maibach, 1985).

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

No animal studies have been conducted to determine the sensitisation potential of glyceryl monothioglycolate. However, the Cosmetic Ingredient Review (CIR, 1991) reported several unpublished animal studies on the sensitisation potential of glyceryl thioglycolate. They reported that glyceryl thioglycolate is also known as glyceryl monothioglycolate. Here, we have treated glyceryl monothioglycolate to be different to glyceryl thioglycolate as they have distinct CAS numbers and molecular formulae. For this reason, the unpublished animal studies on glyceryl thioglycolate have not been considered in this review.

Human Evidence

Surveys

Between January and April 1981, 7 hairdressers presenting to the Shaughnessy Hospital (Vancouver) were patch tested at the environmental allergen test laboratory with the North American standard screen and/or hairdressers' screen (Warshawshki and Mitchell, 1981). Five out of 7 patients reacted positive to GMTG (2.5% pet.). Forty-seven control subjects tested in Portland (Oregon) were negative to GMTG (2.5% pet.). The authors stated that both the Vancouver and Portland test material were from the same batch. No further details regarding methodology were provided. Two other positive cases to GMTG (2.5% pet.) were noted in 20 eczema patients. This study was presented as a short communication (Warshawshki and Mitchell, 1981).

During 1973–1981, 66 patients who stated their occupation as hairdressing were patch tested with the North American Contact Dermatitis Group screening tray and/or their hairdressers' series (Lynde, 1982). Most hairdressers were between the ages 16 and 25 years. The test protocol was not clearly stated. Forty-eight hairdressers (i.e. 72.7%) showed one or more reactions to the allergens tested. Out of the 32 hairdressers tested with the hairdressers' series, 6 (i.e. 18.8%) were sensitised by GMTG (2.5% pet.).

Four of these patients had + responses and 2 patients had ++ responses. Given that GMTG was added to the hairdressers' series in only 1981 (Lynde, 1982), the actual incidence could be higher. However, there is no mention of this fact in the paper.

Twelve dermatologists associated with the North American Contact Dermatitis Group conducted a 64-month (1977–1983) study into cosmetic reactions (Adams & Maibach, 1985). Of the 281,000 patients seen during this period, 13,216 patients were diagnosed with contact dermatitis. However, only 713 patients were diagnosed with cosmetic related dermatitis. A total of 561 of these patients were female and the rest male. A total of 115 patients had a history of atopic dermatitis. Patients were patch tested with ingredients of cosmetics at generally accepted concentrations. Ingredients were obtained from cosmetic manufacturers. Where necessary, controls were performed to exclude irritancy. Of the 536 positive reactions induced by cosmetic ingredients 25 were due to GMTG (concentration and vehicle not given). The results of this study were not clearly presented.

During the period 1978–1982, two studies examined the sensitisation potential of GMTG-containing permanent wave lotion (Springer *et al.*, 1985). The permanent wave lotion contained about 14–15.4% GMTG. In the first study, 100 subjects underwent patch testing with 0.15 ml of Pantene Perfect Transition waving lotion applied under a 1.6 cm^2 patch. In this short communication there is no indication as to whether the subjects were healthy volunteers. After 48 hours the patches were removed, and tests were scored for irritation after a further 15 min and 24 hour period. The patch scoring procedure was repeated once 14 days later. No positive reactions were seen with either the primary patch or the challenge patch. The second study by the same authors was a modified repeated insult patch test with 103 subjects. Pantene Supreme waving lotion (0.5 ml) was applied under a 1.6 cm^2 blotting paper and a semi-occlusive patch achieved. After 48 hours the patches were removed and scored for irritation. A new patch was then applied to the same site. This procedure was followed for a total of 10 times. A further challenge patch was applied after a 14-day rest period. In these repeated insult patch tests no positive reactions were seen. The authors indicated that permanent wave lotion containing GMTG does not cause either irritation or sensitisation.

To explain the persistence of dermatitis in beauty shop clients, the persistence of GMTG-allergens in hair exposed to permanent wave solutions was studied (Morrison & Storrs, 1988). Hair samples were collected from 5 subjects before and after undergoing permanent wave treatment. For the negative control, virgin hair (i.e. hair that has never been permanent waved, dyed or colour treated) was obtained. The antigen loss control consisted of hair obtained from a freshly permanent waved client just before patch testing. Seventeen GMTG-sensitised subjects underwent patch testing to the North American Contact Dermatitis Group's standard series, vehicle and preservative series. Patches were placed for 48 hours, and results read at 30 min after removal and on day 7. All 17 subjects reacted positive (+) to GMTG (1% pet.). None of the subjects were atopic under the Hanifin criteria. Patch testing was then conducted with treated and untreated hair. While none of the subjects reacted positive to the negative control (i.e. virgin hair), 13 of the 17 subjects reacted to the antigen loss control. In addition, several subjects (i.e. 2-3) reacted positive to 2-week old, 6-week old and 3-month old permanent waved hair. These results suggest that GMTG or related allergens are retained in the hair for up to 3 months.

A total of 261 hairdressers' clients – 5 males and 256 females – were patch tested with the Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali (GIRDCA) standard series and hairdressing series (Hermal-Trolab, Bracco) between 1985 and 1990 (Guerra *et al.*, 1992a). These clients had presented to the clinic with suspected contact dermatitis due to hairdresser allergens (mean duration of disease was 2.3 years). Patch test results were read at 2 and 3 days. Forty-seven patients had a personal history of atopy while 36 patients had a family history of atopy. Forty-nine patients were sensitised to one or more allergens in the hairdressers' series. Nine patients (i.e. 3.4%) reacted positive to GMTG (2.5% pet.). The severity of the reactions was not stated and no further details regarding methodology were provided. The authors state that GMTG can persist in the hair for up to 3 months. Hence, clinical symptoms can continue even after the procedure has been stopped. There was no indication of how many GMTG sensitised patients were also atopic.

Guerra *et al*. (1992b) reported patch test results from 9 GIRDCA Italian dermatological centres. The study was limited to hairdressers presenting to the dermatological centres with contact dermatitis from January 1985 to June 1990. Forty-three males and 259 females between the ages of 14 to 66 years (mean age 24.6 years) were patch tested with the GIRDCA standard series and hairdressers' series (Hermal-Trolab allergens). Mean duration of dermatitis in patients was 1.8 years. Patch tests were performed according to the International Contact Dermatitis Research Group (ICDRG) recommendations, and results read at 2 and 3 days. Forty-two hairdressers (13.9%) had a personal history of atopy and 66 hairdressers (21.9%) had a family history of atopy. Out of the 302 patients 184 (i.e. 60.9%) reacted positive to one or more allergens that were occupationally relevant. Out of the 302 patients, 34 (i.e. 11.3%) reacted positive to GMTG (1% pet.). The severity of reactions was not stated. The results of this study showed no relationship between the occurrence of sensitisation and the subject's personal atopic status or duration of work. Vinyl gloves were found to offer no protection against GMTG, as 3 of 8 GMTG-sensitive patients were positive even after wearing gloves.

To obtain data on sensitisation among hairdressers, patch test results to the hairdressing series (Hermal-Trolab) from 9 EECDRG (European Environmental and Contact Dermatitis Research Group) dermatological centres were analysed (Frosch *et al.*, 1993). The majority of the patch test results correspond to the period 1988–1991. Patch tests were read according to the generally accepted criteria of the ICDRG. The data were considered with respect to methodology and time course. GMTG was tested at 1% pet. in eight centres. High Wycombe and Gentofte centres used 2.5% GMTG for the early part of the study. Doubtful or irritant reactions were not included. Out of the 809 hairdressers patch tested, 151 (i.e. 18.7%) were sensitised by GMTG. While the Bordeaux centre recorded no sensitisations (i.e. from 11 patients tested) the centre at Dortmund recorded sensitisations in 28 hairdressers (i.e. 50.9%) from 55 tested. In most centres the incidence of sensitisation to GMTG was greater than 15%. From Leuven, High Wycombe, Barcelona and Oulu clinics 104 hairdressers' clients were patch tested with the hairdresser's series. Six clients (i.e. 5.8%) reacted positive to GMTG. There was no data regarding the severity of the reaction.

One hundred and forty-three hairdressers with hand eczema referred to the St. John's Institute of Dermatology (London) from January 1987 to June 1992 were included in

a study to determine whether atopics and non-atopics are equally sensitised by environmental allergens (Sutthipisal *et al.*, 1993). Patients were divided into eczematous atopics (n=45), mucous membrane atopics (n=32) and non-atopics (n=66). One hundred and twenty-five patients were women and the rest male. Sixty-seven hairdressers were between the ages 15 and 18 years. All patients were patch tested with the standard series and a routine series of hairdressing chemicals from Trolab (Hermal). Patches were applied to the upper back for two days, and results were read at 2 and 4 days. GMTG (0.5 and/or 1%; vehicle not stated) caused skin sensitisation in 23 eczematous atopics (51%), 12 mucous membrane atopics (38%) and 27 non-atopics (41%). GMTG was the commonest sensitiser for all three groups. In terms of the rate of sensitisation to environmental allergens there was no significant difference between the three groups. Hence, atopics and non-atopics are equally sensitised by environmental allergens.

During the period 1980–1993, a total of 379 hairdressers (350 being women) presented to the Occupational Dermatology Service of a medical institute in Madrid, Spain (Conde-Salazar *et al.*, 1995). The patients were patch tested with the standard series of the Spanish Contact Dermatitis Research Group (GEIDC) and with the hairdressers' series. The allergens for the patch tests were supplied by Marti Tor (Barcelona, Spain). The patches were removed on day 2, and results read according to ICDRG recommendations on day 2 and 4. The mean age of the hairdresser population was 21.3 years (range: 15 – 64 years). Only 24 patients had a personal and/or family history of atopic disease. GMTG was added to the hairdressers' series in 1990. Therefore, only 111 patients were patch tested with GMTG. 3 patients (i.e. 2.7%) were sensitised by GMTG (1% pet.).

During the period 1974–1993, 71 hairdressers (all women) with suspected occupational skin disease presented to a Finnish dermatology clinic (Leino *et al.*, 1998). They were patched tested with a standard series, hairdressers' series and substances from their work place. After 1987, the patch application period was increased to 2 days from 24 hours. There was no other information on the experimental protocol. Of the 35 hairdressers patch tested with GMTG (conc. and vehicle not given) 6 (i.e. 17.1%) showed positive responses.

Two hundred and nine hairdressers (27 males and 182 females; 14–72 years) with contact dermatitis who presented to an Italian dermatological clinic from January 1990 to December 1999 were patch tested with a standard series (Trolab-Hermal) and with a hairdressers' series (Iorizzo *et al.*, 2002). Mean duration of the disease was 1.75 years. After the removal of the patch, readings were taken on day 2 and 3. Twenty-five hairdressers (i.e. 12%) reacted positive to GMTG (1% pet.) in the hairdressers' series.

Case Reports

Storrs (1984) reported 12 cases of GMTG sensitisation. Eight were hairdressers (age 21–41 years) and four were hairdressers' clients (age 43–67 years). Seven hairdressers and one client had personal histories of atopy. Patients were patch tested to the North American Contact Dermatitis Group (NACDG) standard series and the hairdressers' series. Patches were applied for 48 hours and read after 30 min and 7 days. GMTG (2.5% pet.) caused no irritant reactions in 21 control men but produced one irritant

reaction in 24 control women. In contrast, GMTG (1% pet.) caused no irritant reactions in 31 control men and 29 control women. Seven hairdressers were sensitised by less than 1% GMTG. Three of these hairdressers were sensitised by 0.25% GMTG. Furthermore, latex and vinyl gloves were not protective as patients wearing these were still sensitised by low concentrations of GMTG.

Tosti *et al*. (1988) reported cases of GMTG sensitisation in three hairdressers (age 16–19 years), two housewives (aged 60 and 70 years) and one teacher (aged 23 years) in Italy. In contrast to current ICDRG guidelines the patch testing was done with GMTG (2.5% aq.). Aguirre *et al*. (1994) reported a single case of GMTG sensitisation in a 27-year old housewife with no history of atopy. While this patient was sensitised to GMTG (1% aq.) she was also sensitised by nickel sulfate, PPD, formaldehyde, 4-aminophenol, hydrogen peroxide and cocamidopropylbetaine. The patch tests were read at day 2 and 4.

A 30-year old hairdresser suffering from insulin-dependent diabetes developed chronic urticaria after an accidental spill of 80% solution of GMTG on her face, chest and arms (Shelley *et al*., 1998). Generalised hives persisted daily except when she was on leave from work. This condition persisted despite daily antihistamines and systemic corticosteroid therapy. A positive urticaria response was seen after a scratch test to a saline dilution of GMTG 1:12500. Ten normal controls were negative to scratch testing with GMTG at this concentration. Patch tests to GMTG (1% pet.) were repeatedly negative. The patient reported that certain inhalants in the beauty shop triggered episodes of hives. However, inhalant provocative testing was not done with GMTG.

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 20 positive reactions for this chemical out of 1,500 workers (1.3%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 59 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

No animal studies have been conducted to determine the sensitisation potential of glyceryl monothioglycolate. However, the Cosmetic Ingredient Review (CIR, 1991) reported several unpublished animal studies on the sensitisation potential of glyceryl thioglycolate. They reported that glyceryl thioglycolate is also known as glyceryl monothioglycolate. Here, we have treated glyceryl monothioglycolate to be different to glyceryl thioglycolate as they have distinct CAS numbers and molecular formulae. For this reason the unpublished animal studies on glyceryl thioglycolate have not been considered in this review.

Many dermatological clinics have reported that GMTG causes sensitisation by skin contact (Warshawshki & Mitchell, 1981; Lynde, 1982; Storrs, 1984; Adams & Maibach, 1985; Morrison & Storrs, 1988; Tosti *et al.*, 1988; Guerra *et al.*, 1992a; Guerra *et al.*, 1992b; Frosch *et al.*, 1993; Sutthipisal *et al.*, 1993; Aguirre *et al.*, 1994; Conde-Salazar *et al.*, 1995; Leino *et al.*, 1998; Iorizzo *et al.*, 2002). These included clinics associated with EECDRG and GIRDCA. While some studies (Warshawshki & Mitchell, 1981; Lynde, 1982; Guerra *et al.*, 1992a) have patch tested the patients with GMTG (2.5% pet.) the current ICDRG recommendations suggest GMTG (1% pet.) to avoid irritant reactions. However, Warshawshki and Mitchell (1981) indicated that no irritant reactions were seen in 47 control subjects when GMTG (2.5% pet.) was used. Storrs (1984) reported that GMTG (2.5% pet.) caused no irritant reactions in 21 control men but produced one irritant reaction in 24 control women. No irritant reactions were seen in 31 control men and 29 control women when GMTG (1% pet.) was used (Storrs, 1984). Hence, those studies that have used GMTG (1% pet.) for patch testing are of particular importance for classifying GMTG as a sensitiser.

In several studies, a high proportion of hairdressers all with occupationally relevant dermatitis were sensitised by GMTG (Guerra *et al.*, 1992b; Frosch *et al.*, 1993; Sutthipisal *et al.*, 1993; Iorizzo *et al.*, 2002). This would indicate that GMTG is capable of inducing skin sensitisation in a considerable number of hairdressers. While GMTG is a significant sensitiser among hairdressers it appears not so outside this occupation. Only two studies examined the incidence of GMTG-sensitisation among hairdresser clients (Guerra *et al.*, 1992a; Frosch *et al.*, 1993). Hence, very little data are available on GMTG-sensitisation outside the salon. This is probably due to the fact that GMTG is not present in any home permanent waving products (Storrs, 1984). This suggests that while the use of GMTG is not widespread in the public, when it is used a considerable number of those using GMTG become sensitised.

There are sufficient data to classify glyceryl monothioglycolate as a skin sensitiser under the NOHSC Approved Criteria. Data do not suggest a concentration cutoff for mixtures containing glyceryl monothioglycolate at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger “Irritant”, risk phrase

R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Cobalt(II) chloride hexahydrate

Chemical Identification

Chemical Name: Cobalt(II) chloride hexahydrate

CAS # 7791-13-1

Synonyms: Cobalt dichloride hexahydrate
Cobalt(2+) chloride hexahydrate
Cobalt chloride hexahydrate

Uses: Hard metal manufacture; invisible ink; humidity & water indicator; in hygrometers; temperature indicator in grinding; in electroplating; paints for glass & porcelain; preparation of catalysts; fertiliser & feed additive; absorbent for military poison gas & for ammonia; in the manufacture of vitamin B12.

Introduction

Cobalt chloride is available in different forms (with unique CAS numbers) differing in their states of hydration. This review searched for literature on the hexahydrate form which is the form available in the Chemotechnique Diagnostics patch test kit. The majority of studies of cobalt chloride located in the literature do not specify the hydration state. Two animal studies and two surveys of human positive patch test data were found in which the hexahydrate form was specified, either through noting the chemical species or the source of commercial patch test kit known to incorporate the hexahydrate form eg. Chemotechnique Diagnostics. These are noted in the text. It may be unlikely that the hydration state would significantly affect sensitisation properties, but in the absence of definitive data supporting this conclusion, the existence of different hydration states and the lack of specification of the hydration state across different studies is noted in this assessment.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard) (hexahydrate)

Wahlberg and Boman (1978) report on a Magnusson and Kligman guinea pig maximisation test of cobalt chloride hexahydrate. The test was conducted in a similar fashion to OECD Test Guideline 406 albeit with additional induction procedures. For induction, groups of 24 animals were assigned to receive by intradermal injection 1% $CoCl_2 . 6H_2O$ in Freund's complete adjuvant and saline. A negative control group of 25 animals received Freund's complete adjuvant and saline. Topical induction was by 5% $CoCl_2 . 6H_2O$ (in pet.). Further details of the induction procedure were not provided. No comment was provided on whether the doses of cobalt chloride used for induction were the highest irritating doses.

Two separate test series based on different challenge procedures were conducted. In the first, animals were challenged topically and then by intradermal injection one week later. In the second, animals were challenged first by intradermal injection and then topically one week later. In both series, topical challenges used doses of 1, 0.5, 0.1 or 0.05% $CoCl_2 . 6H_2O$ (in pet.). The doses chosen for topical challenge were non-irritating according to preliminary experiments. Intradermal challenges used injection of 0.2, 0.1, 0.05 and 0.025% $CoCl_2 . 6H_2O$ in saline. For topical challenges, Finn chambers containing the test chemical were left on for 24 hours. In both series, readings were taken 24 and 48 hours after removal of the chambers (and in the first series prior to intradermal rechallenge). Rechallenge by intradermal injection is not required under Test Guideline 406.

In the first experimental series (topical followed by injection challenge) 30, 74 and 96% of 24 test animals given topical doses of 0.1, 0.5 and 1.0% respectively showed positive reactions to cobalt chloride hexahydrate at 48 hours. In the second series (injection followed by topical challenge) 8, 8, 31 and 73% of 26 test animals given topical doses of 0.05, 0.1, 0.5 and 1.0% respectively showed positive reactions to cobalt chloride hexahydrate at 48 hours. Using the NOHSC Approved Criteria for skin sensitisation which requires positive responses in at least 30% of animals in adjuvant type tests, this documented study shows cobalt chloride hexahydrate to be a sensitiser.

A subsequent study of cross-reactivity to metal compounds by the same group confirmed the sensitisation properties of cobalt chloride hexahydrate (Liden & Wahlberg, 1994). A Magnusson and Kligman guinea pig maximisation test was conducted in a similar fashion to OECD test guideline 406. Induction was as described in the previous paper. However, the animals were challenged with simultaneous separate topical application of 5 different test substances. For the $CoCl_2 . 6H_2O$ challenge, 5 of 15 (30%) and 11 of 15 (73%) of test animals at doses of 0.1 and 0.3% respectively showed positive reactions at 48 hours. Irritant induction and non-irritant challenge doses were used. Two of 15 (13%) and 1 of 15 (7%) negative control animals at doses of 0.1 and 0.3% respectively showed positive responses.

Human Evidence

Surveys

One hundred and twenty patients suffering dermatitis and presenting to a French clinic were patch tested with a variety of allergens. Positive results were found to a 2% cobalt chloride solution in 51% of patients with cement dermatitis and 14% with dermatitis other than cement (Geiser *et al*., 1960).

A study of 300 patients with dermatitis found 12 (4%) to be sensitive to cobalt chloride on patch testing. Occupations of those showing sensitisation were brick, cement and metal workers and home duties (Marcussen, 1963).

Thirty nine out of 853 metal industry workers tested positive in patch testing to cobalt chloride in a Swedish study. The authors also evaluated medical records of about 2,000 workers employed in the industry over a ten year period and determined an incidence rate of about 2.5% with a sensitivity to cobalt (Fischer & Rystedt, 1983).

Patch testing of a cohort of 142 patients with eczema revealed a positive response to cobalt chloride in 3.5% of agricultural workers and 2.5% of non-agricultural workers (Lantinga *et al*., 1984).

Garcia *et al*., (1984) examined the medical records of 34 agricultural workers presenting to a dermatology clinic in Spain. Records were compared with those of 244 non-agricultural workers also presenting with contact dermatitis. In patch testing 11.8% were positive to cobalt chloride.

In an epidemiological study of 12,026 patients presenting to an Austrian clinic, 4494 had positive patch test reactions to at least one allergen. Of those 4.7%, tested positive to cobalt chloride (Enders *et al*., 1988).

Twenty-nine asymptomatic chlorate factory workers in France underwent patch testing to potassium dichromate, nickel sulfate and cobalt chloride. Two tested positive to cobalt chloride (in 1% pet) (Decaestecker *et al*., 1990).

In a study of 72 catering workers during 1987 to 1991, one (1.4%) subject, a kitchen assistant, was diagnosed as sensitive to cobalt chloride following patch testing, (Acciai & Brusi, 1993).

In a study on 271 patients with dermatitis referred to a Saudi Arabian clinic, 152 (51.6%) showed positive reactions in patch testing. Of those 152, 30.9% were positive in patch testing to cobalt chloride. A positive history of atopy was given by 20.4%. Unfortunately, no data are available on whether any atopics tested positive to cobalt chloride (al-Sheikh & Gad el-Rab, 1996).

An epidemiological study by Albert *et al*. (1998) from a dermatitis clinic in the USA on 608 patients over a seven year period found that 60% showed at least one positive reaction in patch testing and 9.4% of the 608 reacted to cobalt chloride.

Sertoli *et al*. (1999) report an epidemiological study in Italy conducted over two five year periods of 42,839 patients. A total of 65.4% of patients were diagnosed with allergic contact dermatitis. It is unclear how many patients with allergic contact dermatitis as opposed to irritant contact dermatitis tested positive in patch testing to cobalt chloride. However over the ten year period, 7.7% of all patients tested positive to the chemical.

Over a ten year period, 4,112 patients presenting to a German clinic with occupational skin disease were patch tested for a series of allergens. Sensitivity to cobalt chloride was found in 13.5%. Atopic dermatitis was found in 19.2% but no data are given on whether any atopics were sensitised to cobalt chloride (Dickel *et al*., 2002).

In a study examining the applicability of a European series of patch test allergens to a Pakistani population, 350 dermatitis patients were patch tested. Positive responses to cobalt chloride were noted in 7.7% (Hussain *et al*., 2002).

In an epidemiological study of 335 construction workers diagnosed with occupational skin disease, 27% were atopics. A total of 67 (19%) workers tested positive to cobalt

chloride in standard series patch testing. The greatest prevalence was in cement workers (13%) then tile setters (3%) then painters (2%) (Bock *et al*., 2003).

Conde *et al*., (1995) report the results of a study in 449 construction workers in Spain who presented to a dermatological clinic. Of these 408 tested positive in at least one patch test. Of the 408, 20.5% tested positive to cobalt chloride. This study noted the use of the Chemotechnique Diagnostic patch test kit with the hexahydrate form.

Five hundred and twenty Swedish army conscripts were tested for sensitivity to nickel sulfate and cobalt chloride. In patch testing, 1% reacted positively to cobalt chloride (Meijer *et al*., 1995). Similarly, this study noted the use of the Chemotechnique Diagnostic patch test kit with the hexahydrate form.

Case Reports

A 44-year old male printer presented with a two-year history of eczema. He had contact with printing inks which contained cobalt and patch testing with cobalt chloride was positive (van Ketel, 1984).

A machine operator presented to a French clinic with a three week history of eczema. Patch testing was positive to cobalt chloride. The patient stopped work and the dermatitis healed. Following a return to work the problem returned. The patient transferred to a different work area where he was not exposed to cobalt and remained free of the condition (Foussereau & Cavelier, 1988).

Torresani *et al*., (1994) report the case of a 56-year old female suffering oral lesions from contact to a dental prosthesis containing cobalt. Patch testing using the European standard series was positive for cobalt chloride.

A 23-year old plumber presented with ashy dermatosis. Patch testing with cobalt chloride was positive (Zenorola *et al*., 1994).

Bagnato *et al*., (1999) report a case of a 42-year old male with no history of atopy who developed urticaria following being tattooed. Patch testing with cobalt chloride was positive.

Yamanaka *et al*., (2003) report a case of sensitisation to cobalt chloride in a nurse who presented with erythema. Following patch testing using a standard allergen series (including cobalt chloride in `% pet) the patient developed erythema at the site of one of the test chambers. Retesting was positive for cobalt chloride and the authors concluded that the nurse was sensitised as a result of the first patch testing.

Other Studies

None

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 14 positive reactions for this chemical out of 1,500 workers (0.9%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 156 cases for this chemical out of a total of 6,067 cases (2.6%). The Occupational Physicians Reporting Activity (OPRA) database contains 1 case for this chemical out of a total of 838 skin cases, (0.1X%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Although frequently without definition as to its hydration state, cobalt chloride is reported as a skin sensitiser from numerous clinics worldwide, from a range of occupations and induction scenarios. In human studies, up to 30% of patients tested positive to cobalt chloride in patch testing. Animal studies on the hexahydrate form conducted in a manner similar to OECD guidelines report more than 30% of animals showing positive reactions.

Although not on the current NOHSC List of Designated Hazardous Substances, anhydrous cobalt chloride (CAS 7646-79-9), is listed in the current Annex 1 to Directive 67/548/EEC of the European Union (EU) as a respiratory (R42) and skin (R43) sensitiser. Therefore, on the basis of animal studies of the hexahydrate form meeting the NOHSC Approved Criteria for skin sensitisation, in addition to classification of the anhydrous form by the EU as both a skin and respiratory sensitiser, cobalt chloride hexahydrate is similarly classified as a skin and respiratory sensitiser.

Similarly, on the basis of a concentration cutoff of ≥ 1% established for the anhydrous form in Annex 1 to Directive 67/548/EEC of the EU, a concentration cutoff for skin and respiratory sensitisation of ≥ 1% is established for the hexahydrate form.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger “Irritant”, risk phrase R43) and Sensitisation by Inhalation (symbol Xn, indication of danger “Harmful”, risk phrase R42) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Diazolidinylurea (Germall II)

Chemical Identification

Chemical Name:	Urea, N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis(hydroxymethyl)-
CAS #	78491-02-8
Synonyms:	Germall II; Germaben II-E; Diazolidinyl urea
Use:	As a preservative in cosmetics, hair and skin care preparations. Less commonly found in cosmetics compared to imidazolidinyl urea (Jackson, 1995).

Evidence for Sensitisation Properties

Diazolidinyl urea and the closely related chemical, imidazolidinyl urea, are formaldehyde releasers (Hectorne & Fransway, 1994). Formaldehyde is a known potent human skin sensitiser (Ziegler *et al.*, 1988).

Animal Studies (Standard and Non-Standard)

Using the modified Magnusson-Kligman maximisation test in Hartley albino guinea pigs the sensitisation potential of diazolidinyl urea was investigated (Biodynamics, 1983). The animals each received two intradermal injections of 50% aqueous solution of Freund's Complete Adjuvant (FCA), 5% aqueous solution of diazolidinyl urea, and 5% diazolidinyl urea in 50% FCA. At one week, following pre-treatment with 10% sodium lauryl sulfate the animals were given a topical booster at the injection site with patches containing 100% diazolidinyl urea. The patches were left on the skin for 48 hours. Two weeks later the animals were challenged on untreated sites with patches containing 50% aqueous diazolidinyl urea. The positive control, 2,4-dinitrochlorobenzene, was also administered in the same manner. When challenged, 3 out of 10 animals (i.e. 30%) had dermal scores of 1 or greater on the Draize scoring scale after 24 hours. The other animals had equivocal scores. In the concurrent controls, 2 out of 6 animals had equivocal scores. While this test protocol is not exactly as stated in the OECD guidelines for the guinea pig maximization test the results indicate that diazolidinyl urea is a skin sensitiser. This summary is based on the Expert Panel of Cosmetics Ingredients Review (1990) review of Biodynamics (1983). The original study has not been sighted.

The sensitisation potential of diazolidinyl urea was determined using a further modified Magnusson-Kligman maximisation test in Dunkin-Hartley guinea pigs (n=10) (CTFA, 1984). The induction phase included either a 5% solution of diazolidinyl urea in propylene glycol or a 5% solution of diazolidinyl urea in 50% aqueous FCA. At one week, following pre-treatment with 5% sodium lauryl sulfate, a topical booster of diazolidinyl urea (50% in pet.) was given. After two weeks, the animals were challenged with patches containing 25% and 50% diazolidinyl urea. No justification was given for the choice of induction and challenge concentrations. Hence, it is possible that the induction and challenge concentrations were not

maximised. When challenged with 25% and 50% diazolidinyl urea, 2 out 10 animals (20%) and 4 out of 10 animals (40%), respectively, reacted positive. With 40% of animals reacting positive to 50% diazolidinyl urea it can be considered as a sensitiser. However, one must also take into account that with 50% diazolidinyl urea 1 out of 10 control animals reacted positive. Even after making the correction for the single positive control response, 30% of animals were sensitised by 50% diazolidinyl urea. This summary is based on the Expert Panel of Cosmetics Ingredients Review (1990) review of CTFA (1984), as the original study has not been sighted.

Stephens *et al*. (1987) investigated the sensitisation potential of diazolidinyl urea and its cross-sensitisation potential with imidazolidinyl urea and formaldehyde in guinea pigs (outbred Hartley albino male & female; 300–350 g). This non-standard test is considered by the authors to be one of the most sensitive for detecting contact sensitivity in guinea pigs (Klecak, 1977). When challenged with 50% diazolidinyl urea (induction injection: 2% diazolidinyl urea in distilled water; induction patch: 50% w/v diazolidinyl urea) 5 out of 25 animals (20%) showed a response of 1 (i.e. slight, well defined, erythema) or more in the grading scale of Magnusson and Kligman (1970). Negative control animals did not respond to the diazolidinyl urea challenge. To be considered a sensitiser the NOHSC Approved Criteria requires a positive response in at least 30% of the animals using such adjuvant type test methods. No justification was given for the choice of induction and challenge concentrations. Hence, it is possible that the induction and challenge concentrations were not maximised. A greater response might have been obtained with higher induction and challenge concentrations. When challenged with imidazolidinyl urea (50% in aq.) and formaldehyde (1% in aq.), 62.5% (5 out of 8 animals) and 75% (6 out of 8 animals) of animals, respectively, showed allergic responses. These results show that there is cross-sensitisation between diazolidinyl urea and imidazolidinyl urea.

The sensitisation potential of diazolidinyl urea was determined using the Landsteiner-Jacobs procedure in guinea pigs (n=9) (Leberco Laboratories, 1981). This test assay is not on the OECD Test Guidelines. Intracutaneous induction injections (0.1% diazolidinyl urea in saline) were given every 48 hours until all 10 injections were administered. After a two-week period a challenge injection of diazolidinyl urea (0.1% in saline; 0.05 ml) was administered. Diazolidinyl urea was not sensitising in this study. However, no justification was given for the choice of induction and challenge concentrations. Both the induction and challenge concentrations are identical. Hence, it is possible that the induction and challenge concentrations were not maximised. Consequently, this non-standard apparently negative study does not provide completely reliable evidence for the lack of skin sensitisation potential. This summary is based on the Expert Panel of Cosmetics Ingredients Review (1990) review of Leberco Laboratories (1981), as the original study has not been sighted.

Human Evidence

Surveys

Perret and Happle (1989) in a dermatological clinic in Netherlands patch tested 2,400 consecutive patients with eczema between July 1984 and September 1988. Both the European standard series (Trolab) and a supplementary series including diazolidinyl urea were utilised. Out of the 2,400 patients, 13 (i.e. 0.5%) were positive to

diazolidinyl urea (2% in aq.). Six patients were also positive to formaldehyde (1% in aq.). Ten of the 13 patients were also allergic to various other contact allergens.

Between 1 January 1984 to 1 May 1985, the North American Contact Dermatitis Group made up of 10 dermatological clinics patch tested patients with their own standard series of allergens, a preservative series and a "special studies" series (Storrs *et al.*, 1989). The patches were placed for 48 to 72 hours, and the results read at one-half hour or one day after removal. A second reading was taken 5–7 days after application. Out of 647 patients tested with diazolidinyl urea (1% in aq.) 12 (i.e. 1.9%) reacted positive and 2 other patients had doubtful reactions. Only 2 of these positive reactions were clinically relevant (i.e. not due to their formaldehyde-release potential). When 155 other patients were tested with diazolidinyl urea (1% in pet.) 2 (i.e. 1.3%) reacted positive and 1 gave a doubtful reaction. Severity of these reactions was not stated.

Hectorne and Fransway (1994) evaluated patch test results from 708 consecutive patients who presented to the Department of Dermatology at the Mayo Clinic with dermatological complaints between November 1989 and October 1991. The patients were patch tested with both the standard series and preservatives series from Chemotechnique Diagnostics (Malmö, Sweden) and Hermal-Trolab (Hamburg, Germany). After the removal of the patch the readings were done on days 2, 3 and 4. Out of the 708 patients, 58 patients (i.e. 8.2%) reacted positive to diazolidinyl urea (2% in aq.). Seven percent of patients allergic to diazolidinyl urea were also allergic to imidazolidinyl urea (2% in pet.) without being allergic to formaldehyde (2% in aq.). This suggests that both diazolidinyl urea and imidazolidinyl urea may cross-react with each other in some individuals as well as being allergenic in their own right in these patients. However, since there was 81% cross-reactivity between diazolidinyl urea and formaldehyde the data suggests that formaldehyde release is the likely primary mode of sensitisation in these patients to diazolidinyl urea.

In a retrospective study, patch test results from 21,265 patients that presented to the St John's Institute of Dermatology between 1982 and 1993 were analysed (Jacobs *et al.*, 1995). The extended standard series included formaldehyde (1% in aq.), imidazolidinyl urea (2% in aq.) and diazolidinyl urea (2% in aq.). The patch tests were done according to the guidelines from the International Contact Dermatitis Research Group. Ninety-one patients (i.e. 0.4%) reacted positive to diazolidinyl urea. Of those sensitised by diazolidinyl urea only 5 (i.e. 5%) patients were solely allergic to diazolidinyl urea. Twenty-three patients (i.e. 25%) were sensitised by both diazolidinyl urea and formaldehyde. Interestingly, 68 patients (i.e. 75%) were sensitised by both diazolidinyl urea and imidazolidinyl urea. These results suggest that sensitisation to diazolidinyl urea can occur independent of its formaldehyde release in some patients. However, sensitisation to diazolidinyl urea is more likely to be due to formaldehyde release, while cross-sensitisation between diazolidinyl urea and imidazolidinyl urea occurs frequently.

Between 1989 and 1994, Swedish Medical Products Agency evaluated 191 reports concerning adverse effects caused by cosmetics and toiletries (Berne *et al.*, 1996). Relevant positive patch test results were obtained from 79 patients. Since the patch tests were not conducted by the agency a protocol for the procedure is not given.

However, patch tests revealed that 3 patients were sensitised by diazolidinyl urea (conc. and vehicle not stated).

Patch test data to preservatives and antimicrobials from 24 dermatological clinics (Information Network of Departments of Dermatology) in Germany were reported (Schnuch *et al.*, 1998). This study was conducted between 1 January 1990 and 31 December 1994. A total of 29,349 patients were patch tested with preservatives of the standard series, 11,485 patients tested with an additional preservative series and 1,787 patients with industrial biocides. The test materials were from Hermal/Reinbek (Germany). Patch test readings were done 72 hours after application of the patch. Of the 7,812 patients tested with diazolidinyl urea (2% in pet.) 98 patients (i.e. 1.3%) showed skin sensitisation, and a further 47 patients (i.e. 0.6%) showed questionable/irritative reactions. About 22% of the patch tested patients had a history of atopic dermatitis.

A retrospective study looked at the patch test results from 5 European dermatological centres during a 4-month period; January to April 1996 (Goossens *et al.*, 1999). Out of 475 patients, 19 patients (i.e. 4%) reacted positive to diazolidinyl urea (conc. and vehicle not reported). Ten of these 19 patients were from a clinic in Belgium and the rest from UK. The procedure for the patch tests was not reported.

Between October 1994 and October 1996, 1,527 eczema patients (females = 992) were consecutively patch tested at the Department of Dermatology of Gentofte University Hospital (Denmark) with the European standard series (Hermal, Germany), common cosmetic ingredients and patients' own cosmetic products (Held *et al.*, 1999). The patches were applied for 2 days, and results read after 2, 3 and 7 days. Tests were read according to the International Contact Dermatitis Research Group guidelines. Out of 1,527 patients, 17 (i.e. 1.1%) were allergic to diazolidinyl urea (conc. and vehicle not reported). However, 3 of these reactions to diazolidinyl urea were considered doubtful.

Between 1 July 1996 to 30 June 1998, the North American Contact Dermatitis Group made up of 12 dermatological clinics patch tested over 3,400 patients with their own standard series of allergens (Chemotechnique Diagnostics AB, Sweden) (Marks *et al.*, 2000). The patches were placed for 48 hours and the results read at 48 and 72 hours. A patch test reaction ≥ 1+ were considered positive. Out of 4,096 patients patch tested 152 (3.7%) reacted positive to diazolidinyl urea (1% in pet.). A total of 91.5% of the positive reactions were considered clinically relevant.

In a British study, during the year 2000, 3,062 patients were consecutively patch tested in seven dermatological clinics with the British standard series (Hermal, Reinbek, Germany and Chemotechnique Diagnostics, Malmö, Sweden) (Britton *et al.*, 2003). The patches were applied for 2 days, and results read after 2 and 4 days. Reactions were scored according to the recommendations of the International Contact Dermatitis Research Group. When patch tested with diazolidinyl urea (2% in aq.) 0.7% (i.e. 21 patients) of patients reacted positive. Severity of these reactions was not stated.

Given that diazolidinyl urea release small quantities of formaldehyde by hydrolysis in aqueous conditions a TRUE test was performed to determine diazolidinyl urea's own

sensitisation potential (Agner *et al*., 2001). In the TRUE test the diazolidinyl urea (600 $\mu g/cm^2$) was incorporated in a dry vehicle (polyvidone), hence, preventing formaldehyde release. In this study, 74 consecutive patients were patch tested with diazolidinyl urea. The study also included 19 other patients that had previously tested positive to this chemical. On day 3, one patient tested positive to only diazolidinyl urea. Three patients tested positive to both diazolidinyl urea and imidazolidinyl urea. Six patients tested positive to both diazolidinyl urea and formaldehyde. Six patients tested positive to all three chemicals. Therefore, out of the 93 patients tested 16 patients had skin sensitisation to diazolidinyl urea. This study suggests that diazolidinyl urea may induce skin sensitisation by either formaldehyde release or independent to formaldehyde release.

Case Reports

De Groot *et al*. (1988) reported four cases of skin sensitisation to diazolidinyl urea. The first patient presented with eye dermatitis after using several cosmetics. This 44-year old woman was initially patch tested with the European Standard Series and her own cosmetics. Patch test results were read on day 3. She reacted to a "hypoallergenic" day and night cream. When tested with the ingredients of the cream she reacted to diazolidinyl urea (1% in aq.). The second patient was a 38-year old woman with atopic dermatitis of the face and eyelids. She presented to the clinic as her condition exacerbated following the use of a day and night cream. When patch tested she reacted only to the day and night cream. When retested with the ingredients of the cream she reacted to diazolidinyl urea (2% in aq.). The third patient was a 23-year old woman with dermatitis of the neck, hands, arms and legs. Her condition worsened after using "hypoallergenic" cream, body lotion and shampoo. When patch tested she reacted to the fragrance-mix, formaldehyde and her cosmetic products. When retested with the ingredients of the cosmetics she reacted to hydroxycitronellal (2% in pet.) and diazolidinyl urea (2% in pet.). The fourth patient was a 55-year old woman known to be allergic to parabens and formaldehyde. When patch tested she reacted to several cosmetic products. Further patch testing showed that she was allergic to imidazolidinyl urea (2% in aq.) and diazolidinyl urea (2% in aq.).

A study was conducted to determine the allergic contact dermatitis potential of preservatives in topical medicines (Skinner & Marks, 1998). Nine volunteers over the age of 18 years were recruited based on a prior history of allergy to formaldehyde-releasing preservatives. One patient was assigned to the diazolidinyl urea test group. The patients were patch tested with topical medications and their respective preservatives. The final reading was done 96 hours after the removal of the patches. Use tests were performed after applying the test material for 14 days on a predetermined area of the forearm. The patient in diazolidinyl urea test group reacted positive to diazolidinyl urea (1% in aq. and 1% in pet.) and Dovonex (0.05%) cream (also containing diazolidinyl urea) after patch testing. However, this patient had no reaction to either Dovonex cream or diazolidinyl urea after use testing. It is suggested by the authors that the concentration of diazolidinyl urea in Dovonex cream is below the threshold that is necessary to cause a positive reaction with use testing.

Zaugg and Hunziker (1987) reported a case of chronic allergic contact dermatitis in a 48-year old woman. Four years prior to the referral she was found to be allergic to formaldehyde. Since then she was treated with topical steroids and a non-alkaline

liquid soap. Patch testing suggested that she was also allergic to the soap. Further patch testing with the ingredients of the soap suggested that she was sensitised to diazolidinyl urea (1% in aq.) and triclosan (1% in pet.). A rechallenge 7 weeks later gave the same results.

A 42-year old man presented to the Cleveland Clinic Department of Dermatology with acute dermatitis of his face and neck (Kantor *et al*., 1985). After the dermatitis had subsided, the patient was patch tested with Standard series of the American Academy of Dermatology, vehicles, permanent wave chemicals and the patient's hair care products. The results were read at 72 hours after the patch was removed. Positive (+ reactions) patch test results were seen to diazolidinyl urea (1%; vehicle not reported) and Soft Sheen's Care Free Curl Naturalizer Gel (also containing diazolidinyl urea). The patch test to formaldehyde (conc. and vehicle not stated) was negative.

Tosti *et al*. (1990) reported three case studies where a 35-year old barmaid and two elderly housewives (one 65 years old and the other 69 years old) presented with contact dermatitis due to diazolidinyl urea. They were patch tested with the Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali (GIRDCA) standard series, preservative series and their own cosmetics. All three reacted positive to diazolidinyl urea (1% in aq.). The two elderly housewives also reacted positive to imidazolidinyl urea (2% in pet.), but not formaldehyde (conc. and vehicle not stated).

Other Studies

To assist with interpretation of patch test results from The North American Contact Dermatitis Group (NACDG), Significance-Prevalence Index Numbers (SPIN) have been calculated and assigned to each allergen in the NACDG allergen series (Maouad *et al*., 1999). The SPIN numbers have been calculated by taking into account the proportion of the population allergic to the test substance and the clinical relevance of the patch test reaction. Based on the calculated SPIN numbers diazolidinyl urea (1%) was ranked as the 15-16th (out of 50-52 allergens) most sensitising test substance between periods 1984–1985, 1992–1994 and 1994–1996.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 13 positive reactions for this chemical out of 1,500 workers (0.9%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 7 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 1 case for this chemical out of a total of 838 skin cases, (0.1%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

The studies by Biodynamics (1983) and CTFA (1984) suggest that diazolidinyl urea is a skin sensitiser. In the Biodynamics (1983) study, 3 out of 10 animals (i.e. 30%) had dermal scores of 1 or greater on the Draize scoring scale after being challenged with 50% aqueous diazolidinyl urea. The other animals had equivocal scores, as did 2 out of 6 controls. In the CTFA (1984) study, 30% of animals were sensitised with diazolidinyl urea (50% in pet.) even after correcting for the positive response in one control animal. There are concerns with both the Stephens *et al*. (1987) and Leberco Laboratories (1981) studies in that the concentrations used for both induction and challenge were not maximised. In both these studies a greater sensitisation response in animals might have been obtained with higher induction and challenge concentrations. These studies support classification of diazolidinyl urea as a skin sensitiser under the NOHSC Approved Criteria 4.67.

Many dermatological clinics have reported positive patch test reactions to diazolidinyl urea in patients (Kantor *et al*., 1985; Zaugg & Hunziker, 1987; De Groot *et al*., 1988; Perret & Happle, 1989; Storrs *et al*., 1989; Tosti *et al*., 1990; Hectorne & Fransway, 1994; Jacobs *et al*., 1995; Berne *et al*., 1996; Schnuch *et al*., 1998; Skinner & Marks, 1998; Goossens *et al*., 1999; Held *et al*., 1999; Marks *et al*., 2000; Agner *et al*., 2001; Britton *et al*., 2003). Diazolidinyl urea is a commonly used preservative in cosmetics (Jackson, 1995). Though a substantial number of people are likely to be exposed, only a low incidence of positive patch test results were reported in patients in some studies (Perret and Happle, 1989; Storrs *et al*., 1989; Schnuch *et al*., 1998; Held *et al*., 1999). Other studies have reported higher incidences of diazolidinyl urea induced skin sensitisation (Hectorne & Fransway, 1994; Goossens *et al*., 1999; Marks *et al*., 2000).

Studies have shown that there is cross-sensitisation potential between diazolidinyl urea and the structurally related skin sensitiser imidazolidinyl urea (Stephens *et al*., 1987; Hectorne & Fransway, 1994; Jacobs *et al*., 1995; Agner *et al*., 2001). Furthermore, diazolidinyl urea may induce skin sensitisation by either formaldehyde release or independent of formaldehyde release (Hectorne and Fransway, 1994; Jacobs *et al*., 1995; Agner *et al*., 2001). Therefore, diazolidinyl urea may elicitate a response in people previously sensitised to another substance (eg. imidazolidinyl urea or formaldehyde).

It is worth noting that the Expert Panel of Cosmetic Ingredient Review (1990) concluded that while diazolidinyl urea was safe for the majority of consumers it should be used at the minimum effective concentration (i.e. 0.2% or less) in cosmetics given that some individuals are sensitive to formaldehyde. However, this conclusion was based on studies conducted up to the year 1990, and since then studies are available that show diazolidinyl urea can also induce skin sensitisation independent of formaldehyde release (Jacobs *et al*., 1995; Agner *et al*., 2001).

Thus, positive animal data are available for diazolidinyl urea, and although the human data suggests a weak skin sensitisation potential, cross-sensitisation may exist for imidazolidinyl urea or formaldehyde (a known potent human skin sensitiser). Consequently, diazolidinyl urea is considered capable of producing skin sensitisation

responses in humans. Therefore, the data supports classification of diazolidinyl urea as a skin sensitiser.

Data do not suggest a concentration cutoff for mixtures containing diazolidinyl urea at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger "Irritant", risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Dowicil 200

Chemical Identification

Chemical Name: 3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride, (Z)-

CAS # 51229-78-8

Synonyms: 1-(3-Chloroallyl)-3,5,7-triaza-1-azoiaadamantane chloride, cis-;
Dowicil 200;
Quaternium 15 (see comment below)

Use: Preservatives in oil recovery drilling muds and packer fluids, metal working cutting fluids, latex paints, industrial adhesives and coatings, latex emulsions, detergent floor wax emulsions, floor polishes, inks, laundry starch, spinning emulsions and paper and pulp coatings, finishes and printing colours as components of paper and paperboard intended for use in contact with aqueous, fatty, dry bulk, and dry foods. Also used in microbiocides/microbiostatics in water treatment.

These specific uses are from the Hazardous Substances Data Bank (HSDB) entry for CAS # 4080-31-3 (see comment below). There are no similar use data for CAS # 51229-78-8 in HSDB.

According to Dow product information, Dowicil 200 is used as a preservative in personal care products.

Evidence for Sensitisation Properties

Comment

This chemical, which exists as a pair of stereoisomers, has two relevant associated CAS numbers on AICS and the CAS National Chemical Inventories: 51229-78-8 (the cis isomer) and 4080-31-3 (the racemic mixture). Moreover, the synonym (or trade name) Quaternium 15 associated with Dowicil 200 in the Chemotechnique Diagnostics catalogue cannot be confirmed as an appropriate additional synonym for this chemical across all data sources (see below).

CAS Number	Trade Name	Reference
4080-31-3	Dowicil 100 & Quaternium 15	Scifinder
	Dowicil 100 & Quaternium 15	NCI
	Dowicil 100 & Quaternium 15	HSDB
	Dowicil 100 & Quaternium 15	RTECS
	Quaternium 15	Reprotox
	Dowicil 200 & Quaternium 15	ECETOC
51229-78-8	Dowicil 200	NCI

	Dowicil 200	Scifinder
	Dowicil 200	Univar MSDS [1]
	Dowicil 200 & Quaternium 15	Chemotechnique Diagnostics
	Dowicil 200 & Quaternium 15	Dow product information
	Dowicil 200	Dow Aust MSDS [2]

[1.] The Univar MSDS is for the product Dowicil 200 which contains 96% CAS # 51229-78-8 and 1% CAS # 58713-21-6. The MSDS is prepared under the Canadian Controlled Products Regulations.
[2.] The Dow Australia MSDS is for the product Dowicil 200 which contains 96% CAS # 51229-78-8 and 1% CAS # 58713-21-6.

This assessment assumes that Dowicil 200 is CAS # 51229-78-8 and that Quarternium 15 is not an appropriate synonym. CAS # 4080-31-3 is assumed to be Dowicil 100 (and Quarternium 15) and that this is likely to be a mixture of the two isomers. Because of the possibility of sensitisation properties differing between the two isomers, only papers that document use of the Chemotechnique Diagnostics patch test kit (using 51229-78-8) or that specifically identify the chemical as the cis isomer were reviewed for this assessment.

Animal Studies (Standard and Non-Standard)

In a mouse ear swelling test, 10 test animals were exposed to 15% Dowicil 200 in acetone: water: Tween 80 (4:3:1) (Maisey & Miller, 1986). Animals were induced by 6 topical applications to the shaved abdomen and thorax over a two week period on days 0, 2, 4, 7, 9 and 11. Ten positive control mice received 0.3% oxazolone in acetone : water : Tween 80 (4:3:1) during induction, and 0.3% oxazolone in acetone : oil (1:1) at challenge. Negative control mice received vehicle only during induction and test substance at challenge. The authors' state that concentrations of test substance used were based on the compounds "toxicity, irritancy and solubility" determined in separate experiments where the compound was applied to the abdomen and ear. Results of the preliminary experiments are not given. The final concentration chosen was noted to be non irritant, non-toxic and soluble in the vehicle.

In the case of Dowicil 200, the induction and challenge doses were identical although the challenge vehicle was acetone : water (1:1). For challenge (day 15), test and control mice had the substance applied to both ears. Ear thickness was measured before challenge and at 24 and 48 hours after. Dowicil 200 significantly increased ear thickness compared with controls. Changes were statistically significant at both 24 and 48 hours (Mann Whitney U test). Compared to the highest individual percentage increase amongst the control animals, 6 test animals showed at least a 50% increase and 3 animals showed at least a 100% increase in ear thickness at 48 hours. Dowicil 200 was considered a potent sensitiser by the authors of this study. The mouse ear swelling test though not approved as a separate OECD Test Guideline, is referred to in Guideline 406 and described as a validated test. No details of approved methodology are given.

Based in part on an unpublished Dow internal animal study using the Draize test (Sabourin, 1997), the Dow Chemical (Australia) Limited MSDS for Dowicil states that the product may cause sensitisation by skin contact at concentrations greater than 1% with the risk phrase R43. A call for any data (published or unpublished) regarding sensitisation on this chemical was made by a notice in the *Chemical Gazette* of

November 2003 under s.48 of the *Industrial Chemicals (Notification and Assessment) Act*. At the time of this assessment, this internal Dow report study was not available for evaluation.

Human Evidence

Surveys

Two hundred patients aged between 9 and 85 years with suspected allergic contact dermatitis attending the Dermatology clinic of the Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India were recruited to be patch tested with the European standard series (Chemotechnique Diagnostics) containing "Quaternium 15" (0.1% pet.) (identified in the current Chemotechnique Diagnostics catalogue as Dowicil 200 CAS # 51229-78-8). Patch tests readings were taken after 2 and 3 days and only reactions still positive at 3 days were considered positive. No other details regarding methodology were provided. A total of 5 (2.5%) showed positive reactions to Dowicil 200. The severity of reactions was not provided (Sharma & Chakrabarti, 1998).

At the Nofer Institute of Occupational Medicine, Lódż, Poland, (Kiec-Swierczynska & Krecisz, 2002)) patch tested 46 dental nurses with suspected dermatitis using the European standard series (Chemotechnique Diagnostics). Patch tests were applied and inspected according to International Contact Dermatitis Research Group (ICDRG) guidelines. One nurse (2.2%) returned a positive response to Quaternium 15 (Dowicil 200).

Case Reports

A 10-year old boy presenting with a 2 year history of eczema on the shins was patch tested using a standard series and a textile series (Chemotechnique Diagnostics). A positive reaction to Quaternium 15 (Dowicil 200) was found (Sommer *et al*., 1999).

Other Studies

None

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 11 positive reactions for Dowicil 200 out of 1500 workers (0.7%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

No data were provided specifically for Dowicil 200. The EPIDERM occupational skin surveillance database contains 14 cases for Quarternium 15 out of a total of 6,067 cases (0.2%). The Occupational Physicians Reporting Activity (OPRA) database

contains 1 case for Quarternium 15 out of a total of 838 skin cases, (0.1%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

This assessment was conducted on the cis isomer Dowicil 200 CAS #51229-78-8. Because of doubts as to the authenticity of Quaternium 15 as an appropriate synonym for this chemical, studies on Quaternium 15 without supplementary comfirmation of chemical identity were not regarded.

A mouse ear swelling test showed Dowicil 200 to be a potent sensitiser (Maisey & Miller, 1986). The mouse ear swelling test though not approved as a separate OECD Test Guideline, is referred to in Guideline 406 and described as a validated test.

In limited human surveys, around 2.2–2.5% of patients tested positive in patch testing with Dowicil 200.

On the basis of both published and unpublished studies, a Dow Chemical (Australia) Limited MSDS for Dowicil 200 states that the product may be a weak skin sensitiser at concentrations greater than 1% aq. The MSDS includes R43 as a risk phrase for this product. An unpublished modified Draize skin sensitisation study of Dow for this chemical (Sabourin, 1997) supports a sensitiser classification. This study has not been sighted to date by NICNAS. Although the human data indicated a low incidence of sensitisation, positive animal evidence from a published mouse ear swelling test as well as classification of this chemical as a skin sensitiser by the manufacturer based in part on an internal Draize skin sensitisation study satisfies the NOHSC Approved Criteria for classification of Dowicil 200 as a skin sensitiser.

Data do not suggest a concentration cutoff for mixtures containing Dowicil 200 at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger “Irritant”, risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Imidazolidinylurea (Germall 115)

Chemical Identification

Chemical Name:	Urea, N,N''-methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-
CAS #	39236-46-9
Synonyms:	Germall 115; Biopure 100; Euxyl K 200; Abiol; Imidurea; Imidazolidinyl urea
Use:	One of the most commonly used preservatives in cosmetics (Fisher, 1980).

Evidence for Sensitisation Properties

Imidazolidinyl urea and the closely related chemical, diazolidinyl urea, are formaldehyde releasers (Hectorne & Fransway, 1994). Formaldehyde is a known potent human skin sensitiser (Ziegler *et al.*, 1988).

Animal Studies (Standard and Non-Standard)

Basketter and Scholes (1992) studied 40 chemicals for their skin sensitisation potential in the guinea pig maximisation test (GPMT) and murine local lymph node assay (LLNA). These chemicals included imidazolidinyl urea (Sutton Labs, USA). While the protocol for the Magnusson and Kligman GPMT was not stated in detail it closely followed the OECD guideline. Albino Dunkin-Hartley guinea pigs (350 g) were used for the GPMT, and CBA/Ca mice (8–12 weeks; 4 animals per dose) were used for the LLNA. For the GPMT, preliminary irritation tests were conducted to determine the concentrations of imidazolidinyl urea suitable for induction and challenge. At induction, guinea pigs were given a series of six intradermal injections to induce sensitisation. The induction injection consisted of 2.5% imidazolidinyl urea (in 0.9% NaCl). After 6-8 days, a 48-hour occluded induction patch containing 75% imidazolidinyl urea (in 0.9% NaCl) was applied over the injection site. On days 20-22, a challenge patch containing the maximum non-irritant concentration (75% imidazolidinyl urea in 0.9% NaCl) was applied to one flank for a 24-hour period. The test sites were evaluated for erythema (scale 0-3) and oedema 24 and 48 hours after the challenge patch was removed. Imidazolidinyl urea caused sensitisation in 80% of the animals tested in GPMT. Hence, it was considered strong sensitiser (Basketter & Scholes, 1992).

Testing in LLNA included 10%, 25% and 50% imidazolidinyl urea (in dimethyl formamide) (Basketter & Scholes, 1992). The test protocol followed the OECD guideline. Briefly, the mice were treated by applying 25 µl of each concentration of imidazolidinyl urea on the dorsal surface of each ear for 3 consecutive days. The mice were injected with 250 µl of phosphate buffered saline containing [^{3}H]methyl thymidine (20 µCi). After 5 hours the mice were killed and the draining auricular

lymph nodes were excised and pooled. [^{3}H]methyl thymidine incorporation was measured by β-scintillation counting. A greater than 3-fold increase in [^{3}H]methyl thymidine incorporation indicates a positive response, and occurred with 25% and 50% imidazolidinyl urea. Hence, imidazolidinyl urea was considered a positive sensitiser in the LLNA (Basketter & Scholes, 1992).

The potential of imidazolidinyl urea to induce skin sensitisation was determined using the open epicutaneous (non-standard) test in albino guinea pigs (outbred strain) (Ziegler *et al*., 1988). Five test groups with 8 animals each were treated topically with 0.3%, 1%, 5%, 25% and 50% imidazolidinyl urea (aq.) on an area of 8 cm^2 clipped flank skin. In the induction phase, treatment was applied topically weekly for 4 weeks. The controls (n=10) were untreated. The challenge was done with 50% imidazolidinyl urea (aq.) 3 days after the induction phase. Two weeks later, animals were exposed to formaldehyde (1% aq.). None of the animals were sensitised with 0.3 and 1% imidazolidinyl urea. Only 12.5% of animals (i.e. 1 out of 8 animals) in each group were sensitised with 5%, 25% or 50% imidazolidinyl urea. Out of the 4 positive reactions to formaldehyde (1% aq.), 2 animals were previously positive to imidazolidinyl urea. Since none of the concentrations (i.e. 0.3 – 50%) of imidazolidinyl urea caused irritation in the pre-induction irritation studies there are concerns that the concentrations were not maximised. Similarly, there is nothing to suggest that the challenge exposure is the highest non-irritant concentration. Therefore, a greater sensitisation response in animals might have been obtained with higher induction and challenge concentrations. This result suggests that the sensitisation to imidazolidinyl urea observed in some animals may be due to the formaldehyde release.

Stephens *et al*., (1987) investigated the cross-sensitisation potential of imidazolidinyl urea and formaldehyde in guinea pigs (outbred Hartley albino male & female; 300–350 g) sensitised to diazolidinyl urea. The structurally related diazolidinyl urea (induction injection: 2% w/v in distilled water; induction and challenge patch: 50% w/v diazolidinyl urea; n = 25) caused mild sensitisation (grade 2) in the modified Magnusson & Kligman guinea pig maximization test in 5 out of 25 animals (20%). This test protocol is not as stated in the OECD guidelines for the guinea pig maximization test and is considered by the authors to be more sensitive for detecting contact sensitivity in guinea pigs (Klecak, 1977). Animals that responded to a challenge of 50% w/v diazolidinyl urea with a score of 0.5 or more were re-challenged with imidazolidinyl urea (50% aq.) or formaldehyde (1% aq.). 62.5% (5 out of 8 animals) and 75% (6 out of 8 animals) of animals showed allergic responses to imidazolidinyl urea (50% aq.) and formaldehyde (1% aq.), respectively. This study showed that there is cross-sensitisation between diazolidinyl urea and imidazolidinyl urea.

Human Evidence

Surveys

Of those patients presenting to three Belgian contact dermatitis units (Tri-Contact Group) 389 patients had contact dermatitis due to cosmetics (Dooms-Goossens *et al*., 1986). 279 patients had allergic reactions and 110 patients had irritant reactions. Of the 279 patients, 3 patients (i.e. 1.1%) reacted positive to imidazolidinyl urea (2% in aq.). The patch test protocol or the severity of the reactions was not described.

Between 1983 and 1984, 2,298 patients (40% males) were consecutively patch tested using the standard series in The Skin Hospital, Manchester, UK (Ford and Beck, 1986). The results were read on days 2 and 4. Out of the 2,298 patients, 16 patients (i.e. 0.7%) reacted positive to Germall 115 (imidazolidinyl urea; 2% in pet.). Fourteen of the positive reactions were clinically relevant (i.e. having a prior history of the patient being exposed to TREGDMA).

The Dutch Contact Dermatitis Group studied the prevalence of skin sensitisation as a result of 27 commonly used preservatives (de Groot *et al.*, 1986). Between the period 1 January–30 April in 1985, 627 patients were consecutively patch tested with the preservative series. Patch testing was conducted according to the International Contact Dermatitis Research Group recommendations. These patients were chosen as they were suspected with contact dermatitis. Out of the 627 patients, 3 patients (i.e. 0.5%) reacted positive to imidazolidinyl urea (2% in pet.). Severity and clinical relevance of these reactions were not stated.

O'Brien (1987) patch tested 178 consecutive patients for suspected contact dermatitis in Victoria, Australia. Germall 115 (2% pet.; imidazolidinyl urea; Hermal-Chemie Kurt Hermann, Hamburg, Germany) was included in the standard series. Out of the 178 patients tested, 7 (i.e. 3.9%) were positive to Germall 115. In three patients products known to contain imidazolidinyl urea also caused skin sensitisation. The clinical relevance of other reactions could not be confirmed. Out of those allergic to Germall 115 only one showed skin sensitisation with formaldehyde.

Hectorne and Fransway (1994) evaluated patch test results from 708 consecutive patients who presented to the Department of Dermatology at the Mayo Clinic with dermatological complaints between November 1989 and October 1991. The patients were patch tested with both the standard series and preservatives series from Chemotechnique Diagnostics (Malmö, Sweden) and Hermal-Trolab (Hamburg, Germany). After the removal of the patches the readings were done on days 2, 3 and 4. Out of the 708 patients, 58 patients (i.e. 8%) reacted positive to diazolidinyl urea (2% in aq.). 7% of patients allergic to diazolidinyl urea were also allergic to imidazolidinyl urea (2% in pet.) without being allergic to formaldehyde (2% in aq.). This suggests that both diazolidinyl urea and imidazolidinyl urea may cross-react with each other in some individuals as well as being allergenic in their own right (i.e. not due to their formaldehyde-release potential) in these patients.

In a retrospective study, patch test results from 21,265 patients that presented to the St John's Institute of Dermatology between 1982 and 1993 were analysed (Jacobs *et al*., 1995). The extended standard series included formaldehyde (1% in aq.), imidazolidinyl urea (2% in aq.) and diazolidinyl urea (2% in aq.). The patch tests were done according to the guidelines from the International Contact Dermatitis Research Group. The authors reported that 156 patients (i.e. 0.7%) reacted positive to imidazolidinyl urea. Of those sensitised by imidazolidinyl urea 53 (i.e. 34%) patients were solely allergic to imidazolidinyl urea. 37 patients (i.e. 24%) were sensitised by both imidazolidinyl urea and formaldehyde. Interestingly, 68 patients (i.e. 44%) were allergic to both imidazolidinyl urea and diazolidinyl urea. While some individuals may have been sensitised by the formaldehyde released by imidazolidinyl urea imidazolidinyl urea can induce sensitisation independent of its formaldehyde release.

Between January 1992 and December 1993 in an Austrian multi-centre (14 centres) study, 11,516 patients (71.5% females) with eczema were patch tested with the Austrian standard series (Reinbek, Germany) (Kränke *et al*., 1996). Patch tests were conducted according to the International Contact Dermatitis Research Group recommendations. When patch tested with Germall 115 (2% in pet.; imidazolidinyl urea) 36 patients (i.e. 0.3%) reacted positive. Severity and clinical relevance of these reactions were not stated.

Angelini *et al*. (1997) conducted patch tests with imidazolidinyl urea (2% in pet.) in 13,647 eczematous patients. Of those tested 0.2% reacted positive to imidazolidinyl urea. While presenting original data this article did not contain a detailed methodology or results section. Severity and clinical relevance of these reactions were not stated.

Patch test data to preservatives and antimicrobials from 24 dermatological clinics (Information Network of Departments of Dermatology) in Germany were reported (Schnuch *et al*., 1998). This study was conducted from 1 January 1990 to 31 December 1994. A total of 29,349 patients were patch tested with preservatives of the standard series, 11,485 patients tested with an additional preservative series and 1,787 patients with industrial biocides. The test materials were from Hermal/Reinbek (Germany). Patch test readings were done 72 hours after application of the patch. Of the 11,452 patients tested with imidazolidinyl urea (2% in pet.), 64 patients (i.e. 0.6%) reacted positive. A further 59 patients (i.e. 0.5%) had questionable/irritative reactions. About 22% of the patch tested patients had a history of atopic dermatitis.

Given that imidazolidinyl urea releases small quantities of formaldehyde by hydrolysis in aqueous conditions a TRUE test was performed to determine imidazolidinyl urea's own sensitisation potential (Agner *et al*., 2001). In the TRUE test the imidazolidinyl urea (600 $\mu g/cm^2$) was incorporated in a dry vehicle (polyvidone), hence, preventing formaldehyde release. In this study, 76 consecutive patients were patch tested with imidazolidinyl urea. The study also included 12 other patients that had previously tested positive to imidazolidinyl urea. On day 3, 2 patients tested positive to only imidazolidinyl urea. Three patients tested positive to both imidazolidinyl urea and diazolidinyl urea. Three other patients tested positive to imidazolidinyl urea and formaldehyde. Six patients tested positive to all three chemicals. Therefore, out of the 88 patients tested for imidazolidinyl urea sensitisation, 14 patients were allergic to imidazolidinyl urea. The results show that imidazolidinyl urea may induce skin sensitisation by either formaldehyde release or independent to formaldehyde release.

In a retrospective study, the Skin and Cancer Foundation (Melbourne) analysed the results of patch tests done on 817 consecutive patients between April 1988 and January 1993 (Ciconte *et al*., 2001). All patients were patch tested with the Skin and Cancer Foundation's (Melbourne) standard series and supplementary allergens (Chemotechnique Diagnostics (Malmö, Sweden) and Hermal (Reinbeck, Germany)). The results were read on day 2 and 4. 436 patients had at least 1 positive reaction to the allergens tested. Out of the 436 patients, 316 patients had clinically relevant reactions. Out of these patients, 17 (i.e. 2.1%) reacted positive to imidazolidinyl urea (2%; vehicle not stated). Thirteen patients were considered to have clinically relevant

patch test reactions to imidazolidinyl urea. In the specified period, 1.6% of patients presenting to the Skin and Cancer Foundation were clinically diagnosed as sensitised to imidazolidinyl urea.

Dickel *et al*. (2001) conducted a retrospective analysis of patch test results to a standard series at the Cleveland Clinic Foundation. Over a 4-year period 991 patients (877 whites and 114 blacks) were patch tested. The allergens were obtained from Chemotechnique Diagnostics (Malmö, Sweden) and Hermal (Reinbeck/Hamburg, Germany). After the removal of the patch the first reading was done on day 3 and later readings on days 4 and 8. With imidazolidinyl urea (2% pet.) 1.9% of whites and 3.5% of blacks reacted positive. When water was used as a vehicle, imidazolidinyl urea caused skin sensitisation in only 1.4% of whites and 2.7% of blacks. The results of this study were in contrast to studies by de Groot *et al*. (1988) and van Neer and van der Kley (1991) in that they found more positive reactions to imidazolidinyl urea when water was used as a vehicle.

Two hundred and nine hairdressers (27 males and 182 females) who presented to a dermatological clinic from January 1990 to December 1999 were patch tested with a standard series (Trolab-Hermal) and with a hairdressers' series (Iorizzo *et al*., 2002). After the removal of the patch the readings were done on days 2 and 3. Three hairdressers (ie. 1.4%) reacted positive to imidazolidinyl urea (2% in pet.) in the standard series.

Case Reports

Fisher (1975) reported two cases of allergic contact dermatitis to Germall 115 (1% in pet.) following patch testing. The patients were initially allergic to "Clinique – Dramatically Different" moisturising lotion concentrate and "Allercreme Liquid Eyeliner". No other information was presented.

A 41-year old woman was patch tested with the European Standard Series and her own cosmetics to determine the cause of dermatitis in both her upper and lower eyelids (de Groot *et al*., 1987). While the patch testing resulted in negative findings repeated open application tests to imidazolidinyl urea (2% in aq.) resulted in positive responses in two occasions. However, subsequent patch and patch-on-scratch tests to preservatives, including imidazolidinyl urea, in concentrations of 3 – 10% in water were negative. Repeated open application tests to formaldehyde (1% aq.) and patch tests to higher concentrations of formaldehyde (3% and 7.5% in aq.) resulted in positive reactions. The authors suggest that in this patient skin sensitisation to imidazolidinyl urea maybe due to its formaldehyde releasing potential.

A 55-year old woman known to be allergic to parabens and formaldehyde was patch tested with a series of cosmetics (de Groot *et al*., 1988). She reacted positive to all 12 cosmetic products. Further patch testing showed that she was allergic to 2% imidazolidinyl urea in aqueous solution but not in petrolatum. Therefore, it is suggested that patch testing for imidazolidinyl urea be conducted with water as a vehicle.

A 47-year old woman with dermatitis tested positive to imidazolidinyl urea (van Neer & van der Kley, 1991). However, a positive result was seen only with imidazolidinyl

urea (2% in aq.), and not with imidazolidinyl urea (2% in pet.). Therefore, it was concluded by the author that patch testing for imidazolidinyl urea should be done in water.

A 47-year old woman with a history of atopy and presenting with exudative eczema on her arms and legs was patch tested with the Grupo Español Investigacion Dermatitis de Contacto (GEIDC) standard series (Ando *et al*., 2000). Since it was suspected that her sunscreen maybe responsible for the skin reaction the patient was also patch tested with Avon sun lotion SPF 3. The patient was found to be allergic to triethanolamine (10% in aq.) in the standard series and the sunscreen. Further patch testing with the individual ingredients in the sunscreen indicated that the patient was sensitised to imidazolidinyl urea (2% in pet.; day 2 and 4). Four years later she developed acute dermatitis to ultrasound gel (Meditec SRL, Italy) also known to contain imidazolidinyl urea. However, this was not confirmed by a patch test as the patient refused.

Other Studies

Becker *et al*. (1997) developed a flow-cytometric screening assay using human blood dendritic cells for predictive testing of contact sensitisers. It was found that human blood dendritic cells resembled that of immature murine lymph cells with respect to the response seen following stimulation with known skin sensitisers. Since this *in vitro* assay is not an OECD test guideline, it is considered to be a non-standard method under the NOHSC Approved Criteria. Nevertheless, imidazolidinyl urea (50 µg/ml) caused a statistically significant reaction in the assay (10 independent experiments) suggesting sensitising potential.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 10 positive reactions for this chemical out of 1,500 workers (0.7%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 6 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Imidazolidinyl urea caused sensitisation in 80% of the animals tested in the Magnusson and Kligman guinea pig maximisation test (Basketter & Scholes, 1992). Furthermore, it was also classified as a sensitiser in the murine local lymph node assay (Basketter & Scholes, 1992). Both animal studies closely followed the OECD

guidelines. In the open epicutaneous (non-standard) test in albino guinea pigs, imidazolidinyl urea (50% in aq.) sensitised 12.5% of animals (i.e. 1 out of 8 animals) (Ziegler *et al.*, 1988). However, there are concerns that the concentrations used for both induction and challenge in this study were not maximised. A greater sensitisation response in animals might have been obtained with higher induction and challenge concentrations. In a guinea pig study, Stephens *et al*., (1987) showed that there is cross-sensitisation between diazolidinyl urea and imidazolidinyl urea. Therefore, imidazolidinyl urea should be classified as a skin sensitiser under the NOHSC Approved Criteria.

Many dermatological clinics have reported positive patch test reactions to imidazolidinyl urea in patients (Fisher, 1975; de Groot *et al.*, 1986; Ford & Beck, 1986; de Groot *et al.*, 1988; van Neer & van der Kley, 1991; Hectorne & Fransway, 1994; Kränke *et al.*, 1996; Angelini *et al.*, 1997; Schnuch *et al.*, 1998; Ando *et al.*, 2000; Agner *et al.*, 2001; Ciconte *et al.*, 2001; Dickel *et al.*, 2001; Iorizzo *et al.*, 2002). Imidazolidinyl urea is one of the most commonly used preservatives in cosmetics (Fisher, 1980). Though a substantial number of people are likely to be exposed, overall, only a low incidence of positive patch test results were reported in patients (de Groot *et al.*, 1986; Dooms-Goossens *et al.*, 1986; Ford & Beck, 1986; O'Brien, 1987; Kränke *et al.*, 1996; Angelini *et al.*, 1997; Schnuch *et al.*, 1998; Ciconte *et al.*, 2001). Similarly, only a few positive case studies are available (Fisher, 1975; de Groot *et al.*, 1987; de Groot *et al.*, 1988; van Neer & van der Kley, 1991; Ando *et al*., 2000).

Several studies have shown that there is cross-sensitisation potential between imidazolidinyl urea and the structurally related diazolidinyl urea (Dooms-Goossens *et al.*, 1986; Stephens *et al.*, 1987; Jacobs *et al.*, 1995; Agner *et al.*, 2001). Furthermore, imidazolidinyl urea may induce skin sensitisation by either formaldehyde release or independent to formaldehyde release (de Groot & Weyland, 1987; O'Brien, 1987; Hectorne & Fransway, 1994; Jacobs *et al.*, 1995; Agner *et al.*, 2001). Therefore, imidazolidinyl urea may elicitate a response in people previously sensitised to another substance (eg. diazolidinyl urea or formaldehyde).

Thus, imidazolidinyl urea is positive in animal studies, and although the human data suggests a weak skin sensitisation potential, cross-sensitisation may exist for diazolidinyl urea or formaldehyde (a known potent human skin sensitiser). Consequently, imidazolidinyl urea is considered capable of producing skin sensitisation responses in humans. Therefore, the data supports classification of imidazolidinyl urea as skin sensitiser.

Data do not suggest a concentration cutoff for mixtures containing imidazolidinyl urea at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger “Irritant”, risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Cl+Me-isothiazolinone (Kathon CG)

Chemical Identification

Chemical Name: 5-Chloro-2-methyl-3(2H)-isothiazolone, mixt. with 2-methyl-3(2H)-isothiazolone

CAS # 55965-84-9

Synonyms: Mixture of 3(2H)-Isothiazolone, 5-chloro-2-methyl- (CAS No 26172-55-4) & 3-Isothiazolone, 2-methyl- (CAS No 2682-20-4);

3(2H)-Isothiazolone, 5-chloro-2-methyl-, mixt. with 2-methyl-3(2H)-isothiazolone;

Cl+Me-isothiazolinone;

Kathon CG (CG meaning "cosmetic grade") is a 3:1 mixture of 3(2H)-Isothiazolone, 5-chloro-2-methyl- and 3-Isothiazolone, 2-methyl- (Lee and Lam, 1999)

Trade Names

Kathon CG
Kathon 886MW
Kathon CG/ICP
Kathon LX
Kathon WT

Use: Biocide and preservative used in cosmetics such as foundations/concealers; bronzers/self-tanners; eye shadows; mascaras; make-up removers; moisturizers; sunscreens; shampoos/conditioners; bubble baths; soaps; baby wipes; creams/lotions/gels. In OTC and prescription medicines, household and industrial products such as detergents and cleaners; fabric softeners; polishes; pesticides; adhesives/glues; latex emulsions; curing agents; jet fuels; printing inks; diesel fuels.

Comment

This product under CAS Number 55965-84-9 is classified as a sensitiser (ie R43) in the EU in concentrations of greater than 0.0015% in the current Annex 1 to Directive 67/548/EEC. It is not currently listed in the NOHSC *List of Designated Hazardous Substances* (1999).

It should be noted that the concentration cut-off value for this chemical in the current Annex 1 is extremely low and not the default value.

References

Annex 1 to Directive 67/548/EEC

Lee TY & Lam TH (1999) Allergic contact dermatitis due to Kathon CG in Hong Kong. *Contact Dermatitis* **41**(1): 41-42.

2-nitro-4-phenylenediamine

Chemical Identification

Chemical Name:	1,4-Benzenediamine, 2-nitro-
CAS #	5307-14-2
Synonyms:	2-nitro-4-phenylenediamine; 2-nitro-4-aminoaniline, o-nitro- p-phenylenediamine; 2-nitro-1,4-phenylenediamine; 2NPPD
Use:	Dye in semi-permanent hair dye preparations

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

In the Unilever Environmental Safety Laboratory, 259 organic compounds were tested for sensitisation using the guinea pig maximisation test (Magnusson & Kligman) (Cronin & Basketter, 1994). While the experimental protocol was not stated in any detail, the conclusions were listed in a table. 2-nitro-4-phenylenediamine (2NPPD) was considered a strong sensitiser. This conclusion was confirmed by NICNAS in personal communications with the author (David Basketter, Unilever Environmental Safety Laboratory). The actual guinea pig maximisation test on 2NPPD has not been published in detailed form. According to the author, these data are currently in preparation for publication.

The skin sensitisation potential of 2NPPD was studied in guinea pigs (n = 20). 3% 2NPPD made up in 2% Natrosol 250 HR, 2% Tween 80, 0.05% sodium sulfite, and 10% isopropanol was applied on a shaved area of the flank. 2NPPD was applied daily for 6 days per week for a total of 3 weeks. Of the 20 guinea pigs tested, 4 (20%) were sensitised by 2NPPD. The researchers considered this to be a "weak reaction". The experimental protocol was not given in detail. Furthermore, from the limited information available, this study appears not to follow the OECD guidelines for testing of chemicals for skin sensitisation. This study was reviewed by the Expert Panel of Cosmetics Ingredients Review (Expert Panel of Cosmetics Ingredients Review, 1985). The original study (CTFA, 1976) has not been sighted by NICNAS.

Human Evidence

Surveys

During 1973-1981, 66 patients who stated their occupation as hairdressing were patch tested at the Environmental Allergen Test Laboratory (Shaughnessy Hospital, Vancouver, Canada) with the North American Contact Dermatitis Group screening tray and/or their hairdressers' series (Lynde & Mitchell, 1982). Most hairdressers were between the ages 16 and 25 years. The test protocol was not clearly stated. Out of the 32 hairdressers tested with the hairdressers' series, 2 (i.e. 6.3%) showed positive reactions to 2NPPD (2% pet.). The severity of reactions was not stated.

Guerra *et al*. (1992a) reported patch test results from 9 GIRDCA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali) Italian dermatological centres. The study was limited to hairdressers presenting to the dermatological centres from January 1985 to June 1990. Forty-three males and 259 females between the ages of 14 to 66 years (mean age 24.6 years) were patch tested with the GIRDCA standard series and hairdressers series (Hermal-Trolab allergens). Patch tests were performed according to the ICDRG recommendations and results read at 2 and 3 days. Forty-two hairdressers (13.9%) had a personal history of atopy and 66 hairdressers (21.9%) had a family history of atopy. Out of the 302 patients, 184 (i.e. 60.9%) reacted positive to one or more allergens that were occupationally relevant. The mean duration of dermatitis in these 184 patients was 2.1 years. Out of these 302 patients, 24 (i.e. 7.9%) reacted positive to 2NPPD (1% pet.). The severity of reactions was not stated. The results of this study showed no relationship between the occurrence of sensitisation and the subject's personal atopic status or duration of work.

261 hairdressers' clients (5 males and 256 females) were patch tested with the GIRDCA standard series and hairdressing series (Hermal Trolab, Bracco) between 1985 to 1990 (Guerra *et al*., 1992b). These clients had presented to the clinic at the Department of Dermatology, University of Bologna, Italy with suspected contact dermatitis due to hairdresser allergens. Patch test results were read at 2 and 3 days. 47 patients had a "personal" history of atopy while 36 patients had a family history of atopy. 49 patients were sensitised to one or more allergens in the hairdressers' series. 12 patients (i.e. 4.6%) reacted positive to 2NPPD (1% pet.). There was no indication of how many 2NPPD sensitised patients were also atopic.

Patch test reactions to the hairdressing series (Hermal Trolab) from 9 European Environmental and Contact Dermatitis Research Group (EECDRG) dermatological centres were analysed (Frosch *et al*., 1993). The majority of the patch test results corresponded to the period 1988-1991. Patch tests were read according to the generally accepted criteria of the International Contact Dermatitis Research Group (ICDRG). Out of the 798 hairdressers patch tested, 33 (4.1%) were sensitised by 2NPPD (1% pet.). The severity of reactions was not stated. The centre in Barcelona recorded the highest sensitisation rate (13.9%) to 2NPPD with 5 out of 36 hairdressers reacting positive. 104 hairdressers' clients were also patch tested with the hairdresser's series. 7 clients (i.e. 7.7%) reacted positive to 2NPPD (1% pet.). Doubtful or irritant reactions were excluded.

A total of 209 hairdressers (27 males and 182 females; 14 – 72 years) who presented to a dermatological clinic at the Department of Dermatology, University of Bologna, Italy from January 1990 to December 1999 were patch tested with a standard series (Trolab-Hermal) and with a hairdressers' series (Iorizzo *et al.,* 2002). After the removal of the patch, the readings were done on day 2 and 3. Ten hairdressers (i.e. 4.8%) reacted positive to 2NPPD (1% pet.) in the hairdressers' series.

Fautz *et al*. (2002) studied the cross-sensitisation pattern of new hair dyes used by hairdressers. Forty hairdressers with known allergy to either 4-phenylenediamine (PPD), 2,5-diaminotoluene sulfate (DTS) or 2NPPD were recruited from the hairdressers' clinic of the Centrum voor Huid en Arbeid in Arnhem (the Netherlands). The optimum non-irritant patch test concentration was determined in 10 healthy volunteers. 2NPPD was obtained from Chemotechnique Diagnostics AB (Sweden)

while other dyes were obtained from their respective manufactures. Eight (i.e. 20%) hairdressers reacted positive (+) to 2NPPD (1% pet.). This study showed that there is no cross-sensitisation with other dyes such as D&C Red 33, D&C Yellow 10, D&C Orange 4, Formulation dyes and acid dyes.

Case Reports

None.

Other Studies

A TOPS-MODE (topological substructural molecular descriptors) computational approach was developed to predict the skin sensitisation potential of chemicals. TOPS-MODE approach is based on developing linear quantitiative structure-activity relationships (QSARs) based on chemical bond contributions as estimated from corresponding physicochemical or molecular properties (Estrada *et al*., 2003). A total of 93 chemicals with sensitisation data from local lymph node assays (LLNA) conducted under similar conditions were selected from the database of Unilever. Data for these chemicals were then used to build TOPS-MODE predictive models. While the LLNA data and test methodologies were not described in any detail in this article, 2NPPD was considered to be a Class 1 (i.e. moderate and strong) sensitiser based on LLNA studies. Furthermore, the TOPS-MODE QSAR model predicted 2NPPD to be a Class 1 sensitiser.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 8 positive reactions for this chemical out of 1,500 workers (0.53%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 194 cases for this chemical out of a total of 6,067 cases (3.2%). The Occupational Physicians Reporting Activity (OPRA) database contains 1 case for this chemical out of a total of 838 skin cases, (0.12%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

The guinea pig study reviewed by the Expert Panel of Cosmetics Ingredients Review suggests that 2NPPD is a weak sensitiser (Expert Panel of Cosmetics Ingredients Review, 1985). This early study falls into the non-standard animal study category given that OECD guidelines were not followed. The Expert Panel of Cosmetics Ingredients Review (1985) concluded that 2NPPD is a skin sensitiser in guinea pigs. There is evidence in the literature that 2NPPD is a strong sensitiser in both the guinea

pig maximisation test and LLNA studies (Cronin & Basketter, 1994; Estrada *et al*., 2003). While these studies have not yet been published in detail, in a personal communication to NICNAS Dr David Basketter (Unilever Environmental Safety Laboratory) confirmed that 2NPPD is a strong sensitiser.

Many dermatological clinics have reported that 2NPPD causes sensitisation by skin contact (Lynde & Mitchell, 1982; Guerra *et al*., 1992a,b; Frosch *et al*., 1993; Fautz *et al*., 2002). These included clinics associated with EECDRG and GIRDCA. Studies with large number of subjects suggest a notable incidence of 2NPPD induced skin sensitisation in hairdressers (Lynde & Mitchell, 1982; Guerra *et al*., 1992; Frosch *et al*., 1993). This was especially so in one EECDRG clinic in Barcelona. Given that 2NPPD is found in hair dyes, hairdressers appear especially at risk from developing sensitisation. Another group at risk are the hairdressers' clients. While the hairdressers' clients are less exposed to 2NPPD than hairdressers, the study of Frosch *et al*. (1993) reported a significant rate of sensitisation also in the clients. Given the sensitisation rates seen in these studies, it is conceivable that a considerable number of hairdressers sensitised to 2NPPD.

Based on a LLNA dataset for 93 chemicals, the TOPS-MODE QSAR study predicted that 2NPPD is a Class 1 (i.e. moderate and strong) sensitiser. Under NOHSC Approved Criteria, appropriate structure-activity studies can be utilised as supporting evidence for the classification of sensitisers. Therefore, this study adds further weight to suggest that 2NPPD is a skin sensitiser.

Using a weight-of-evidence approach to sensitisation potential across animal, human and QSAR studies, there appears sufficient data to classify 2-nitro-4-phenylenediamine as a skin sensitiser.

Data do not suggest a concentration cutoff for mixtures containing 2-nitro-4-phenylenediamine at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger "Irritant", risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Abietic acid

Chemical Identification

Chemical Name:	1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4a-dimethyl-7-(1-methylethyl)-, [1R-(1a,4ab,4ba,10aa)]-
CAS #	514-10-3
Synonyms:	(-)-Abietic acid; Abietic acid; l-Abietic acid; Sylvic acid; 13-Isopropylpodocarpa-7,13-dien-15-oic acid; Podocarpa-7,13-dien-15-oic acid, 13-isopropyl-
Use:	Manufacturing esters used in lacquers; varnishes; soap; glues; cutting oils; adhesive tapes; printing inks; cosmetics; glues

Evidence for Sensitisation Properties

Introduction

Colophony (or rosin) is a resin derived from various species of conifers which has been implicated in causing skin sensitisation. Resin acids are considered to be the main allergens in colophony (rosin) and the main allergic component is considered to be abietic acid (Karlberg *et al*., 1980). At 50-80%, abietic acid is the main resin acid in most colophony types (Hausen *et al*., 1989).

Animal Studies (Standard and Non-Standard)

In a guinea pig maximisation test conducted, as stated by the authors, in accord with the method of Magnusson and Kligman, 20 test and 20 control animals were induced with 4% commercial abietic acid (Carl Roth, Germany) in olive oil by intradermal injection and by 25% abietic acid epicutaneously in petrolatum (Karlberg et al., 1980). Epicutaneous challenge was performed with 10, 5 and 1% abietic acid in petrolatum. In this report, no details were provided on how test doses were chosen. However, the authors state that non irritant doses were established from a previous study by the same group (Wahlberg, 1978). No other details regarding methodology were provided.

For the 5 % dose, 8 of 20 animals (40%) showed a positive response both at 24 and 48 hours. For the 10% dose, 11 of 20 (55%) and 12 of 20 (60%) showed a positive response at 24 and 48 hours respectively. These results were statistically significantly different from controls where only 1 of 20 animals showed a positive response at 48 hours.

Further work by this group (Karlberg *et al*., 1985) tested purified abietic acid in a guinea pig maximisation test under the same test conditions. Commercial abietic acid was purified by dissolution in solvent followed by silica gel chromatography. No sensitisation was found. However, in this same study, the two commercial samples of abietic acid from Carl Roth, Germany and BC Research, Canada showed positive reactions in at least 30% of animals. With the two commercial samples (one of which was from the same supplier for the 1980 study), 6 of 20 (30%) and 10 of 20 (50%) treated animals respectively showed positive responses at 48 hours. Only 1 of 20 control animals showed a positive response.

Hausen et al., (1989) conducted a guinea pig maximisation test with commercial abietic acid (FLUKA), which the authors state was chromatographically pure. Unfortunately, no details of the purification procedures were given. The test procedure differed from OECD Test Guidelines. Only 10 animals were tested per dose and these were subjected to two additional inductions by injection on days 5 and 9. Animals were challenged with 1% and 10% abietic acid but no details were given on the length of time the challenge dose was applied to the skin. The 10% dose was found to be slightly irritating in preliminary studies and to account for this any sensitisation score for this dose was reduced to the next level. At 24, 48 and 72 hours across both doses, a total of 2 of 20 (10%), 7 of 20 (35%) and 8 of 20 (40%) test animals showed positive responses respectively. No results for control animals were given. The authors conclude abietic acid is a weak sensitiser.

In a later paper by this group (Hausen et al., 1990) similar guinea pig maximisation tests were conducted on synthetically prepared oxidation products of abietic acid. Sub irritant doses of each chemical for challenge were established in pilot experiments. 10 animals were tested per dose. Nine oxidation products were tested at doses of 10, 3, 1 or 0.3%. Six were classified as either weak or moderate sensitisers. At 72 hours, all animals tested showed a positive reaction to 8,12-peroxido-$\Delta^{13(14)}$-dihydro-abietic acid and to a chromatographically isolated polar fraction of commercial abietic acid (FLUKA).

Gafvert et al., (1994) synthesised the 13,14(α)-epoxide and the 13,14(β)-epoxide of abietic acid then tested these for sensitisation potential using a guinea pig maximisation test. Except for exposing animals to two additional induction intradermal injections, and using 15 animals per test and control groups, the study was undertaken according to OECD Test Guidelines. Test animals were induced with either the α or the β epoxide at 5% and challenged with the oxidation products at 5, 1 or 0.2%. These doses were shown in a pretest to be nonirritating. Only one positive reaction was noted in control animals. Except for challenge with 0.2% β-epoxyabietate, all other challenge exposures resulted in positive responses in 33% to 100% of animals and the number of animals showing positive responses were statistically significantly different from controls. In the same study β-epoxyabietate was tested in a Cumulative Contact Enhancement Test. Fifteen test animals (species not specified) were dosed with β-epoxyabietate by topical application on days 0, 2, 7 and 9 and injected intradermally with Freund's Complete Adjuvant in water twice on day 7. Controls were treated in the same manner but given vehicle for the topical applications. Animals were challenged with both epoxides. Challenge resulted in positive reactions in more than 90% of animals to both epoxides. In contrast to the

guinea pig maximisation test, challenge with 0.2% β-epoxyabietate in this experiment was positive in 73% of animals. The sensitisation properties of the abietic acid oxidation product 7-oxodehydroabietic acid were shown by Karlberg et al., (1988). In a Magnusson and Kligman guinea pig maximisation test with 20 animals per dose using 5% intradermal and 25% epidermal induction doses and 10, 5 and 1% challenge doses, 40 - 45% of animals at 48 hours and between 20 – 55% of animals at 72 hours showed positive responses.

Human Evidence

Surveys

In an addendum to a case report, (Dooms *et al*., 1979) briefly report that 2.1% of 1,360 dermatology clinic patients patch tested with a standard series including abietic acid 5% pet. returned positive results to abietic acid. 2.9% also showed reactions to colophony. No other details were given.

The records of 5,875 dermatology patients patch tested between 1983 and 1987 in the Department of Dermatology, Hamburg and several other clinics were reviewed and a total of 137 (2.3%) were found to be positive to colophony. A sub-group of 44 patients was patch tested with commercial abietic acid (FLUKA) and 38.6% of these showed a positive response (Hausen & Mohnert, 1989).

In a study of the records of 839 dermatology patients who were patch tested with a plastics and glues series, 8 patients out of 343 (2.3%) tested with abietic acid showed an allergic response (Tarvainen, 1995).

Soderberg et al., (1990) examined the records of 179 dermatology patients with a history of eczema linked to the use of adhesive tape containing colophony. 14 of these showed a positive patch test to colophony and 7 of these 14 (3.9 % of the total cohort) reacted positively to abietic acid.

Eighteen patients diagnosed with allergic contact dermatitis or contact urticaria caused by wood dusts were patch tested at the Finnish Institute of Occupational Health between 1976 and 1999. Three (16%) showed a positive response to abietic acid (Estlander *et al*., 2001).

During 1991 to 1996 at the Finnish Institute of Occupational Health (Kanerva et al., 1999) patch tested 307 patients suffering occupational skin disease for sensitivity to a range of allergens including abietic acid, using a plastics and glue series. 4 (1.3%) showed a positive response to abietic acid.

Karlberg et al., (1985) as part of their study comparing commercial to purified abietic acid (see animal studies above) patch tested 10 patients with previously proven sensitivity to colophony. Seven and 8 patients tested positive to two different commercial samples of abietic acid respectively. Only one patient tested positive to the purified abietic acid which had been stored for one month, but no patients reacted to purified abietic acid prepared immediately before application. The authors suggest that from these human data and results from animal tests oxidation products of abietic acid are the likely allergens in cases of colophony sensitivity.

In addition to animal studies, twelve patients with allergy to rosin were patch tested with the 13,14(α)-epoxide and the 13,14(β)-epoxide of abietic acid and 15-hydroperoxyabietate as part of the study described above (Gafvert et al., 1994). Five patients reacted positively to β-epoxyabietate, 3 to α-epoxyabietate and 4 to 15-hydroperoxyabietate. The authors also patch tested a further 7 patients with rosin allergy by exposing them to differing concentrations of 15-hydroperoxyabietate and 15-hydroperoxydehydroabietate. There were no positive reactions to 15-hydroperoxydehydroabietate whereas 15-hydroperoxyabietate elicited positive responses in 3 subjects. Healthy control subjects showed no response in either experiment.

Karlberg et al., (1988), in addition to the animal studies above, patch tested 10 patients with sensitivity to colophony and found positive responses to the oxidation products 15-hydroperoxyabietic acid methyl ester, 15- hydroxydehydroabietic acid methyl ester and 7-oxodehydroabietic acid methyl ester.

Sadhra et al., (1996) investigated the contact allergens in unmodified colophony by using chromatography to separate components which were then patch tested on colophony-sensitive individuals. A total of 1,553 patients were patch tested with the European Standard Series at the Skin Hospital, Birmingham between 1983 and 1988. Of these, 61 were recorded as colophony sensitive. Of 35 subjects available for testing, 21 (60%) showed positive patch testing reactions to abietic acid in a commercial patch test kit (Trolab). A smaller number 19 (54%) reacted to purified abietic acid suggesting that commercial abietic acid is more active than the purified acid. In a smaller patch testing series, 7-oxy dehydroabietic acid was found to be the most dermatologically active single component tested. These results confirm abietic acid as an important allergen in colophony but also support previous findings that oxidised resin acids are stronger sensitisers than resin acids themselves.

Case Reports

Few case reports were found in the literature. Positive reactions in patch testing to abietic acid are reported in a 47-year old non-atopic male exposed to colophony for 25 years at work (Matos & Mariano, 1988); a 26-year old female suffering contact dermatitis to eye make-up (Dooms et al., 1979) and a 48-year old male newspaper seller with no history of atopy (Castelain et al., 1980). A small number of other reports describe positive patch testing reactions to colophony but these did not test for abietic acid.

Other Studies

None

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 4 positive reactions for this chemical out of 1,500 workers (0.3%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 173 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 2 cases for this chemical out of a total of 838 skin cases, (0.2%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Guinea pig maximisation tests conducted in a similar fashion to OECD guidelines show that commercial grade abietic acid and certain oxidation products possess sensitisation properties. In several of these studies, animal data are supported by human patch test data showing sensitivity to commercial abietic acid and oxidation products in subjects with colophony allergy. Notwithstanding the possibility that oxidation products themselves possess sensitisation properties, the extent of positive results in the guinea pig maximisation tests (> 30% of animals in several studies) using readily available commercial grade abietic acid are sufficient to classify abietic acid as a sensitiser according to the NOHSC Approved Criteria.

Data do not suggest a concentration cutoff for mixtures containing abietic acid at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger "Irritant", risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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N-cyclohexylbenzothiazole-2-sulphenamide

Chemical Identification

Chemical Name:	2-Benzothiazolesulfenamide, N-cyclohexyl-
CAS #	95-33-0
Synonyms:	N-cyclohexylbenzothiazole-2-sulphenamide; N-Cyclohexyl-2-benzothiazolesulfenamide; 2-(Cyclohexylaminothio)benzothiazole; 2-Benzothiazolesulfenic acid N-cyclohexylamide; Accel CZ; Accelerator CZ; Accicure HBS; Benzothiazyl-2-cyclohexylsulfenamide
Use:	Accelerator used in rubber products.

Comment

The original CAS# 3081-14-9 as supplied by Chemotechnique Diagnostics AB was incorrect. The correct CAS# for chemical 2-Benzothiazolesulfenamide, N-cyclohexyl-sulphenamide is 95-33-0.

This chemical under this correct CAS# 95-33-0 is already classified as a sensitiser (i.e. R43) by the EU in the current Annex 1 to Directive 67/548/EEC. It is not currently listed in the NOHSC List of Designated Hazardous Substances (1999).

References

Annex 1 to Directive 67/548/EEC

Zinc dimethyldithiocarbamate (Ziram)

Chemical Identification

Chemical Name:	Zinc, bis(dimethylcarbamodithioato-S,S')-, (T-4)-
CAS #	137-30-4
Synonyms:	Carbazinc; Zimate; Zinc bis(dimethyldithiocarbamate); Zinc dimethyldithiocarbamate; Zinc bis(dimethyldithiocarbamato)-; Ziram
Use:	Used in the rubber processing industry as an accelerator or promoter. Small amounts are used in industrial fungicides, in combination with 2-mercaptobenzothiazole, in adhesives (including those used in food packaging), paper coatings (for non-food contact), industrial cooling water, latex-coated articles, neoprene, paper and paperboard, plastics (polyethylene and polystyrene) and textiles. Also used as an agricultural fungicidal control and as a repellent for birds and rodents.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Matsushita *et al.,* (1977) as part of a study on cross sensitisation, exposed 10 animals to dimethyldithiocarbamic acid, sodium salt and to Ziram, a fungicide product containing dimethyldithiocarbamate in a Magnusson and Kligman guinea pig maximisation test. The methods used differed from OECD Test Guideline 406. Only 10 animals were used and no controls were included. A preliminary study was conducted to determine induction and challenge doses. No details are given on whether the doses used for induction were the highest mildly irritating dose but for challenge the doses used (5 and 1%) were below the highest mildly irritating dose. Results were read 24 hours after patch removal. Challenge with Ziram at 5% in 70% ethanol was positive in 40% of animals and at 1% in 70% ethanol, 30% of animals showed a positive response. No guinea pigs showed a sensitisation response to dimethyldithiocarbamic acid sodium salt at 5% and 1% in ethanol.

The IUCLID dataset for Ziram reports two unpublished guinea pig maximisation tests conducted in 1989 by UCB Chemicals according to OECD Test Guideline 406 and to Good Laboratory Practice (GLP) guidelines. Apart from stating compliance with OECD and GLP guidelines, no other test details are provided and so the robustness of the studies cannot be determined. No Klimisch scores are given. The chemical is reported in these studies as being a sensitiser.

Workers at the National Institute of Public Health and the Environment in The Netherlands report a series of sensitisation studies on various chemicals. The first study exposed animals to zinc dimethyldithiocarbamate (90%, Fluka, The Netherlands) in a local lymph node assay (LLNA) using a method similar to OECD Test Guideline 429 except that animals were pre-treated with 1% sodium dodecyl sulfate (SDS) in 4:1 acetone/olive oil to enhance the proliferation response and only 3 animals were used per dose group. Test doses were 0.375%, 0.75%, 1.5%, 3% and 6%, differing from the concentration series recommended by the OECD. It is unclear whether a positive control was used. Also, ^{3}H labelling of lymph node cells was done after harvesting in tissue culture rather than by injection of ^{3}H-methyl thymidine prior to animal sacrifice. A stimulation index (SI) of 3 was found at an estimated concentration of 2.67% identifying the chemical as a sensitiser (van Och *et al*., 2000).

In the next study by the same authors, zinc dimethyldithiocarbamate (90%, Fluka) was tested for sensitising potential in a Magnusson and Kligman guinea pig maximisation test (GPMT) and compared with results of the LLNA reported above (van Och *et al*., 2001). The authors state that the GPMT was conducted according to OECD Test Guideline 406 however only 5 animals were used per dose group. Induction and challenge doses were chosen based on preliminary studies. The authors state that the highest slight to moderately irritating dose was selected for induction and the highest non-irritating dose for challenge. However, the results indicate a range of doses was used for induction and challenge. No preliminary study data are presented so the actual highest mildly irritating and non-irritating doses are unknown. The induction method used two applications of substances instead of the one recommended in the OECD Guidelines. Each animal was challenged with three different doses, which is not recommended in the Guidelines. The time period between challenges is not stated. Results for the GPMT cannot be interpreted. More than 60% of animals given vehicle only at induction gave a positive response to challenge with 30% Zinc dimethyldithiocarbamate. No clear dose response is seen in the various test permutations. The methods and results are not completely clear.

The third report from this group used the mouse local lymph node assay to determine sensitisation potential and also investigated whether use of SDS pre-treatment enhanced the proliferation response. Animals were exposed to zinc dimethyldithiocarbamate (90%, Fluka) at doses of 0.1%, 1.0% and 5.0% in 4:1 acetone/olive oil. The procedure used was similar to OECD Test Guideline 429, however no details of the number of test animals per group are given nor information regarding the days post exposure that the animals were sacrificed. Also, although three test doses are used these were not the concentration series recommended by the OECD. Animals in the highest dose group showed an SI of 30.8 identifying the chemical as a sensitiser. Lower doses gave an SI below 3 (1.3 - 1). A dose response is suggested. SDS pre-treatment at 1% enhanced the proliferation response to the test substance and was not itself a sensitiser at this dose, but at 10% the SI for SDS was above 3 (De Jong *et al*., 2002).

In a fourth study by this group using the modified LLNA as described above (De Jong *et al*., 2002a), an SI of 3 at an estimated concentration of 2.7% was reported for zinc dimethyldithiocarbamate (90%, Fluka) confirming its sensitisation potential.

Human Evidence

Surveys

Two hundred subjects were patch tested with a set of agricultural chemicals at the Instituto di Clinica Dermatologica e Venereologica, University of Perugia, Italy. Of these, 162 were tested with Ziram (1% pet.). Patch tests were performed according to the International Contact Dermatitis Research Group (ICDRG) standards and read after 48 and 72 hours. No positive reactions were found (Lisi *et al*., 1986). In another study by this group, 274 patients diagnosed with allergic skin disorders and 378 patients with non-allergic skin disorders were patch tested with the same series of chemicals. Of 348 patch tested with Ziram (1% pet.), one positive response was recorded (Lisi *et al*., 1987).

At the Department of Medicine Clinic and Department of Internal Medicine and Public Health, University of Bari, Italy, Nettis *et al*., (2002) patch tested 295 of 316 hospital employees reporting latex glove induced dermatological symptoms. Of the patients tested, 72 (24.4%) were considered atopic. Patients were tested with a rubber additive series to ICDRG guidelines and none returned a positive reaction to zinc dimethyldithiocarbamate (1% pet.).

Case Reports

A 70-year old farmer presenting with a red scaly trunk was patch tested with the ICDRG standard series and pesticides. He showed a strong positive reaction to Ziram (1% pet.) (Manuzzi *et al*., 1988).

Kiec-Swierczyska *et al*.(2001) report the case of a 44-year old farmer with eczema on the hands and face. Patch testing with zinc dimethyldithiocarbamate (1% pet.) produced a strong positive response.

Other Studies

Nil

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 8 positive reactions for this chemical out of 1,500 workers (0.5%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 1 case for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains nil cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Animal data from 4 studies (Matsushita *et al*, 1977; van Och et al. 2000; De Jong, *et al.*, 2002, 2002a) point to the chemical being a sensitiser. Positive results were reported from both GPMT and LLNA tests. The IUCLUD dataset for this chemical also lists 2 studies indicating the chemical as a sensitiser, although details of these studies could not be verified.

Data do not suggest a concentration cutoff for mixtures containing zinc dimethyldithiocarbamate at variance with the NOHSC Approved Criteria default concentration cutoff for sensitisation of ≥ 1%.

Conclusion

Data are sufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact (symbol Xi, indication of danger "Irritant", risk phrase R43) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999). A concentration cutoff of ≥ 1% is recommended.

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Wool alcohols

Chemical Identification

Chemical Name:	Alcohols, lanolin
CAS #	8027-33-6
Synonyms:	Woolwax alcohol; lanolin alcohols; Eucerit**;** wool alcohols
Use:	Lanolin is used in cosmetics, toiletries, skin care products, drugs, shoe polish, waxes, paper, textile finishes, printing ink, and leather dressing (Kligman, 1983; Kligman, 1998).

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

In a review article, Kligman (1983) described previously unpublished guinea pig maximisation tests with wool wax alcohols. The experiments were conducted by Bertil Magnusson in groups of 25 guinea pigs. None of the animals were sensitised by hydrous lanolin (conc. not stated) or wool wax alcohols (30% in pet.). Repeated cycles maximisation tests in guinea pigs were also negative. While the experimental protocols were not presented in detail, one can safely assume that these experiments would have been done to acceptable guidelines given that Prof. Bertil Magnusson and Prof. Albert Kligman were instrumental in developing maximisation tests for sensitisation (Magnusson & Kligman, 1969).

Human Evidence

Surveys

The incidence of sensitisation to 29 ingredients of topical medicaments was studied at the University Clinic of Dermatology, Università Bari, Italy (Meneghini *et al*., 1971). Patients suffering from various forms of eczematous dermatitis (including atopic and stasis) were included in the study. The highest concentration tolerated in a 48-hour occlusive patch test was determined for 28 chemicals in 50 healthy volunteers. Wool alcohols were not included in this irritancy test (possibly because it has already been determined by others). Patches were applied for 2 days and results read on days 2 and 3. Of the 1,270 patients patch tested with wool alcohols (30% in pet.; Trolle Lassen, Denmark), 13 patients (i.e. 1.0%) reacted positive. Severity and relevance of these reactions were not stated.

Epstein (1972) presented patch test results of patients presenting to his private dermatological clinic over a three-year period. A particular emphasis was made to determine the best patch test material to detect lanolin allergy. Patches were applied for 2 days, and results read at 2–3 hours after removal. A further reading was taken at 1–3 days. Between 1967 and 1969, 298 patients were patch tested with wool alcohols (30% in pet.; Malmstrom Chemicals). While 10 patients initially showed positive reactions to wool wax alcohol (also wool alcohols) repeated testing indicated that only

5 (i.e. 1.7%) were sensitised (each with strong reactions). The other five had false-positive irritant reactions. Only 1 of the wool wax alcohol-sensitive patients reacted positive to lanolin. 10% wool wax alcohol also detected lanolin allergy in these 5 patients. However, the patch test reactions were less pronounced. Since wool wax alcohol is a more concentrated source of lanolin allergens than lanolin itself (Epstein (1972), wool wax alcohol was determined in this study to be the material of choice for patch testing (Epstein, 1972).

Hannuksela *et al*. (1976a) analysed the results of a three-year patch test study with various ingredients of vehicles. A total of 4,097 patients (61% female and 39% male) suffering from eczema and presenting to the Department of Dermatology, University Central Hospital, Finland were included in the study. The patches were applied for 20–24 hours and results were read 30 min after removal of patches. Further readings were made on days 2 and 4–5. No further methodological details were reported. Of the 2,538 patients patch tested with wool alcohols (30% in pet.), 31 patients (i.e. 1.2%) reacted positive. In contrast to wool alcohols, only 14 patients (i.e. 0.6%) reacted positive to lanolin (concentration "as is"). These results suggest that 30% wool alcohols is the material of choice for detecting lanolin allergy. The severity of reactions was not stated. Clinical relevance of positive reactions to wool alcohols was not discussed.

Between 1 April 1975 and 31 January 1976, a total of 1,206 patients (701 females and 505 males) were patch tested with a standard series and an emulsifier series at the Department of Dermatology, University Central Hospital, Finland (Hannuksela *et al*., 1976b). The patches were applied for 24 hours and the initial results were read at 20 min after removal. Further readings were taken on 2 and 4–5 days from application. Disease duration or the severity of reactions was not stated. 22 patients (i.e. 1.8%) reacted positive to wool alcohols (30% in pet.; Trolab). There was no evidence of cross-sensitisation between wool alcohols and Lanette N (composition not provided) (20% pet.). No irritant reactions were recorded against wool alcohols on days 4–5. Clinical relevance of positive reactions to wool alcohols was not discussed.

Mortensen (1979) compared the frequency of lanolin sensitisation in two different periods. The first period of the study was between 2 January 1971 and 31 December 1973. The second period of the study was between 2 January 1974 and 31 August 1975. In the first period, 1,230 consecutive patients with eczema were patch tested with wool alcohols (30% in soft yellow paraffin). In the second period, 899 consecutive patients with various forms of skin conditions (including leg ulcers and stasis eczema) were patch tested with wool alcohols and various lanolin derivatives. The patches were applied for 48–72 hours and results read after 72–96 hours. Erythema and infiltration or stronger reactions were considered positive. In the first period, 33 patients (i.e. 2.7%; 21 females and 12 males) reacted positive to wool alcohols. Similarly, 29 patients (i.e. 3.2%) reacted positive to wool alcohols in the second period. A further 31 patients (i.e. 3.4%) were allergic to lanolin derivatives other than wool alcohols in the same period. The results of the study suggested that testing with only wool alcohols is insufficient to detect lanolin allergy (Mortensen, 1979).

Hammershoy (1980) reported patch test results from 3,225 consecutive patients (1,774 female and 1,451 male) presenting to the Department of Dermatology, Odense

University Hospital, Denmark. These patients were patch tested between 1973 and 1977 with the Scandinavian standard series (Trolab, Copenhagen, Denmark). The patches were applied for 48 hours and results were read according to International Contact Dermatitis Research Group (ICDRG) recommendations at 72 hours. Only reactions ≥ ++ were considered positive. A total of 1,038 patients reacted positive to one or more allergens in the series. The most frequent site of dermatitis was the hand and the average duration of their dermatitis was 3 years. Of the 1,038 patients only 82 (i.e. 8%) were diagnosed with occupational dermatitis. Of the 3,225 patients patch tested, 123 patients (i.e 3.8%) reacted positive to wool alcohols (conc. and vehicle not stated).

To study the frequency of cosmetic-related skin sensitisation, 11 dermatologists from the North American Contact Dermatitis Group (NACDG) patch tested 8,093 patients presenting to their clinics between 15 May 1977 and 15 September 1980 (Eiermann *et al.*, 1982). During this period, a total of 179,800 patients were seen at the clinics. Patients were patch tested with the standard series, perfume series or the vehicle-preservative series of the NACDG. Patches were applied for 2 days, and results read at 2–3 and 4–5 days post application according to the procedures outlined by the NACDG and the International Contact Dermatitis Group. Positive results were confirmed by subsequent retesting. Irritant dermatitis was diagnosed on the basis of medical history, physical examination, negative patch tests for sensitisation and further follow-up. Of the 8,093 patients patch tested, 487 patients (i.e. 6%; 385 females and 102 males) were sensitised by cosmetics. Of those patients patch tested, 7 patients (i.e. 0.09%) reacted positive to lanolin alcohol (wool alcohol). In addition, 11 and 2 patients reacted positive to lanolin and lanolin oil, respectively. While the patch test concentrations and vehicles were not indicated, the authors stated that the tests were conducted with previously published or generally accepted concentrations. Hence, it is more than likely that 30% lanolin alcohol in petrolatum was utilised. The severity or the clinical relevance of these reactions was not discussed.

In a review article, Kligman (1983) described a previously unpublished maximisation test with wool wax alcohols in human volunteers. The test procedure involved a pre-treatment with sodium lauryl sulfate to chemically damage the test area. This was followed by five 48-hour induction exposures. The challenge patch testing was done 2 weeks later using a similar provocative sodium lauryl sulfate procedure. Using this procedure, none of 25 healthy female volunteers were sensitised by hydrous lanolin or by 30% wax alcohol in petrolatum. Similarly, the sensitisation potential of wool wax alcohols (30% in pet.) was determined in 25 different healthy female volunteers. In this case, the test subjects were not initially pre-treated with sodium lauryl sulfate as the test area became inflamed after a few induction exposures with wool wax alcohols. On challenge testing, none of the subjects reacted positive to wool wax alcohols (30% in pet.).

Following the conclusion of the above experiments, the same subjects were chosen for a repeated cycles maximisation experiment (Kligman, 1983; Kligman, 1998). The 25 subjects were exposed to 5 maximisation cycles with wool wax alcohols. Each cycle included 5 induction exposures (30% wool wax alcohols in pet.) and a challenge with wool wax alcohols (30% in pet.). At the conclusion of each cycle a new test site was chosen. One of the subjects developed a weak allergic reaction on the fourth cycle. However, upon rechallenge 2 weeks later no reaction was noted. This subject

proceeded to complete the fifth maximisation cycle without another positive reaction. Another subject gave a 2+ reaction in the fifth cycle. A repeat patch test 1 month later confirmed this to be an allergic reaction. The repeated cycles maximisation experiment is thought to be sensitive in detecting weak sensitisers (Kligman, 1983). Given the results of these studies, Kligman (1983; 1998) considered wool wax alcohols to be non-sensitising.

While the experimental protocols described above were not presented in detail, one can safely assume that these experiments would have been done to internationally accepted standards given that Prof. Albert Kligman was instrumental in developing these maximisation tests for sensitisation (Kligman, 1966). To our knowledge, there are no OECD guidelines for human maximisation tests.

Malten and Kuiper (1985) analysed patch test results from 100 consecutive patients (78 females and 22 males) with leg ulcers presenting to their Occupational Dermatology Clinic in the Catholic University Nijmegen (Netherlands). The authors stated that at the time of patch testing, all patients had a florid ulcus cruris and majority of patients suffered from venous insufficiency. The patients were patch tested with the ICDRG standard series, their own standard series and the leg ulcer series. No other methodological detail was provided. When patch tested with wool alcohols (conc. and vehicle not stated), 17 patients (i.e. 17%) reacted positive. Three patients had '+' reactions and the rest had reactions greater or equal to '++'. Between 1970 and 1971 the same clinic found that 22 of 100 (22%) patch tested leg ulcers patients were sensitised by wool alcohols.

De Groot *et al*. (1988) interviewed 982 female beautician clients over a 5-month period for adverse effects from cosmetics and toiletries. It was determined that 254 clients suffered from cosmetic-related side effects during the preceding 5 years. Thirty-two, 13 and 48 clients had atopic eczema, asthma and hay fever, respectively. Out of the 254 clients, 150 were patch tested with the European standard series (Hermal-Chemie, Reinbek, Germany) and the cosmetic series (Hermal-Chemie and Chemotechnique Diagnostics AB, Sweden) at the Department of Dermatology, State University Hospital, Netherlands. While it was stated that patch testing was done according to the ICDRG recommendations, no further details were given. Of those patch tested, 3 clients (i.e. 2%) reacted positive to wool alcohols (30% in pet.; Hermal-Chemie). The severity of reactions was not stated. None of the positive reactions were considered clinically relevant. Irritant dermatitis was seen in 34 clients to other cosmetics.

Chemical contact sensitisation trends were studied over a 7-year period from 1977 to 1983 (Gollhausen *et al.*, 1988). During this period, 11,962 patients (40 males and 60% females) were patch tested with a standard series according to the ICDRG guidelines at the Dermatology clinic of the Ludwig-Maximilians-Universität (Germany). The series included wool alcohols (30% pet.). Patches were applied for 48 hours and test results were read on days 2 and 3. A positive reaction consisted of at least papulo-vesicles and/or infiltration. The authors presented the sensitisation rates for wool alcohols in a graph. With a gradient of 0.22+, sensitisation to wool alcohols seems to be on the rise. Over the 7-year period, the mean frequency of sensitisation to wool alcohols was 4.3%. In terms of sex differences, females (4.7%) had a higher mean sensitisation frequency compare to males (3.6%). The clinical relevance of these

reactions was not discussed. There was no indication of whether the patients were suffering from eczema or venous leg ulcers.

Katsarou *et al*. (1991) studied the immediate patch test (IPT) reactions of common allergens. Between November 1996 and April 1998, 664 patients (308 males and 356 females) presenting to the Center of Occupational Skin Disease at the University of Athens (Greece) were patch tested with the European standard series. The patches were partially removed after 30 min and results read after a further 5 min period. After recording the IPT reactions the patches were re-applied until day 2. Test sites were evaluated for delayed sensitivity reactions on Day 2 and 4 according to ICDRG guidelines. Almost all allergens in the European standard series gave IPT reactions. When tested with lanolin alcohol, 6 patients gave positive IPT reactions. In addition, 13 patients (i.e. 2%) gave delayed sensitivity reactions to lanolin alcohol. Doubtful reactions were not included as positive. This study showed that there was no significant difference in the frequency of IPT reactions in patients with and without atopy. IPT reactions are not always irritation reactions, some may be immunological (Katsarou *et al*., 1999).

A retrospective study analysed patch test results of 81 patients (27 males and 54 females) with venous leg ulcers that presented between January 1988 and July 1989 to either the Department of Dermatology or the ulcer clinic of the Slade Hospital, Oxford (Wilson *et al*., 1991). Patients were patch tested with the European standard series, preservative series, medicament series, ointments and dressings. The allergens were obtained from Chemotechnique, Hermal-Chemie and the hospital pharmacy. Patches were applied for 2 days and results read according to generally accepted guidelines at 2 and 4 days. Only reactions greater than '+' were considered positive. Of the 81 patients, 19 (i.e. 23.5%) reacted positive to wool alcohols (conc. and vehicle not stated). The authors noted that positive reactions to wool alcohols are likely to be relevant to leg-ulcer treatment.

Katoh *et al*. (1994) reported the patch test results of patients presenting to the Department of Dermatology at the Osaka Kaisei Hospital (Japan) between 1982 and 1991. Of the 4,839 patients patch tested 97 patients (i.e. 2%) reacted positive to 30% wool alcohols. Fewer subjects were sensitised by anhydrous lanolin (29 patients) and hydrogenated lanolin (82 patients). Given that this article was written in Japanese, no other detail could be ascertained.

One hundred and one patient records with patch test results were randomly selected from a database in York District Hospital (UK) (Henderson *et al*., 1995). All patients had presented to the hospital with suspected eczema during 1990 and 1991. Sixty patients were female and the rest male. 33 patients had hand eczema, 10 had atopic eczema and 2 had atopic plus hand eczema. Patch test results were read on days 2 and 4 in 63 patients, and day 3 in 38 patients. Out of the 101 patients, 5 reacted positive to lanolin. 3 of these patients reacted positive (2 patients with + and 1 with ++ reactions) to wool alcohols (30% in pet.). A doubtful positive reaction was seen in one additional patient. The other lanolin-sensitive patient gave a doubtful positive reaction to Amerchol L 101 (50% in pet.).

Matthieu and Dockx (1997) compared the sensitisation potential of wool alcohols to Amerchol L-101 (a commercial product containing 10% wool alcohols in mineral oil)

in patients presenting to the Department of Dermatology at the University Hospital Antwerp in Belgium. Between April 1991 and February 1992, 393 patients (female to male ratio being 1.9:1) were patch tested with the standard series (Chemotechnique Diagnostics AB) and Amerchol L-101 (100%; Chemotechnique Diagnostics AB). From September 1991 to February 1992, 223 patients were also patch tested with Amerchol L-101 (50% in pet; containing 5-10% wool alcohols; Trolab). Patch testing was conducted according to the ICDRG guidelines and the readings were taken on days 2 and 4. Doubtful reactions were not included. No other experimental details were provided. Of the 393 patients patch tested, 12 (i.e. 3.1%) reacted positive to both wool alcohols (30% in pet.) and Amerchol L-101 (100%). One patient (i.e. 0.3%) reacted positive to wool alcohols (30% in pet.) only. In total, 44 patients (11.2%) reacted positive to Amerchol L-101 (100%). Of the 223 patients tested with Amerchol L-101 (50% in pet; Trolab) 27 (i.e. 12.1%) reacted positive. This study showed that Amerchol L-101 has a significantly higher sensitisation rate compared to wool alcohols (30% in pet.). The exact reason for this difference is yet to be discovered. However, Amerchol L-101 is a commercial product containing mineral oil and possibly other additives.

Bakkum and Oei (1998) patch tested atopic children less than 10 years of age presenting to their clinic in Drechtsteden Hospital (Netherlands). Eighty-four children were patch tested with the European standard series. Eight children had multiple positive reactions. 3% of patch-tested children reacted positive to wool alcohols (conc. and vehicle not stated). The authors stated that the influence of irritant reactions could not be ruled out completely. Furthermore, the clinical relevance of these positive reactions could not be determined given the existence of atopic dermatitis. This study was presented at the 54th Annual Meeting of the American Academy of Allergy and only an abstract is available.

Gallenkemper *et al*. (1998) studied the sensitisation frequency of known allergens and modern wound dressings in patients with chronic venous insufficiency. Those patients (n=36) with suspected chronic venous insufficiency and presenting to the Department of Dermatology at the University of Bonn (Germany) were included in the study. The severity of chronic venous insufficiency was measured by the Widmer classification. Their average age was 64.5 years (range 37-89 years), and 24 patients had 3rd degree (i.e. suffering from venous ulcers) chronic venous insufficiency. The patients were patch tested with the European standard series (Hermal® and Hal®, Germany), other allergens and with modern wound dressings. The allergens were applied for 2 days and the results were read according to the ICDRG recommendations on days 2 and 3. A further reading was taken on day 4 to resolve doubtful reactions. When patch tested with wool alcohols (30% in pet.), 12 patients (i.e. 33.3%) reacted positive. The severity of the reactions was not reported. One would assume that these reactions are clinically relevant given that wool alcohols are present in ointments used to treat these patients.

Katsarou-Katsari *et al*. (1998) studied the frequency of sensitisation to common allergens in patients with leg ulcers. Between 1994 and 1995, 25 patients with leg ulcers were patch tested at the Centre of Occupational Skin Disease at the University of Athens (Greece). A further 325 unselected, consecutive control patients (i.e. those without leg ulcers) were patch tested. Patients were patch tested with the European standard series and other allergens according to the ICDRG guidelines. Patches were

applied for 48 hours and results read at 30 min after removal. A final reading was taken at 96 hours. Three patients (i.e. 12%) with leg ulcers and 8 control patients (i.e. 2.5%) reacted positive to wool alcohols (30%). The severity of the reactions was not reported.

Geier *et al*. (1999) analysed the patch test results to 15 standard allergens at day 3, 4, 5 and 6 to determine the optimum day for the 2nd patch test reading. Between 1990 and 1995, 3,526 patients were patch tested with the TRUE Test or Hermal preparations at the Department of Dermatology, University of Göttingen (Germany). The testing was conducted according to the guidelines of the ICDRG and German Contact Dermatitis Research Group (DKG). The patients were assigned to the following three groups: D3/D4 (1,096 patients), D3/D5 (1243 patients) and D3/D6 (1,136 patients). In all three groups, a similar percentage (23.3–24.7%) of patients suffered from atopic dermatitis. Occupational dermatosis ranged from 17.7% to 21%. The analysis indicated that 2.6% of patients had positive reactions to wool wax alcohols (30% in pet.) on day 4. However, these positive reactions diminished on day 5 and 6 to 0.9% and 0.5%, respectively. Compared to day 4, one additional reaction was observed in day 5.

A retrospective study looked at the patch test results to cosmetics ingredients from 5 European dermatological centres during a 4-month period (January and April, 1996) (Goossens *et al.*, 1999). Out of 475 patients allergic to cosmetics, 48 patients reacted positive to wool alcohols (conc. and vehicle not stated). Twenty-six of these patients were from a dermatology clinic in Belgium, 14 from UK and the rest from Germany. No other detail was reported. Whilst not reported, the actual total number of patients patch tested over this period is likely to be very much higher than 475 patients. Previously, it has been shown that only 6% of those patch tested were sensitised by cosmetics (Eiermann *et al.*, 1982).

Gooptu and Powell (1999) studied the frequency of hypersensitivity reactions (type I and type IV) to rubber allergens in patients with stasis eczema and/or venous leg ulcers. Patients presenting to the Department of Dermatology of the Oxford Radcliffe Hospital (UK) between July 1996 and December 1997 were patch tested with an extended European standard series, face and topical series and other relevant allergens (obtained from Chemotechnique, Hermal or the hospital pharmacy). One hundred and nine patients (31 males and 78 females; mean age was 75 years) with either stasis eczema and/or venous leg ulcers were included in the study. The duration of disease ranged from 3 months to 50 years. Only 4 patients had a history of atopy. Patch tests were read on days 2 and 4. Doubtful and irritant reactions were not included as positives. The patients also underwent prick tests to negative controls (chemical not indicated), positive controls (chemical not indicated) and a fresh extract of natural rubber latex (1g of glove in 5 ml saline). When patch tested with wool alcohols (conc. and vehicle not stated) 12 patients (11.0%) reacted positive. 14 patients also reacted positive to Amerchol L-101 (containing 10% wool alcohols in mineral oil). The severity of these reactions was not stated. When prick tested with natural rubber latex, only one patient showed a type I hypersensitivity reaction. Positive reactions to wool alcohols are likely to be relevant in this patient group (Wilson *et al.*, 1991).

Katz (1999) analysed patch test results of 383 patients who presented to the occupational and contact dermatitis clinic at the Wake Forest University School of

Medicine, North Carolina, USA. These patients were patch tested during October 1995 and October 1997. Those patients (n = 85; mean age = 47 years) with facial dermatitis were included in the study. The average duration of dermatitis in 70 of the patients was 23 months. Out of the 85 patients with facial dermatitis, 25 were atopic (asthma, hayfever or eczema). Patients were patch tested with the North American Contact Dermatitis Group (NACDG) standard series and other allergens. The patches were applied for 2 days and results were read according to the NACDG guidelines on days 2 and 3. When patch tested, 4 patients (i.e. 4.7%) had relevant positive reactions with lanolin alcohol. The severity of reactions was not stated.

Uter *et al*. (2001) studied the seasonal variation in patch test results to several chemicals including lanolin alcohol. Between January 1992 and April 1997, patients presenting to the 27 centres of the German Information Network of Departments of Dermatology (IVDK) were patch tested. The patch test results were read on day 3 according to the ICDRG guidelines. Environmental data (i.e. temperature and humidity) was also collected each day. During this period, of 46,887 patients tested (34.9% male), 15.5% suffered from occupational dermatitis and 18.5% had a history of atopic dermatitis. Of the 40,931 patients patch tested with lanolin alcohol (in petrolatum; conc. not stated) 890 patients (i.e. 2.2%) reacted positive (+). There was no mention of strong positive (i.e. ++ or +++) reactions in addition to those weak-positive reactions. The authors noted that there was only a weak association between positive reactions to lanolin alcohol and environmental variables.

The largest single-centre retrospective study on lanolin sensitisation was conducted at the St John's Institute of Dermatology, UK (Wakelin *et al*., 2001). A total of 24,449 patients (14,357 females & 10,092 males) were patch tested with the standard series between 1 January 1982 and 31 December 1996. Patches were applied for 2 days and the readings were taken according to internationally accepted criteria on days 2 – 5. A '+' or stronger allergic reactions were recorded as positive. Of the 24,449 patients patch tested, 431 (i.e. 1.8%) reacted positive to wool alcohols (30% pet.; Trolab). Statistical analysis suggested that atopic eczema was not a factor contributing to wool alcohols allergy. The highest rates of wool alcohol-sensitisation were seen in patients with dermatitis on the lower legs (6% of tested) and anogenital area (3.2% of tested). Wakelin *et al*. (2001) also analysed the 15-year patch test results for Amerchol® L-101 (containing 10% wool alcohols in mineral oil). Of 2,227 tested, 133 patients (i.e. 6%) reacted positive to Amerchol® L-101. The authors suggested that some reactions to Amerchol® L-101 may be false positives (i.e. irritant reactions) due to mineral oil or contaminants such as detergents. The clinical relevance of positive cases to wool alcohols was not discussed.

At the Department of Dermatology of the University of Graz (Austria) 724 patients with eczema or leg ulcers were patch tested with the German Contact Dermatitis Research Group (DKG) standard series (Trummer *et al*., 2002). 50 patients (6.9%) showed a + reaction to wool alcohols (30% in pet.; Hermal, Germany). These 50 patients (mean age 61 years) were further patch tested with the DKG ointment and emollient series. Forty-two of these patients reacted positive to Amerchol L-101 (50% in pet). A repeated open application test to wool alcohols containing Diprobas (AESCA, Austria) cream indicated that only 8 of the 50 patients were allergic. The authors reported that the weak + reactions may be irritant reactions (Trummer *et al*., 2002). Previously it has been shown that wool alcohols cause a higher sensitisation

rate in patients with leg ulcers (Katsarou-katsari *et al.*, 1998). This article appeared in a section that did not undergo peer-review.

A retrospective analysis of patch test results was made to study the prevalence of skin sensitisation in elderly patients with and without leg dermatitis (Uter, 2002). Between January 1996 and December 1999, 38,893 patients were patch tested at 32 IVDK dermatology centres. The patients were divided into three groups as following: patients ≤ 60 years (29,860 patients), 61–75 years (6,533 patients) and patients ≥ 76 years (2,500 patients). 63.8% were females and 8.8% of patients had a history of leg dermatitis. The patients were patch tested with the European standard series and other allergens. No other information on the patch test protocol was provided. Since IVDK members are also members of the German Contact Dermatitis Research Group it is likely that generally accepted guidelines were followed when patch testing. Of the 34,794 patients patch tested with lanolin alcohol (30% in pet.), 1,587 patients (i.e. 4.6%) reacted positive. Of the 1,587 lanolin alcohol-sensitive patients, 760 patients were over the age of 60 years. The authors cautioned that the prevalence indicated in this study is not representative of the general population as the study included a high proportion of patients with lower leg dermatitis.

Geier *et al*. (2003) studied the usefulness of the known irritant sodium lauryl sulfate (SLS) as an irritancy control in interpreting the weak reactions to other allergens such as wool alcohols. The study was conducted at IVDK dermatological centres between July 1996 and June 2001. A total of 1,600 consecutive patients were patch tested with SLS (0.5% in aq.; Sigma Chemicals, Germany) to determine those individuals susceptible to irritant reactions. Of the 1,600 patients, 721 were males and 348 patients had occupational dermatitis. 356 patients (i.e. 22.2%) had a history of atopic dermatitis. Of the 1,600 patients, 1,536 were patch tested with the standard series (Hermal, Reinbek, Germany). Of those, 644 patients reacted positive to SLS (0.5% in aq.), and 892 patients had no reactions. Of the 892 patients, 3.7% had erythematous reactions (possible irritant reactions) to lanolin alcohol (30% in pet.) and a further 3.7% had weak positive reactions (i.e. + reactions). In this group, only 0.9% of patients had strong positive reactions (i.e. ++, +++ reactions). In the SLS (0.5% in aq.) positive group, 7% of patients had erythematous reactions (possible irritant reactions) to lanolin alcohol (30% in pet.) and a further 5.6% had weak positive reactions. While the irritant and weak positive reactions were significantly higher in the SLS (0.5% in aq.) positive group, this was not the case with the strong positive reactions. Only 0.8% of patients had strong positive reactions to lanolin alcohol (30% in pet.) in the SLS (0.5% in aq.) positive group. This study indicates that only a low proportion of definite allergic reactions are caused by lanolin alcohol.

Case Reports

In addition to the above surveys several case studies have reported 9 positive patch test reactions to wool alcohols in their patients (De Beukelaar, 1968; van Ketel & Wemer, 1983; van Ketel, 1984; Foussereau & Cavelier, 1988; Marston, 1991; O'Donnell & Hodgson, 1993).

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 10 positive reactions for this chemical out of 1,500 workers (0.7%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 34 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 2 cases for this chemical out of a total of 838 skin cases, (0.2%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Wool alcohols are derived from lanolin, which is purified from the secretory products of the sheep sebaceous gland (Anonymous, 1980, for Cosmetic Ingredient Review). Wool alcohols are a mixture made up of two-thirds sterols and one-fourth aliphatic alcohols (Anonymous, 1980, for Cosmetic Ingredient Review). Wool alcohols may contain other contaminants from the deodorising and bleaching process of lanolin. Lanolin has been used for centuries, and commercial recovery of lanolin for cosmetic use occurred in the mid 19th century (Kligman, 1983; Wolf, 1997). Wolf (1997) suggests that lanolin is probably second only to water as an ingredient of skin care products, cosmetics and topical medicines.

Based on patch test results with various derivatives of lanolin it was found that wool alcohols (30% in pet.) were the materials of choice to determine lanolin sensitisation (Epstein, 1972). Wool alcohols are thought to contain a higher concentration of lanolin allergens than lanolin itself (Wolf, 1997). Wool alcohols were added to the international standard series in 1969 (Trummer *et al.*, 2002).

In a review article, Kligman (1983) described previously unpublished guinea pig maximisation tests with wool alcohols. None of the animals were sensitised by wool alcohols (30% in pet.). Repeated cycles maximisation tests in guinea pigs were also negative. While the experimental protocols were not presented in detail one can safely assume that these experiments would have been done to acceptable guidelines given that Prof. Bertil Magnusson and Prof. Albert Kligman were instrumental in developing maximisation test techniques (Magnusson & Kligman, 1969). The available animal data indicate that wool alcohols do not cause skin sensitisation.

Kligman (1983, 1998) also described a previously unpublished maximisation test with wool alcohols in human volunteers. On challenge testing, none of the 25 female subjects reacted positive to wool alcohols (30% in pet.). The same volunteers were chosen for a repeated cycles maximisation experiment. Only 1 of the 25 subjects (i.e. 4%) gave a positive reaction upon rechallenge with wool alcohols (30% in pet.). The repeated cycles maximisation experiment is thought to be sensitive in detecting weak sensitisers (Kligman, 1983). Given the results of these studies Kligman (1983; 1998) considered wool alcohols to be non-sensitising.

Several retrospective studies with large number of patients have shown the rate of wool alcohols-induced skin sensitisation to be quite small (Eiermann *et al.*, 1982; Uter *et al.*, 2001; Wakelin *et al.*, 2001). While the study by Uter (2002) indicated a somewhat higher sensitisation rate, this incidence is not representative of the general population as the study included a high proportion of patients with lower leg dermatitis. Several studies have shown that the rate of positive reactions to wool alcohols increase in patients with leg ulcers, lower leg dermatitis and stasis eczema (Malten & Kuiper, 1985; Gallenkemper *et al.*, 1998; Katsarou-katsari *et al.*, 1998; Gooptu & Powell, 1999; Trummer *et al.*, 2002). It seems that the incidence of wool alcohols-induced skin sensitisation is relatively small given the high exposure to lanolin. In fact, Clark (1975) estimated lanolin sensitisation in the general population to be 5.5 ± 4.2 per 1,000,000 people.

The study by Geier *et al*. (2003) showed that most patch test reactions to wool alcohols (30% in pet.) are either irritant reactions or weak positive reactions (i.e. + reactions). Only a very small percentage of definite allergic reactions (i.e. ++, +++ reactions) are caused by wool alcohols (30% in pet.) (Geier *et al.*, 2003).

Taking into consideration both the animal and human data, wool alcohols is not classified as a hazardous substance with respect to skin sensitisation.

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Coconut diethanolamide (Coco. DEA)

Chemical Identification

Chemical Name:	Amides, coco, N,N-bis(2-hydroxyethyl)
CAS #	68603-42-9
Synonyms:	Cocamide DEA; amides, coco, N,N-bis(hydroxyethyl); Coconut diethanolamide; coconut oil acid diethanolamine; ETHYLAN LD; NINOL 2012E
Uses:	Foam stabiliser in shampoos & dishwashing liquids; viscosity builder in shampoos; ingredient in textile dyeing, in hand cleaners and in lubricating oils.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

The IUCLID dataset (2000) includes the results of a single Buehler test in guinea pigs and two guinea pig maximisation tests. All studies showed cocamide DEA to be nonsensitising, but as the original studies were not reviewed by NICNAS their robustness could not be determined. The Buehler test was of a product containing 78.8% coconut diethanolamide and it was not conducted according to GLP. Details of the method used were not given except that it was in accord with a Proctor & Gamble test method. Also, no details were provided on animal numbers or doses used.

One maximisation test was conducted using a method described in Directive 84/449/EEC, B.6 with the pure substance. No details on animal numbers or doses used were provided and the test was not conducted to GLP. For the other maximisation test, no information on GLP was provided. However the method used was cited as that of Magnusson and Kligman. The pure substance was used but no other details were given.

No signs of skin sensitisation were reported in 14 week and 2 year repeated dose dermal studies in rats and mice (NTP, 2001).

Human Evidence

Surveys

In a study of 993 cases of occupational skin disease over an eight year period in one Western Australian clinic, 368 patients were diagnosed with allergic contact dermatitis. Of these 2.3% of males and 11.5% females tested positive to cocamide DEA. Of the 993 cases, 954 patients were available to follow-up. Of these, 177 females and 262 males were atopic however no details of the atopic status of the 368 allergic contact dermatitis patients was given (Wall & Gebauer, 1991).

Case Studies

Nurse (1980) describes the case of a 55 year old female with a 3 month history of dermatitis who tested positive to a hand gel used at work. Patch testing with the ingredients of the gel was positive for cocamide DEA but not for the other components. The symptoms settled on avoidance and testing with a second sample of cocamide DEA also proved positive.

A 27-year old coal miner presented with a 3 week history of acute eczema following 3 months exposure to a lubricating oil which contained cocamide DEA. He tested positive in patch testing to cocamide DEA but not to those components of the oil that were tested (Hindson & Lawlor, 1983).

De Groot *et al*., (1987) report the case of a 73-year old male who became sensitised to cocamide DEA in a shampoo. He developed a dermatitis and psoriasis after using a shampoo for many years. The shampoo contained cocamide DEA for which he was positive in patch testing. The dermatitis cleared following avoidance. The patient bought a different shampoo which contained lauramide DEA but not cocamide DEA. His symptoms returned on the first use of the new product. The patient was retested several months after using the second shampoo and tested positive to each product, and to cocamide and lauramide DEA. The authors suggest a possible cross sensitivity exists between cocamide and lauramide DEA.

A 55-year old female dentist was exposed to the chemical via hand washing liquids more than twenty times per day. She was in practice for 28 years before symptoms of dermatitis presented, however, the duration of exposure to the chemical could not be determined from the case report. The patient tested positive to coconut diethanolamine in patch testing down to 0.1% in a dilution series. A positive reaction was also found to resins used in the dental practice. The dermatitis healed when the patient was on vacation and returned when the patient was again at work (Kanerva *et al*., 1993). The same clinic reported six cases of allergic contact dermatitis caused by coconut diethanolamine between 1985 and 1992 (Pinola *et al*., 1993) of which the case of the dentist (op cit) was one. Three patients, including the dentist were atopic.

Fowler, (1998) reported three cases of dermatitis in patients with no history of atopy. All tested positive to patch testing with cocamide DEA. The dermatitis cleared following avoidance of products containing cocamide DEA.

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 16 positive reactions for this chemical out of 1,500 workers (1.1%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 4 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Animal studies do not indicate that cocamide diethanolamide is a sensitiser. It should be noted that these are in the form of IUCLID dataset summaries only and do not provide sufficient information for detailed analysis. Notwithstanding this, at least one maximisation test was noted as being conducted according to modern test guidelines and this provided a negative result. Overall, the limited animal data are negative.

With respect to human studies, the retrospective study by Wall and Gebauer shows that about 5% of patients in an Australian clinic diagnosed with allergic contact dermatitis tested positive to cocamide diethanolamide. Only limited case studies report sensitisation to cocamide diethanolamide, with cross-reactivity also reported to other occupationally relevant antigens in some cases. ODREC reports only 1.1% of their patient population with positive reactions to cocamide diethanolamide. The EPIDERM database contains 4 cases out of 6,067 and the OPRA database contains no cases for this chemical.

Given the widespread uses of the chemical in consumer products, the small number of case reports and the negative animal results, cocamide diethanolamide would not be regarded as a sensitiser according to the NOHSC Approved Criteria.

Conclusion

Data do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Basic Red 46

Chemical Identification

Chemical Name:	C.I. Basic Red 46
CAS #	12221-69-1
Synonyms:	Synacril Red; Anilan Red; Astrazon Red; Kayacryl Red; Maxilon Red.
Use:	Textile dye

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

None.

Human Evidence

Surveys

From 1987 to 1991, 3,336 patients were tested for contact dermatitis with the European Standard series (Trolab) at the Department of Medical Research (Dermatology), Katholieke Universiteit Leuven, Belgium (Dooms-Goossens, 1992). 159 patients were further tested with a textile series (Chemotechnique) containing 15 dyes. While it was stated that only 28 out of 3,336 patients tested positive to textile dyes, not all 3,336 patients were patch tested with the textile series. Out of the 159 patients tested with the textile series only 1 patient (i.e. 0.6%) was positive for Basic Red 46 (conc. and vehicle not stated).

In a study looking at purpuric allergic contact dermatitis, 30 of 103 patients tested positive to the Textile Color & Finish Series (Chemotechnique Diagnostics) (Lazarov & Cordoba, 2000). Nine out of the thirty patients were clinically diagnosed with purpuric allergic contact dermatitis. The patients were patch tested at the Dermatology Clinic of the Meir Hospital (Israel). The patches were applied for 2 days and the results read on days 2, 3, and 7. Of the 103 patients, 1 (i.e. 1%) reacted positive to Basic Red 46 (conc. and vehicle not stated). While the severity of the positive reaction was not stated this was a clinically relevant reaction.

Case Reports

A 41-year old woman developed a case of contact dermatitis to her arms and trunk after wearing a new sweater (Foussereau, 1986). The sweater contained various dyes. The patient had no prior history of personal or family history of allergy. When patch tested at the dermatological clinic of the Hospital Civil (France), the patient reacted positive (++) to Basic Red 46 (2% in petrolatum). The patient was also allergic to other dyes (Disperse Orange 3 (++), Disperse Blue 106 (++), and paraphenylenediamine (+)) not present in the sweater. It was suggested that there might be cross-reactions between dyes.

A 55-year old man developed allergic contact dermatitis to a flame-retardant clothing coloured with Basic Red 29 and Basic Red 46 (Scheman, 1998). The patient was patch tested at the Department of Dermatology, Northwestern University Medical Center, USA. Patch testing with a North American Contact Dermatitis Group (NACDG) standard series, textile series and a sample of the clothing revealed he was allergic to Basic Red 46 (conc. and vehicle not stated).

Saunders and Nixon (2003) reported a case of septic arthritis in a 32-year old male concrete worker as a complication of allergic dermatitis. The allergic dermatitis persisted for a 16-month period. The patient was patch tested at the Occupational Dermatology Research and Education Centre, Skin and Cancer Foundation, Australia. They patch tested the patient with an extended European standard series, textile dye series, a rubber series (Chemotechnique Diagnostics), and samples of socks, boots and mould-release oil (soaked in both oil and water). Positive reactions were seen with Basic Red 46 (1% in pet.; +++ reaction) and ethylenediamine (1% in pet.; ++ reaction). Equivocal reactions were seen to samples of socks and boot leather. It was speculated that the Basic Red 46 dye from acrylic work socks was responsible for the contact dermatitis and hence, the septic arthritis. This case report appeared in a section of the journal that does not undergo peer review.

Chave *et al*. (2003) reported a single case of allergic dermatitis in a 17-year old student due to contact with Basic Red 46. She had bilateral hand dermatitis following exposure to the dye at her course in textiles and graphic design. Following a patch test, a positive result (+) was seen for Basic Red 46 (1% in pet.) on both days 2 and 4. This case report appeared in a section of the journal that does not undergo peer review.

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 6 positive reactions for this chemical out of 1,500 workers (0.4%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 0 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 0 cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Several dermatological clinics have reported that Basic Red 46 causes sensitisation by skin contact in some patients (Foussereau, 1986; Dooms-Goossens, 1992; Scheman, 1998; Lazarov and Cordoba, 2000; Chave *et al*., 2003; Saunders and Nixon, 2003). However, available literature indicates that only six patients were positive to Basic Red 46 in patch tests. The Dooms-Goossens (1992) study indicated a low incidence of skin sensitisation. Given that the sample is biased towards skin sensitisation by textile dyes the actual incidence in the general population is expected to be even lower.

Given the small number of reported cases, it is considered that Basic Red 46 causes isolated episodes of allergic contact dermatitis as per NOHSC Approved Criteria. Neither animal studies nor studies on structure-activity relationships have been conducted to determine the skin sensitisation potential of Basic Red 46. Furthermore, some of the case reports on this chemical have not been peer reviewed. Therefore, to be classified under R43 further supportive evidence is required in the form of animal tests or structure-activity relationships. Therefore, it is considered that there is insufficient information to classify this chemical as a skin sensitiser.

Conclusion

Data available for the assessment are insufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Benzalkonium chloride

Chemical Identification

Chemical Name: Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides

CAS # 8001-54-5

Synonyms: Benzalkonium chloride;
Alkylbenzyldimethylammonium chlorides

Use: Bactericide and fungicide in consumer products such as opthalmic preparations and cosmetics. Used also to denature ethanol, as a binding agent in plaster of Paris casts and as an excipient in veterinary products.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Woolhiser *et al*. (1998) tested a number of substances classified as sensitisers and irritants in a modified murine local lymph node assay (LLNA). They combined the standard LLNA with a mouse ear swelling irritancy test. Benzalkonium chloride produced a statistically significant increase in lymph node cell proliferation and ear swelling. The exact stimulation index was not reported but was of the order of two times the vehicle control. The authors considered this increase to be low.

In a modified Murine Local Lymph Node Assay (LLNA), Sikorski *et al*., (1996) determined benzalkonium chloride to be an irritant. The study was aimed at comparing a varied LLNA test in which cell phenotypes were characterised by flow cytometry with the standard LLNA test. Induction was performed in the same manner as the LLNA but instead of measuring cell proliferation by [^{3}H]-thymidine uptake, cell number per node as determined by flow cytometry was used. Using this measure, a 4.5 times increase in the number of cells per node compared to vehicle control was observed. In a previous paper by one of the authors (Gerberick *et al* 1992), benzalkonium chloride was subjected to a modified LLNA. OECD test guideline 429 for the LLNA requires female mice to be used but no details of the sex are given in this paper. The guideline also specifies induction for three consecutive days but in this study induction occurred over 4 days. The results are not presented as a stimulation index (SI) instead the disintegrations per minute (dmp)-fold increase of treated compared with controls is given. This calculation is in effect the SI so the variations from guideline 429 are considered minor. A dilution series of 0.5, 1 and 2% benzalkonium chloride in acetone was used; control animals were treated with acetone. The chemical showed greater than a three times dmp increase at all dilutions which indicates a sensitising potential, but without a dose response. However, the authors of the later study using the modified LLNA state that based on their later results in which cell phenotypic analysis was used to distinguish irritant from allergic

reactions, this was a misclassification and that benzalkonium chloride is an irritant. It should be noted that the LLNA can produce false positives with strong irritants (and false negatives with weak sensitisers) (NTP, 1999).

Goh (1989) exposed 10 guinea pigs to benzalkonium chloride using a Buehler test modified to increase sensitivity. The number of animals used was less than recommended by OECD Test Guideline Number 406. As well, the induction phase (10% pet.) was once a week application for three weeks compared with three applications over two weeks as required by the Guidelines. Challenge phase consisted of a single application in week 5 (0.5% pet.) compared with challenge in the 4th week as per the Guidelines. Induction and challenge doses and post challenge observations were determined according to the Guidelines. Both positive (DNBC) and negative controls behaved accordingly. Two animals (20%) showed positive responses with the chemical. Individual scores were not reported.

Gad *et al* (1986) as part of a study to validate the mouse ear swelling test (MEST) found no sensitisation by benzalkonium chloride using the guinea pig maximisation test. Interestingly, based on the results of their MEST the authors suggest the GPMT result is a false negative. It is not clear on what basis the claim of a false negative result in the GPMT is made.

Human Evidence

Surveys

In the first epidemiological study of contact dermatitis in Spain, the Spanish Contact Dermatitis Group studied a total of 30,873 patients visiting a dermatology clinic during 1977. Of these, 2,806 were diagnosed with eczema with a contact etiology. Each of these eczema patients were patch tested with a variety of compounds in a Spanish patch test series which included benzalkonium chloride (0.1% pet.). 60 patients (2.1%) showed a positive response (Camarasa, 1979).

One hundred patients from an ophthalmology clinic who had been treated for chronic conjunctivitis for 3 months or longer were patch tested with benzalkonium chloride (0.07% aq.) (Afzelius & Thulin, 1979). No data regarding methodology were provided. Six (6%) showed positive reactions. These six were patch tested with a serial dilution of the chemical and again all showed positive responses. The authors also report that 3 patients in their clinic out of 371 (0.8%) patch tested with benzalkonium chloride from 1972–1973 showed a positive response.

The Departments of Dermatology and Oto-Rhino-Laryngology, Universities of Kuopio and Turku, Finland conducted a study of 142 patients suffering chronic external otitis between 1978 and 1983. Nine patients, (6.3%) showed a positive response to patch testing with 0.1% benzalkonium chloride (Fraki *et al*., 1985).

Patch testing with a number of preservatives was conducted by the Dutch Contact Dermatitis Group in 627 patients with suspected contact dermatitis. Test procedures were according to ICDRG recommendations. Eight patients (1.3%) showed a positive reaction to benzalkonium chloride (0.1% aqueous). The authors determined that this was too low for the chemical to be considered a sensitiser and also considered that the

reactions observed could have been irritant in nature, rather than allergic (De Groot *et al*., 1986).

Positive patch test results to benzalkonium chloride were reported in 5 of 32 patients (16%) from a dermatology clinic at the University of Innsbruck. No data regarding methodology were provided. Four were nurses who used a disinfectant containing 0.05% benzalkonium chloride as a surface cleaner. Testing with the cleaner in three of the four nurses produced no reaction in two. The authors concluded that despite a positive patch test, the negative reaction to the cleaner indicated the patients were not sensitive to benzalkonium chloride (Klein *et al*., 1991).

According to the English abstract of a paper written in German, 2,146 patients were tested over a one-year period in eight dermatology clinics. A positive allergic reaction to benzalkonium chloride was shown in 225 cases (10.5%) with irritant reactions seen in an additional 258 cases. The authors stated that only 12 of the 225 cases were clinically relevant and classified benzalkonium chloride as a weak allergen (Fuchs *et al*., 1993).

In a study by the Swiss Contact Dermatitis Research Group over a one year period, 2,295 patients with suspected allergic contact dermatitis attending 5 different university clinics were patch tested with a number of different topical preservatives. Benzalkonium chloride (0.1% aq., Hermal-Chemie, Reinbek, Germany) produced positive results in 5.5% of patients (Perrenoud *et al*., 1994). The authors note the high irritancy potential of benzalkonium chloride even in low concentrations and the need for caution in interpreting positive reactions.

Schnuch *et al*., (1998) report a multicentre retrospective study over five years in 11,485 dermatological patients. Data were taken from the Information Network of Departments of Dermatology (IVDK) in Germany which recorded information from 24 allergy departments. Patch tests were performed according to recommendations of the International Contact Dermatitis Research Group (ICDRG) and the German Contact Dermatitis Group. Benzalkonium chloride (0.1% pet., Hermal-Chemie, Reinbek, Germany) produced 207 (1.8%) positive responses and 338 doubtful/irritant reactions. No data were provided on the number of positive responses in atopic individuals.

From 1991–1998, 948 patients were patch tested with benzalkonium chloride (0.01, 0.1 but mostly at 1.0% pet.) at the Finish Institute of Occupational Health. Three patients (0.3%) showed a positive reaction. Two case reports are presented. The first were a female non-atopic cook with dermatitis on the face and hands who returned a strong reaction to an aqueous solution of 0.1% benzalkonium chloride. The second patient was a female cleaner with hand dermatitis who showed a strong positive reaction to 0.1% benzalkonium chloride (Kanerva *et al*., 2000).

Case Reports

Corazza and Virgili (1993) report a case of a female farm worker who presented with widespread eczema. She had used detergents and disinfectants in her work. Patch testing with 0.01% benzalkonium chloride produced a positive response.

Cusano and Luciano (1993) report the case of a 36 year old dental nurse with widespread eczema. Patch testing with benzalkomium chloride was strongly positive.

A 78-year old female was referred to a dermatology clinic with facial rash. Patch testing with benzalkonium chloride was mildly positive. She had used an ophthalmological preparation containing benzalkonium chloride as the preservative (Cox, 1994).

A 35-year old female with no history of atopy presented to a dermatology clinic with eczema of the feet following use of an antifungal preparation for tinea. Patch testing with 0.1% and 0.01% benzalkonium chloride proved positive. Patch testing of 5 control subjects was negative (Park & Eun 1995).

A 14-year old boy presented to a dermatology clinic in Sydney with a severe dermatitis on the forearm which had been encased in a plaster of Paris cast for a month. He gave no history of atopy. Patch testing with 0.1% and 0.01% aqueous solutions of benzalkonium chloride were strongly positive (Stanford & Georgouras 1996). Another case of allergic contact dermatitis to plaster of Paris containing benzalkonium chloride is reported by Wong and Watson (2001). An 81-year old female developed symptoms post operatively which were confined to the areas of skin in contact with a plaster back-slab. Patch testing with benzalkonium chloride was mildly positive. The authors report that a search of the literature found only seven previously documented cases of allergic contact dermatitis caused by plaster of Paris bandages.

Oritz-Frutos (1996) report the case of a 41-year old female who soaked a neck scarf in ethanol to treat pharyngitis and presented with erythematous lesions on the neck. Patch testing with benzalkonium chloride was positive at 0.01% and 0.1% in water. The authors state that benzalkonium chloride is used in concentrations of 1 in 1000 in ethanol to impart an unpleasant taste.

A 17-year old male with erythaema on the eyelids showed a positive reaction to patch testing with benzalkonium chloride. He had been using eye drops containing the chemical as a preservative (Henta *et al*., 1998).

Chowdhury and Statham (2002) report the case of a 65-year old male with no history of atopy who developed a rash after using a cream preparation containing benzalkonium chloride. Patch testing resulted in a minor positive response to the chemical.

Other Studies

Gerberick (1992) report the findings of Kligman (1966) who failed to sensitise 24 human subjects with an induction dose 25% benzalkonium chloride followed by challenge with a 10% dose. The paper of Kligman was not sighted in this assessment.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 6 positive reactions for this chemical out of 1,500 workers (0.4%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 2 cases for this chemical out of a total of 6,067 cases (0.3%). The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Benzalkonium chloride is considered by some workers to be a rare but increasingly important sensitiser (Stanford & Georgouras 1996). A Buehler test in guinea pigs modified to increase sensitivity showed only 20% of animals with positive responses to benzalkonium chloride. However, the test only used 10 animals and in additional respects did not conform with OECD test guidelines. Similarly, a modified LLNA test showed a 4.5 times increase in the numbers of cells per lymph node with benzalkonium chloride as measured by flow cytometry but importantly this measure of cell numbers differs from the thymidine uptake index as a measure of cell proliferation as required by test guidelines. In an earlier study using the standard LLNA the chemical was shown to be a contact allergen however, the authors of the later study state that based on their later results using cell phenotypic analysis this was a misclassification and that benzalkonium chloride is an irritant. Another later LLNA test showed cell proliferation but only of the order of 2 times the vehicle control. On a weight of evidence approach, the animal data are insufficient to support classification of benzalkonium chloride as a sensitiser and the results of Gerberick *et al* (1992), though generated using the OECD guidelines (with only a minor variation) are considered to be a false positive.

Large scale human studies of dermatological cases report the proportion of positive responses to patch testing with benzalkonium chloride of the order of 0.3-16%, with an average of approximately 6%. Higher percentages are found in small patient population studies. One of these studies in humans reported that the reactions could have been due to irritation

Benzalkonium chloride is used widely in consumer products as a bactericide and fungicide. Given the widespread exposure to the chemical, results of animal studies and limited human evidence of sensitisation only in relatively small proportions of individuals, benzalkonium chloride is not considered a sensitiser.

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Phenol formaldehyde resin (P-F-R-2)

Chemical Identification

Chemical Name:	Phenol, polymer with formaldehyde
CAS #	9003-35-4
Synonyms:	Phenol resin; phenol-formaldehyde polymer; phenolic resin.
Use:	Widely used in glues, wood preservatives, adhesives and brake linings (Bruze *et al.*, 1985). Also used for electric insulation and impregnation of textiles and paper in laminate.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Not applicable.

Human Evidence

Surveys

Not applicable.

Case Reports

Not applicable.

Other Studies

Not applicable.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 6 positive reactions for this chemical out of 1,500 workers (0.4%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 298 cases for phenol resin out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 44 cases for this chemical out of a total of 838 skin cases, (5.3%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Phenol formaldehyde resins are formed from a polymerisation reaction between phenol and formaldehyde. There are two basic types of phenol formaldehyde resins (P-F-R). These are resol resins (methylol terminated) and novolak resins (phenol terminated), differentiated on the basis of phenol-to-formaldehyde ratio and different types of catalysts (Hagdrup *et al.*, 1994). A resol resin is formed when phenol reacts with a molar excess of formaldehyde under alkaline conditions (Bruze, 1985). In this process several simple methylol phenols are formed (Bruze, 1985). A novolak resin is formed when formaldehyde reacts with a molar excess of phenol under acidic conditions (Bruze, 1985). This reaction gives rise to both simple methylol phenols (MP) and dihydroxydiphenyl methanes (HPM). However, in novolaks MPs are formed transiently in very small concentrations (Bruze, 1985).

While a single CAS number and chemical name has been assigned to P-F-R (i.e. 9003-35-4, phenol, polymer with formaldehyde), a literature survey shows that a wide variety of P-F-Rs are available. A review indicated the presence of the following P-F-Rs: P-F-R-1, P-F-R-2, P-F-R-3, P-F-R-4, P-F-R-5, P-F-R-6, P-F-R-7, P-F-R-8 and P-F-R-9 (Bruze *et al.*, 1986). P-F-R-1 to 7 are resol resins and P-F-R-8 and P-F-R-9 are novolak resins. In addition, P-F-R:X (low degree of condensation), P-F-R:Y (high degree of condensation), P-F-R:Z (with a flame-retardant property) are also in use (Isaksson *et al.*, 1999).

Many known and unknown substances are formed as impurities during the production of phenol formaldehyde resin (Bruze & Zimerson, 1985). Due to the nature of the production process, a single P-F-R may consist of many distinct chemical substances (Bruze, 1985; Bruze *et al.*, 1986). The production process may give rise to P-F-Rs with different compositions even if the mean molecular weights are equivalent (Bruze *et al*., 1985). Bruze *et al*. (1986) reported the presence of 14 MPs and HPMs in P-F-R and several studies have isolated a number of MPs and HPMs from P-F-R (Bruze, 1985; Bruze *et al.*, 1987). Some of these chemicals had differing sensitisation potentials and profiles (Bruze, 1985; Bruze *et al.*, 1985). P-F-R-1 to P-F-R-9 have different concentrations of each of the 14 MPs and HPMs. It must also be noted that many of these MPs and HPMs that arise from the polymerisation process have their own CAS numbers.

Given the wide variety of available P-F-Rs of different composition, it is likely that the sensitising potential of these resins may differ from one to another. In a study of patch test reactions to different P-F-Rs and reactant impurities, Bruze *et al*. (1985) has shown that P-F-R-1 and P-F-R-2 have very different sensitisation profiles in the same

patients. In another study, while P-F-R-1 to 9 contains free un-reacted formaldehyde (a known skin sensitiser), it was shown not to be a main sensitiser in P-F-R (Bruze, 1985). There was no cross-sensitisation between formaldehyde (2% aq.) and P-F-R-1 (5% pet.) or P-F-R-2 (5% pet.) in 25 out of 26 patients (Bruze *et al.*, 1985). Because of apparently very different sensitisation reaction profiles between different P-F-Rs, it is suggested that patients should be patch tested with a battery of P-F-Rs, not just with P-F-R as available in patch test kits, but also with the actual P-F-Rs that are encountered by the patient during daily activities.

In conclusion, P-F-R is a poorly characterised mixture of chemicals. The composition of P-F-R and apparent sensitisation properties appear to depend on particular synthesis conditions giving rise to different molecular weight distributions of the resultant polymer and levels of low molecular weight reactant impurities. In the absence of adequate characterisation of concentrations of reactant impurities and polymer molecular weight, in particular low molecular weight species, it is not possible to form reliable conclusions with regards to sensitisation profiles according to the NOHSC Approved Criteria.

Conclusion

Data available for the assessment are insufficient for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Toluenesulfonamide formaldehyde resin

Chemical Identification

Chemical Name:	Benzenesulfonamide, 4-methyl-, polymer with formaldehyde
CAS #	25035-71-6
Synonyms:	Toluenesulfonamide Formaldehyde Resin (TSFR); Formaldehyde-p-toluenesulfonamide resin; Santolite MS
Use:	Used in cosmetic products such as nail polish. Adhesion promoter for film-forming resins.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Basketter *et al*. (1999) reported the skin sensitisation potential of 134 chemicals, including TSFR. The results from the local lymph node assays (LLNA) and guinea pig maximisation tests (GPMT) were presented. According to the authors, the LLNA studies were conducted using the standard protocol and the majority of the guinea pig tests (i.e. Magnusson & Kligman and Buehler) were conducted according to standard methodology. Those chemicals tested with a non-standard guinea pig test were indicated in the text. No other detail was given on either the LLNA protocol or the GPMTs. The authors reported that the results of the guinea pig tests were read according to European Union criteria and WHO guidelines. TSFR was not a sensitiser in either the LLNA or the standard-GPMT. These studies were conducted by the Unilever and Zeneca laboratories.

In support of the murine LLNA test method, results for 209 chemicals (which included the 134 of Basketter *et al*., 1999) were submitted by Procter & Gamble (UK), Zeneca (UK) and Unilever (UK) to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Center for the Evaluation of Alternative Toxicological Methods (NICEATM) for independent peer review (National Institute of Environmental Health Sciences USA, 1999). A standard operating procedure for the LLNA was also submitted. The assays were conducted according to Good Laboratory Practice and reported in extensive detail. CBA/Ca strain female mice (8–12 weeks; Harlan UK Ltd or Charles River UK Ltd) were utilised for the assays. The test substances were assayed at 3-5 different doses. A 25 µl volume of the test substance was spread over the dorsal side of the ear once daily for three consecutive days. Five days after the first topical application with the test substance 20µCi ^{3}H-methyl thymidine (^{3}HTdR) was injected intravenously via the tail vein. Five hours after ^{3}HTdR administration mice were sacrificed and the draining auricular lymph nodes excised and pooled (8 nodes per group). Single cell suspensions of pooled lymph node cells were washed 3 times and counted by a β-scintillation counter. As reported in Basketter *et al*. (1999) this Unilever data, for which methodology is provided, indicated that TSFR is not a sensitiser in the LLNA. While the GPMTs are not described in detail, the report also states that TSFR is not a sensitiser in the GPMT.

Human Evidence

Surveys

A multicentre study in Netherlands evaluated the sensitisation potential of ingredients in cosmetic products (de Groot *et al*., 1988). Those presenting to the dermatological clinics between 1 March 1986 and 31 July 1987 were patch tested according to internationally accepted guidelines. Patients were patch tested with the European standard series, cosmetics ingredients and their own personal products. The patches were applied for 2 days, and results read after 20 min, 1 and 2 days. Of the 119 patients (102 females and 17 males) patch tested, 17 were affected by atopic dermatitis. 17 patients were affected by irritant dermatitis. When patch tested with TSFR (10% pet.) 15 patients (i.e. 12.6%) reacted positive. The severity of reactions was not stated. The authors speculated that the presence of formaldehyde in a particular nail hardener would have increased the risk of sensitisation to TSFR in 10 patients.

Between October 1989 and December 1991, 18 patients with contact allergy to nail varnish were identified in a Swedish multicentre study (Liden *et al*., 1993). Most patients suffered for long periods (6 months–20 years) with dermatitis before presenting to the clinic. These patients were patch tested at the Department of Occupational Dermatology, Karolinska Hospital (Sweden) with the Swedish standard series and TSFR (Chemotechnique AB, Sweden). Patches were applied for 2 days and results read after 3 days. Seventeen of the 18 patients allergic to nail varnish reacted positive to TSFR (10% pet.). Four of these patients were also sensitised by formaldehyde and quaternium 15 (conc. and vehicle not given). When the 1,991 patch test results to the standard series were analysed retrospectively, 12 female patients (i.e. 3.3%) out of 368 (136 men and 232 women) were sensitised by TSFR (10% pet.). The severity of reactions was not stated.

Between January 1987 and September 1992, 888 consecutive women who used nail polishes were patch tested with TSFR (10% pet.; Hermal-Trolab, Reinbek, Germany) in an Italian clinic (Tosti *et al*., 1993). Patch testing was conducted according to the International Contact Dermatitis Research Group (ICDRG) recommendations. Results were read at 48 and 72 hours. Fifty-nine patients (i.e. 6.6%) reacted positive to TSFR. Fifty-four of these cases were considered clinically relevant. Only 5 of the TSFR-sensitised patients were also sensitised by formaldehyde (1% aq.) in the ICDRG standard series. Twelve patients sensitised by TSFR were further patch tested with their dried nail polishes. Eleven of these patients reacted positive to dried nail polish.

Between April 1992 and June 1993 an Italian dermatological clinic recorded results of patch tests to TSFR (10% pet.) in 366 consecutive patients (Giorgini *et al*., 1994). The authors reported that 14 patients (i.e. 3.8%) were sensitised by TSFR. The severity of reactions was not stated. All 14 patients were females and within the ages 16 and 59 years. In these patients, dermatitis was localised on the face, neck, lips, perioral skin and upper eyelids. When 10 of the 14 patients were further patch tested with dried (polymerised) nail varnishes, 9 patients still reacted positive. In this short communication no other methodological detail was given.

Between 1989 and 1994, the Swedish Medical Products Agency evaluated 191 reports concerning adverse effects caused by cosmetics and toiletries (Berne *et al*., 1996).

Relevant positive patch test results were obtained from 79 patients. Since the patch tests were not conducted by the agency a protocol for the procedure was not given. However, patch tests revealed that 19 patients were sensitised by TSFR (conc. and vehicle not given).

Fuchs and Gutgesell (1996) reported their findings on the sensitisation frequency of TSFR in a letter to the editor. A total of 1,018 consecutive patients (687 females and 331 males) presenting to their clinic between January 1993 and July 1995 were patch tested with TSFR (10% pet.) and the German Contact Dermatitis Research Group (DKG) standard series. Patches were applied for 2 days and results read after 2 and 3 days according to the ICDRG guidelines. Five females and 3 males gave doubtful reactions to TSFR. These were considered to be clinically irrelevant. However, 3 (i.e. 0.3%) other female patients reacted positive (2 patients with ++, and 1 with + reactions) to TSFR. The TSFR-sensitised patients had eczema over the face, eyelids, neck and around the fingernails. Of these 11 patients, none reacted positive to formaldehyde (1% aq.). Given the low incidence of sensitisation, Fuchs and Gutgesell (1996) recommended that TSFR not be included in the standard series.

Kanerva *et al*. (1997) evaluated patch test results from 174 patients who presented to their dermatological clinic at the Finnish Institute of Occupational Health over a 3-year period. Patients were patch tested with a modified European standard series and their own substances. Those patients who were exposed to plastics were further tested with the clinic's own plastics and glues series. Patches were applied for 2 days and results read according to ICDRG guidelines on days 2, 3 and 4. Irritant and doubtful reactions were separated from allergic reactions. Out of the 174 patients patch tested, 1 (i.e. 0.6%) was sensitised by TSFR (10% pet.; Chemotechnique Diagnostics AB). No irritant reactions were seen with TSFR.

Between 1991 and 1996, 360 patients exposed to plastics presented to a dermatological clinic at the Finnish Institute of Occupational Health (Kanerva *et al*., 1999). This complete study appears to include results from Kanerva *et al*., (1997). Patients were patch tested with a modified European standard series and their own substances. Those patients who were exposed to plastics were further tested with the clinic's own plastics and glues series. Patch test materials were obtained from Chemotechnique Diagnostics AB (Malmö, Sweden), Trolab Hermal Chemie (Reinbeck/ Hamburg, Germany) and Epikon Oy (Helsinki, Finland). Test material was applied and left occluded for 2 days. Results were read according to ICDRG guidelines on days 2, 3 and 4 after removal of the patch. Those that were doubtful or irritant were classified as irritant reactions. When patients were patch tested with the clinic's plastics and glues series, 1 out of 269 patients (i.e. 0.4%) were sensitised by TSFR (10% pet.; Chemotechnique Diagnostics AB). Two patients (i.e. 0.7%) had irritant reactions to TSFR (10% pet.). When TSFR was included in the modified European standard series, 6 out of 525 patients (i.e. 1.1%) were sensitised by TSFR (10% pet.). The severity of reactions was not stated.

Case Reports

Within a 5-month period in 1986–1987, eight female patients presented to a dermatological clinic with contact dermatitis due to a nail hardener containing TSFR (de Wit *et al*., 1988). While most nail lacquers contain usually 7% TSFR, this

particular nail hardener contained 4% formaldehyde and 9.1% TSFR. The patients were patch tested with the European standard series and their own cosmetics. Results were read on day 3. All patients patch tested positive to the nail hardener. Four patients reacted to nickel sulphate, fragrance-mix, benzocaine and ρ-tert-butylphenolformaldehyde resin in the standard series. All of the 7 patients that were patch tested with TSFR (10% pet.) reacted positive (3 with + and 4 with ++ reactions). However, none of the eight patients were sensitised by formaldehyde in the standard series.

Kanerva *et al*. (1995) reported a single case of TSFR sensitisation in a 32-year old hairdresser. She was patch tested with a modified European standard series and the hairdressers' series under internationally recommended guidelines. While it was assumed that the patient was allergic to nickel, patch testing with TSFR (10% pet.; Chemotechnique Diagnostics, Sweden) revealed that she was sensitised to TSFR.

Guin *et al*. (1998) reported three cases of subungual hyperkeratosis, eczematous fingertips and fingernail dystrophy due to the use of artificial nails. However, in only one patient was patch testing to TSFR positive (+++ reaction) (conc. and vehicle not stated). This 54-year old woman was also sensitised by fragrance mix and ethyl methacrylate in the Chemotechnique standard and acrylate series.

A 50-year old female patient presented to a dermatological clinic in Israel with persistent perianal and eyelid pruritus (Lazarov, 1999). The patient also had a history of seasonal rhinitis and mild asthma. Contact dermatitis was suspected and patch testing was conducted at the dermatological clinic of Meir Hospital (Israel) with the standard series (TRUE test), cosmetic series, plastic and glue series, and the patient's own cosmetics (including dried nail varnishes). Patch test results indicated that the patient was sensitised by her nail lacquers and TSFR (10% pet.). With TSFR the patient had a ++ reaction. After the patient stopped using nail lacquers her condition subsided completely.

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 5 positive reactions for this chemical out of 1,500 workers (0.3%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains no cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

The LLNA studies indicate that TSFR is not a skin sensitiser (Basketter *et al*., 1999; National Institute of Environmental Health Sciences USA, 1999). Although details of the guinea pig tests were not presented, their results also indicate that TSFR is not a skin sensitiser. Hence, the available animal data suggest that TSFR is not a skin sensitiser.

In contrast to the animal data, a number of dermatological clinics have reported that TSFR causes sensitisation by skin contact (de Groot *et al*., 1988; de Wit *et al*., 1988; Liden *et al*., 1993; Giorgini *et al*., 1994; Kanerva *et al*., 1995; Fuchs & Gutgesell, 1996; Kanerva *et al*., 1997; Guin *et al*., 1998; Kanerva *et al*., 1999; Lazarov, 1999). While de Groot *et al*. (1988) reported a high incidence of skin sensitisation due to TSFR, other larger studies reported a low incidence of skin sensitisation (Fuchs & Gutgesell, 1996; Kanerva *et al*., 1997; Kanerva *et al*., 1999). TSFR has been used widely in nail polishes and hardeners since 1938 (Fuchs & Gutgesell, 1996). Some authors report that 99% of nail lacquers sold worldwide contain TSFR (Hausen, 1995).

Several other studies (Staines *et al*., 1998; Goosens *et al*., 1999 and Held *et al*., 1999) also mention skin reactions to tosylamide/formalehyde resin but identity of the chemical cannot be confirmed sufficiently to include the results in this report.

Given such widespread use, the number of people affected by TSFR-induced skin sensitisation is relatively small. At most, these are isolated episodes of skin sensitisation. Hence, without further supportive evidence, the data for TSFR does not meet the Approved Criteria for classification as a hazardous substance according to the NOHSC Approved Criteria.

De Groot *et al*. (1988) speculated that the presence of formaldehyde in a particular nail hardener would have increased the risk of sensitisation to TSFR. However, there seems to be no concrete evidence of cross-sensitisation between formaldehyde and TSFR. In fact, in several studies, TSFR-induced skin sensitised patients were not sensitised by formaldehyde (de Wit *et al*., 1988; Fuchs & Gutgesell, 1996).

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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4-tert-Butylphenol, formaldehyde resin (PTBP)

Chemical Identification

Chemical Name: Formaldehyde, polymer with 4-(1,1-dimethylethyl)phenol

CAS # 25085-50-1

Synonyms: 4-(1,1-Dimethylethyl)phenol, formaldehyde polymer;
4-tert-Butylphenol-formaldehyde copolymer;
Formaldehyde-p-tert-butylphenol resin;
p-tert-Butylphenol, formaldehyde resin

Use: Adhesives, varnishes, lacquers, antioxidants, germicides, de-emulsifiers, oil additives, plasticisers, insecticides, deodorants, printing inks, lip liner pencils, leather products.

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Twenty-five female guinea pigs were exposed to a 30% solution of paratertiary butylphenol formaldehyde resin in ethylacetate by application on bare skin behind the ears once daily for three weeks. No further identity or molecular weight information for the resin was provided. Following two weeks rest, animals were challenged by application of paratertiary butylphenol formaldehyde resin (0.5% in ethylacetate) to one nipple. The authors state that in earlier experiments this dose had been shown "not to be noxious". Forty-eight hours after challenge nipple biopsies were taken. Histologically, 15 (75%) of animals showed contact allergic reactions to paratertiary butylphenol formaldehyde resin (Malten, 1967). No further details regarding positive histological findings were provided.

The suitability of this non-standard test to reliably identify skin sensitisation is questionable as the nipple is a tissue that is not evaluated in OECD test guidelines and it may not be possible to distinguish allergic and irritant reactions with histological assessment. Thus, it is considered that no reliable conclusions can be drawn from this study.

Human Evidence

Surveys

One hundred and sixty-five patients of the Department of Dermatology, University of Bari, Italy diagnosed with non-occupational contact dermatitis of the feet were patch tested with a shoe screening series containing paratertiary butylphenol formaldehyde resin (1 % pet.) (Trolle Lassen). Nine (5.5%) responded positively to paratertiary butylphenol formaldehyde resin. The severity of reactions was not stated (Angelini *et al*., 1980).

Geldof *et al.*, (1989) at the Departments of Dermatology at Erasmus University Rotterdam, The Netherlands and University of North Sumatra, Medan, Indonesia undertook a retrospective study on clinical aspects of patients with putative allergies to para-tertiary butylphenol formaldehyde resin, para-tertiary butyl phenol and phenol formaldehyde resin. During the period 1985 to 1988, a total of 1,966 patients, of whom 43.3% were atopic were patch tested with the above allergens according to International Contact Dermatitis Research Group (ICDRG) guidelines. Thirty (1.5%) were positive to paratertiary butylphenol formaldehyde resin (1% pet.). No further detail regarding methodology or severity of reactions was provided. No clear association of para-tertiary butylphenol formaldehyde resin sensitisation with allergies to free para-tertiary butyl phenol or phenol formaldehyde resin and no allergic reactions to formaldehyde were seen. On this basis, the authors recommended addition of para-tertiary butylphenol formaldehyde resin to the ICDRG standard series.

In a retrospective cohort study over 5 years, 2,270 patients of the dermatology clinic at the Department of Dermatology, Royal Victoria Hospital, Belfast, Northern Ireland were patch tested with the European standard series (Trolab). Grading of reactions was conducted to ICDRG guidelines. Patients who showed a + or greater response at either 3 or 4 days were included in the study. Seven patients (0.3%), of which 2 were atopic, gave a positive response to paratertiary butylphenol formaldehyde resin (1% pet.) (Handley *et al*., 1993).

From 1983 to 1992, 3,106 patients presenting to the Allergology Unit of the Department of Dermatology, University Hospital of Coimbra, Portugal were patch tested with the standard series of the Portugese Contact Dermatitis Group including paratertiary butylphenol formaldehyde resin (1% pet.) (Trolab). Seventy-four positive reactions (2. 4%) were observed (Marques *et al*., 1994). No further details regarding methodology or severity of reactions were provided.

A total of 10,280 patients visiting the University dermatology clinic in Helsinki, Finland were patch tested with a Finnish standard series which included paratertiary butylphenol formaldehyde resin (1% aq.) (Epikon Oy, Helsinki, Finland). Of this group, a subset of 839 patients was also tested with a plastics and glue series which included paratertiary butylphenol formaldehyde resin (1% pet.) (Epikon Oy, Helsinki, Finland). Test sites were evaluated on removal of patches (day 2) and then on days 3 and 4 according to ICDRG guidelines. Reactions from ++ to +++ were considered positive. Of 343 patients who were tested with paratertiary butylphenol formaldehyde resin (1% pet.), 2.6% reacted positively (Tarvainen, 1995).

During the period January 1987 to January 1988, a total of 437 patients at the Department of Community Medicine, The University of Hong Kong were patch tested using the European standard series (Trolab). One (0.2%) patient showed a positive reaction to paratertiary butylphenol formaldehyde resin 1% in pet (Lee & Lam, 1996).

Mancuso *et al*., (1996) at the Department of Dermatology, Municipal Hospital of Lugo, Ravenna, Italy patch tested 246 workers (with or without current skin disorders) from 5 different shoe manufacturers in Italy between 1992 and 1994 using the European standard series (Firma Diagent, Italy). Duration of employment ranged from 1 month to 34 years (mean 16 years). Patches were removed after 2 days and

read at days 3 and 4 according to ICDRG guidelines. Five (2.0%) tested positive to paratertiary butylphenol formaldehyde resin 1% (pet.).

Of all patients referred to the Skin and Cancer Foundation in Sydney over a 10-year period, 55 (1.5%) had a diagnosis of shoe allergy confirmed by patch testing. Forty-three percent of these were defined as atopic (defined as a personal history of eczma and/or asthma) and all 55 were tested with the European standard series (Trolab) including paratertiary butylphenol formaldehyde resin 1% (vehicle not stated). Patches were applied for 2 days (3 days from 1992 onwards) and reactions were evaluated at 2 and 4 days (3 and 7 days from 1992 onwards) according to ICDRG guidelines. Twenty percent of patients showed a positive response to paratertiary butylphenol formaldehyde resin (Freeman, 1997).

In a study of admissions to the Contact Dermatitis Clinic, Royal Hallamshire Hospital, Sheffield, UK, patch testing of 83 children using the European standard series (Trolab) resulted in 2 (2.4%) showing a positive response to paratertiary butylphenol formaldehyde resin (1% pet.). The children chosen were a sub group of 1,972 patients patch tested between January 1991 and December 1995. Atopy was common but the exact prevalence was not stated (Shah *et al*., 1997).

Two hundred patients aged between 9 and 85 years with suspected allergic contact dermatitis attending the Dermatology clinic of the Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India were recruited to be patch tested with the European standard series (Chemotechnique) containing paratertiary butylphenol formaldehyde resin (1% pet.). Patch tests readings were taken after 2 and 3 days and only reactions still positive at 3 days were considered positive. No other details regarding methodology were provided. Two (1.0%) showed positive reactions to paratertiary butylphenol formaldehyde resin. The severity of reactions was not provided (Sharma & Chakrabarti, 1998).

Over 6 years from 1992 to 1997, children up to 14 years of age attending the Allergy Department, Hospital Clínico, Barcelona, Spain were patch tested using allergen series from either TRUE Test (Pharmacia) or Chemotechnique. 141 patients (out of a total of 5,014 clinic patients) were tested and 71 showed a positive response to at least one allergen, with 4 (2.8%) reacting to paratertiary butylphenol formaldehyde resin (concentration and vehicle not given). Of the 71 showing a response, 44 (62%) were considered atopics. Further details regarding methodology or severity of reactions were not provided (Romaguera & Vilaplana, 1998).

Kanerva *et al*., (1999) at the Section of Dermatology, Finnish Institute of Occupational Health, Helsinki, Finland reviewed the results of patch tests performed over a 6 year period on patients with a suspected occupational skin disease. A total of 1,422 patients were tested with a standard series containing paratertiary butylphenol formaldehyde resin (1% pet.) (Chemotechnique Diagnostics). Patch testing was conducted with 2 days occlusion and 3 readings on days 2, 3 and 4-6. Allergic reactions were scored according to ICDRG recommendations. 1+ and above were considered positive.Sixteen patients (1.1%) showed positive reactions.

During the years 1989 to 1996, a total of 373 patients with suspected contact allergy presenting to the Dermatology Clinic at Tawam Hospital, Al Ain, United Arab

Emirates were patch tested with the European standard series from either Trolab or TRUE Test (Pharmacia). Of these, 86 (23.1%) were atopic. Patch test were applied for 2 days and reactions read at patch removal and one day later.A total of 28 (7.5%) tested positive to paratertiary butylphenol formaldehyde resin (1% pet.). The severity of reactions was not stated. On a percentage basis, twice as many patients reacted to the paratertiary butylphenol formaldehyde resin in the TRUE Test series compared to the Trolab series. However, these comparative results were not statistically significant (Lestringant *et al*., 1999).

Trattner *et al*., (2002) patch tested 244 patients with suspected contact dermatitis aged between 12 to 80 years between January 1977 and December 2000 using the European standard series (Chemotechnique Diagnostics). The tests were conducted at the Contact Dermatitis Clinic of the Rabin Medical Centre, Tel Aviv University, Israel. Patches were removed after 2 days and readings were made on day 2 and 3 as recommended by the ICDRG. Two (0.8%) showed a positive reaction to paratertiary butylphenol formaldehyde resin 1% in pet.

Ciconte *et al*., (2001) at the Skin and Cancer Foundation, Carlton, Victoria, Australia retrospectively examined the records of 817 consecutive patients patch tested between April 1988 and January 1993. Allergens were supplied by either Chemotechnique Diagnostics or Hermal. Of the 817 patients, 316 were considered to have clinically relevant reactions ie. reactions for which a history of prior exposure to the chemical was possible. Of those 316, four (1.7%) reacted positively to paratertiary butylphenol formaldehyde resin (1%, vehicle not stated).

In order to determine the usefulness of sodium laury sulfate in interpreting weak allergic reactions, from 1 July 1996 to 30 June 2001, patients presenting to a number of dermatology clinics in Germany were assigned to be patch tested with sodium lauryl sulfate and a range of allergens, or with the allergens alone at the Department of Dermatology, Dortmund. Patch testing was conducted to international guidelines (Wahlberg, 2001). Patches were placed for 2 days and results read on days 2 and 3 according to ICDRG recommendations with slight amendments by the German Contact Dermatitis Research Group. Of a total of 1536 patients patch tested with paratertiary butylphenol formaldehyde resin (1% pet.) (Hermal, Reinbek, Germany) with or without SLS, 1.2% showed a positive response (Geier *et al*., 2003).

Case Reports

Kalimo *et al*., (1980) describe a 46-year old non-atopic female who presented with breathing difficulties and loss of voice after working with glass wool. She was positive to paratertiary butylphenol formaldehyde resin (1% pet.) from the European standard series (Trolab).

Following a positive patch test to a glue 14 years earlier, a 41-year old man developed dermatitis on his hand. ICDRG patch testing gave a positive response to paratertiary butylphenol formaldehyde resin (concentration and vehicle not stated) (Dahlquist, 1984).

Two patients presenting with dermatitis from a leather watch strap and leather shoes respectively were patch tested with paratertiary butylphenol formaldehyde resin (1%

pet.). Both returned positive results (Fisher, 1987). Another patient who worked in a beauty salon applying artificial nails presented with a dermatitis on the fingertips after using an adhesive to affix the nails. Patch testing with paratertiary butylphenol formaldehyde resin (5% pet.) was positive (Fisher, 1987a).

Two patients are reported as showing a positive response to patch testing with paratertiary butylphenol formaldehyde resin 1% in pet (Trolab). The paper however is in Japanese and further details cannot be elicited (Kaniwa *et al*., 1991).

Massone *et al*., (1991) describe the case of a 44-year old female who developed dermatitis on the foot at the site where a orthopaedic foot support was worn. She showed a positive response to paratertiary butylphenol formaldehyde resin 1% in pet from the GIRDCA standard series.

From an English abstract of a paper in Japanese, allergic contact dermatitis is reported in a 35-year old female who drew on her skin with a marker pen repeatedly over two days. She showed a positive reaction to paratertiary butylphenol formaldehyde resin. No other details could be elicited (Nakagawa *et al*., 1991).

Shono *et al*., (1991) report five cases of contact dermatitis, four in schoolgirls and one in a 38-year old female. The schoolgirls gave no history of atopy and no information on atopic status is given for the 38 year old. All patients showed a positive response in patch testing to paratertiary butylphenol formaldehyde resin 1% in pet (Trolab).

A 53-year old female with no history of atopy was patch tested with the European standard series and a shoe series without results. Twenty-three days following testing a strong positive reaction was found at a test area previously tested with paratertiary butylphenol formaldehyde resin 2% in pet. Retesting with the shoe series was positive to paratertiary butylphenol formaldehyde resin 2% in pet but again the reaction took 21 days to develop. The authors conclude this was a case of active sensitisation by the initial patch test (Chalidapongse & Aldridge, 1992).

Angelini *et al*., (1993) describe a 21-year old female patient who presented with dermatitis around the margin of the lips following use of a lip liner pencil. Patch testing with the TRUE Test panel of allergens showed a positive response to paratertiary butylphenol formaldehyde resin. Patch testing with the pure substance at 2% was also positive. The lip liner was extracted in n-hexane and the presence of paratertiary butylphenol formaldehyde resin confirmed by GC-MS. The authors comment that the resin is not commonly used in cosmetics.

A 67-year old female was seen at a dermatology clinic with an eight month history of dermatitis of the ear in which she wore a hearing aid. Patch testing with paratertiary butylphenol formaldehyde resin 1% in pet was positive (Matrolonardo *et al*., 1993).

A 53-year old non-atopic female developed a dermatitis on the hand at the site of an adhesive dressing. Patch testing with the European standard series gave a positive reaction to paratertiary butylphenol formaldehyde resin 1% in pet (Burden AD *et al*., 1994).

Hagdrup *et al*., (1994) report the case of a 13-year old boy who developed dermatitis on the hand following using a marking pen. He was patch tested using the European standard series (Hermal) and responded positively to paratertiary butylphenol formaldehyde resin 1% in pet.

On two occasions after wearing a knee brace and later a raincoat, a 32-year old male presented with a dermatitis. Patch testing with paratertiary butylphenol formaldehyde resin 1% in pet was positive (Hayakawa *et al*., 1994).

Kaniwa *et al*., (1994) patch tested 5 patients with suspected allergic contact dermatitis using a number of chemicals. Of these, one patient, a 14-year old female was positive to paratertiary butylphenol formaldehyde resin 1% in pet (Nichiban).

A 22-year old female presented with a dermatitis around the foot and ankle. Patch testing with the European standard series and the shoe series (Chemotechnique) showed a positive reaction to paratertiary butylphenol formaldehyde resin 1% in pet (Lee *et al*., 1995).

Downs and Sansom, (1997) report six cases of patients testing positive in patch testing to paratertiary butylphenol formaldehyde resin. Five were non-atopic. No details on the atopic status of the remaining patient were given.

Eight cases of dermatitis on the buttocks and hip areas of infants aged 9 months to 4 years are reported. In patch testing with the European standard series, 3 patients showed a positive response to paratertiary butylphenol formaldehyde resin 1% in pet (Roul *et al*., 1998).

A 51-year old female with a 1.5-year history of dermatitis of the wrist in an area in contact with a watch strap attended a dermatology clinic. Patch testing with the European standard series was positive for paratertiary butylphenol formaldehyde resin 1% in pet (Ozkaya-Bayazit, 2001).

A case of active sensitisation to paratertiary butylphenol formaldehyde resin 1% in pet is reported (Arpa *et al*., 2002). The patient, a 32-year old nurse presented with hand dermatitis and was patch tested with the Grupo Español Investigacion Dermatitis de Contacto (GEIDC) standard series. Results were negative but after 5 weeks an erythematous macule appeared on her back at the site corresponding to paratertiary butylphenol formaldehyde resin. Re-testing with paratertiary butylphenol formaldehyde resin 1% in pet was positive. The authors conclude that the patient was sensitised by the initial patch test.

Three patients presenting with localised contact dermatitis on the trunk were patch tested with the European standard series (Trolab). The dermatitis corresponded to the sites where ECG electrodes had been applied. Two patients had no history of atopy and no details were provided on the atopic status of the third. All three showed a positive response to paratertiary butylphenol formaldehyde resin shown to be present in the ECG adhesive and electrode (Avenel-Audran *et al*., 2003).

Other Studies

None

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 4 positive reactions for this chemical out of 1,500 workers (2.7%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 2 cases for this chemical out of a total of 6,067 cases (0.03%). The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Evidence for sensitisation for paratertiary butylphenol formaldehyde resin in this assessment is based substantially on human data. A single animal study showed histological evidence of sensitisation in 75% of animals. Unfortunately, no further details were provided regarding the histological data on which the positive results were based. The robustness of the results from this non-standard study could not be determined and no reliable conclusion could be drawn.

Sensitisation to paratertiary butylphenol formaldehyde resin was first described in 1958 (Angelini *et al*., 1993) and it is now included in standard patch test series. Results from large scale patient surveys show positive reactions to the paratertiary butylphenol formaldehyde resin as presented in patch test series. The positive results range from 0.2% up to 7.5% with an average of approximately 2%. In contrast, one single Australian survey in a small number of patients (55) found sensitisation in 20% of patients (Freeman, 1997). A number of case reports are also found in the literature regarding sensitisation to paratertiary butylphenol formaldehyde resin.

Overall, these positive patch test results are observed in subsets of patients presenting to dermatological clinics as a result of preexisting episodes or histories of contact dermatitis. Given the likelihood of widespread use and likely exposure of a large proportion of the general population to this chemical, episodes of sensitisation as a percentage of the general population are likely then to be much smaller. Overall, the sensitisation rate in humans appears to be small and insufficient to meet the NOHSC Approved Criteria with regards to practical experience of sensitisation in a substantial number of persons.

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Sodium metabisulfite

Chemical Identification

Chemical Name:	Disulfurous acid, disodium salt
CAS #	7681-57-4
Synonyms:	Sodium metabisulfite; Sodium disulfite; disulfurous acid; disodium salt; disodium pyrosulfite; disodium disulfite
Use:	Sodium metabisulfite is used as an antioxidant preservative in the food, cosmetic, and drug industries (Vena *et al.*, 1994).

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

A 10-day repeated epidermal application study in guinea pigs outlined in the SIDS Initial Assessment Report (SIAR) for this chemical indicated that sodium metabisulfite is non-sensitising. The SIAR reported that this non-standard study by Eastman Kodak Company was not well documented (SIAR, 2001). None of the 10 guinea pigs reacted positive, however, some irritation was noted. Hence, it was concluded that disodium disulfite (also called sodium metabisulfite) is not sensitising. The original study (TSCATS, 1994) has not been sighted.

Human Evidence

Surveys

Angelini *et al*. (1997) patch tested 980 eczematous patients with sodium metabisulfite (1% pet.). Of those tested 1.4% (i.e. 14 patients) reacted positive to sodium metabisulfite. While presenting original data this article did not contain a detailed methodology or results section.

Within a two-year period 2,894 consecutive eczematous patients (953 males & 1,941 females) were patch tested with sodium metabisulfite in an Italian dermatological clinic (Vena *et al.*, 1994). The patients were patch tested with a modified European standard series, which included sodium metabisulfite (1% pet.). Those with positive reactions to sodium metabisulfite were further tested with sodium sulfite (1% pet.), sodium bisulfite (1% pet. & 5% pet.) and potassium metabisulfite (1% pet.). All sulfites for patch testing were obtained from Sigma Chemical (St. Louis, Missouri, USA). Patch test results were read on days 2, 3, 4, and 7. Results indicated that 50 patients (i.e. 1.7%) were sensitised by sodium metabisulfite. The severity of reactions was not stated. All 50 of these patients (24 females and 26 males) were also sensitised by potassium metabisulfite and sodium bisulfite. However, only 2 of these patients were sensitised by sodium sulfite. Of those reacting positive to sodium metabisulfite, 6 had a family history of atopy and 4 had a personal history of atopy. Out of the 50 positive cases only 7 were occupationally related (i.e. hand lesions with a positive history of contact with the chemical). No irritable reactions to sodium metabisulfite

were seen in any of the patients. Prick tests and intradermal tests with sodium metabisulfite solution (10 mg/ml) were negative in all of 20 patients tested (12 males and 8 women). This study is cited in a recent Cosmetics Ingredient Review of sodium metabisulfite (Nair & Elmore, 2003).

In a study looking at cumulative irritancy of topical corticosteroid formulations, 2 out of 50 subjects were inadvertently sensitised (both with ++ reactions) by sodium metabisulfite (Heshmati & Maibach, 1999). This study was conducted at the Department of Dermatology, University of California, USA. One percent hydrocortisone contained an unspecified concentration of sodium metabisulfite. Following an edematous patch test result to a 1% hydrocortisone formulation (sodium metabisulfite concentration not stated), individual ingredients were tested. The patch test results were read on days 2 and 4. Two subjects reacted positive to sodium metabisulfite (1% pet.). As irritancy controls, 20 volunteers were patch tested with sodium metabisulfite (5% pet.). Slight erythema was seen on day 2, but not on day 4. The authors failed to mention the number of subjects exhibiting erythema with sodium metabisulfite (5% pet.).

Case Reports

A 39-year old male baker presented to a Portugal dermatological clinic with dermatitis on the back of his hands and fingerwebs (Apetato & Marques, 1986). At work he handled dough containing approximately 0.04% sodium metabisulfite. The patient was patch tested with the Portuguese standard series, benzoyl peroxide and sodium metabisulfite (2, 5 and 10% aq.). The patient reacted positive to sodium metabisulfite. The severity of reactions was not stated. Additional control tests with sodium metabisulfite (10% aq.) in five subjects were negative. No further details regarding methodology were provided.

Several case studies report allergic reactions following injection of sodium metabisulfite containing solution during dental procedures. A 40-year old woman developed severe edema of the face and neck after receiving a local anesthetic from her dentist (Dooms-Goossens *et al.*, 1989). Neo-lidocaton™ a local anaesthetic contained 0.2% sodium metabisulfite. Hence, the patient was later patch tested at the dermatological clinic of the University Hospital Katholieke (Belgium) with the standard series, Neo-lidocaton (Pharmaton SA, Belgium) and sodium metabisulfite (5% pet.). While there was no reaction at 30 min, a positive reaction (++) was seen for both Neo-lidocaton and sodium metabisulfite at 48 and 96 hours. The authors speculated that the patient had an allergic reaction with features of both type I and type IV reactions.

Fisher (1989) reported a case where a 46-year old atopic woman developed severe asthma and urticaria as a result of receiving an injection of procaine (Novocain®) containing sodium metabisulfite. This patient also reacted to carbocaine, also known to contain sodium metabisulfite. Intradermal tests with both anesthetics produced a large urticarial wheal. A response was not seen in three non-asthmatic control subjects. A 48-hour patch test with sodium metabisulfite (2% pet.) was negative. No other information on the test protocol was provided.

A 37-year old female photographic processing technician developed asthma-like symptoms whenever she went close to the machine that mixes and heats the processing chemicals (Jacobs & Rycroft, 1995). Although she had no history of childhood atopy, she had a mild eczema on her upper arms. Since starting work the eczema has worsened. Prick test results to common allergens were negative. She was then patch tested with European standard series, photographers' series and her own samples. No further details regarding methodology were provided. The patient reacted positive only to sodium metabisulfite (5% pet.). The severity of the reaction was not stated. Material data sheets indicated that some of the photographic chemicals included sodium sulfite and potassium sulfite. The authors stated that sodium metabisulfite contained some sodium sulfite and sodium sulfate.

In a letter to the editor, Levanti *et al*. (1996) reported a case where a 51-year old woman developed burning mouth syndrome after undergoing a dental intervention. Since an allergen was suspected, a prick test with lidocaine was performed according to the protocol suggested by the Italian Society of Allergy and Clinical Immunology (SIAIC). Given the prick test was negative, patch tests were done with the GIRDCA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali) standard series, acrylate series, dental series, and spices and food additive series. When results were read at 72 hours, a positive reaction to sodium metabisulfite (5% pet.) was observed. The severity of the reaction was not stated.

Tucker *et al*. (1999) reported two case studies where patients were allergic to sodium metabisulfite in Trimovate® (GlaxoSmith Kline) cream. In both cases, Trimovate was prescribed to treat existing dermatological conditions. The 26-year old patient was suffering from bilateral otitis externa while the 47-year old patient was suffering from perianal discomfort. The use of Trimovate cream exacerbated both their skin conditions. The two male patients were patch tested with the dermatological clinic's standard series, their own medicaments, Trimovate cream and sodium metabisulfite. Test results were read on day 2 and day 4. Both patients reacted positive to Trimovate (++ in 47-year old and + in 26-year old) and sodium metabisulfite (++ in 47-year old and + in 26-year old).

A 55-year old butcher with no prior history of atopy developed pruritic, erythematous scaly plaques on the perianal area and on the upper limbs after using Hubber® antihemorrhoidal cream containing sodium metabisulfite (Sanchez-Perez *et al*., 2000). On presenting to a Spanish dermatological clinic, the patient was patch test with the Grupo Español Investigacion Dermatitis de Contacto (GEIDC) standard series, Hubber antihemorrhoidal cream, and its components. The results were read on day 2 and 4. The patient reacted positive to neomycin sulfate (20% pet.; ++), promethazine (1% pet.; ++); propylparaben (3% pet.; ++) and sodium metabisulfite (2% pet.; ++). Patch tests with sodium metabisulfite (2% pet.) in 37 normal controls were negative.

23-year old baker presented to the occupational dermatology service of Monash Medical Centre (Victoria, Australia) with an 8-month history of a rash (Lee & Nixon, 2001). Her rash involved the left ventral wrist and both dorsal surface of hands. The patient had a history of asthma and hay fever. She was patch tested with a modified European standard series, a cosmetic series, bakery allergens, diallyl disulfide, sodium metabisulfite and her own samples. The results were read on day 2 and 5. The patient reacted positive to sodium metabisulfite (1% pet.) and dodecyl gallate (0.25% pet.).

The severity of the reaction was not stated. Prick tests to her flours, spices and foods were negative.

A 75-year old woman developed widespread eczematous eruptions over the face, eye lids, back and upper arms after using Trimovate® (GlaxoSmith Kline) cream containing sodium metabisulfite (Harrison & Smith, 2002). She had a past history of asthma, and possible sensitisation with chloramphenicol eye drops. The patient was patch tested with European standard series, medicaments series, Trimovate cream and ingredients of Trimovate. She reacted positive to Trimovate, and clobetasone butyrate (0.5% & 1% pet.) and sodium metabisulfite (as is, 0.1% aq., 2% pet. & 5% aq.) also in Trimovate. No other information on the test protocol or the severity of the reaction was provided.

Other Studies

None

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 4 positive reactions for this chemical out of 1,500 workers (0.3%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 7 cases for this chemical out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains 0 cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

A single non-standard guinea pig study reported in the SIAR indicated that sodium metabisulfite is not sensitising (SIAR, 2001). However, this study was not well documented. No other animal studies on sodium metabisulfite were found.

While several dermatological clinics have reported that sodium metabisulfite causes skin sensitisation, many of these are single case reports (Apetato & Marques, 1986; Dooms-Goossens *et al.*, 1989; Fisher, 1989; Jacobs & Rycroft, 1995; Levanti *et al.*, 1996; Tucker *et al.*, 1999; Sanchez-Perez *et al.*, 2000; Lee & Nixon, 2001; Harrison & Smith, 2002). In fact, only two studies have examined the frequency of sodium metabisulfite-induced sensitisation (Vena *et al.*, 1994; Angelini *et al.*, 1997). Both studies reported low sensitisation rates with sodium metabisulfite. Furthermore, Vena *et al*. (1994) reported that only 7 out of 50 patients sensitised by sodium metabisulfite were occupationally relevant. Given that sodium metabisulfite is extensively used as an antioxidant in the food, cosmetic, and drug industries (Vena *et al.*, 1994; Harrison

& Smith, 2002) the number of cases of sensitisation seen to date is relatively small. In view of its widespread use, a substantial number of people are not sensitised by this chemical.

While there is some possibility of cross-sensitisation with sodium sulfite, sodium bisulfite, potassium sulfite, and potassium metabisulfite (Vena *et al.*, 1994; Jacobs & Rycroft, 1995) this has not been conclusively shown.

The draft SIAR report on disodium disulphite (CAS: 7681-57-4; also called sodium metabisulfite) indicates that this chemical is not a sensitiser. This conclusion was also reached by the Cosmetics Ingredient Review (Nair & Elmore, 2003) and The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP, 2003).

The weight of evidence suggests that data for sodium metabisulfite does not meet the guidelines for skin sensitisation under NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Triethyleneglycol dimethacrylate

Chemical Identification

Chemical Name:	2-Propenoic acid, 2-methyl-, 1,2-ethanediylbis(oxy-2,1-ethanediyl) ester
CAS #	109-16-0
Synonyms:	Triethyleneglycol dimethacrylate (TREGDMA); Polyglycol dimethacrylate; TEDMA
Use:	Used in dental composite resin materials (Björkner, 1984). TREGDMA used in sealants and artificial nails (Hemmer *et al.*, 1996; Geukens & Goosens, 2001). TREGDMA has wide industrial use (Hemmer *et al.*, 1996). Methacrylates in general are used in paints, lacquers, varnishes, resins, glues, coatings and adhesives (Geukens & Goosens, 2001). Methacrylates are also used in engineering, electronics and other metal manufacturing industries (Conde-Salazar *et al.*, 1988).

Evidence for Sensitisation Properties

Animal Studies (Standard and Non-Standard)

Björkner (1984) studied the sensitising capacity of commonly used multifunctional acrylates in guinea pigs. TREGDMA was obtained from Koch-Light Laboratories Ltd. (England) and Freund's Complete Adjuvant was purchased from Difco Laboratories (USA). Albino Dunkin-Hartley guinea pigs (female) weighing 300–400g were used for the study. Both the treatment group and control group had 15 animals. The test was conducted according to previously published methods (Magnusson & Kligman, 1969; Magnusson & Kligman, 1970). A pilot study was done with 3 animals to determine the optimal intradermal and topical induction concentrations. 1% w/w TREGDMA (in olive oil/acetone) was used for the intradermal injection. After pre-treatment with 10% sodium lauryl sulphate (in petrolatum) a topical induction patch containing 50% TREGDMA (in pet.) was applied to the test site. The guinea pigs were challenged with a patch containing 1% TREGDMA (in pet.). After one week the animals were rechallenged with other acrylates to determine cross-sensitisation. Only 1 out of 15 animals (i.e. 6.6%) were sensitised by TREGDMA (in pet.). To be considered a sensitiser, the NOHSC Approved Criteria requires a positive response in at least 30% of the animals using an adjuvant type test method. There was no cross-sensitisation between TREGDMA and 1,4-butanediol diacrylate, 1,6-hexanediol diacrylate, triethylene glycol diacrylate, 1,4-butanediol dimethacrylate or ethylene glycol dimethacrylate. Although there was no mention of a standard positive control, neopentyl glycol diacrylate caused sensitisation in 100% of animals.

Parker and Turk (1983) studied the sensitising potential of acrylate compounds in guinea pigs. The Polak method was used to sensitise the outbred Hartley guinea pigs (400–500 g) to TREGDMA. On day 0, the animals received 4 injections to the

footpad of 0.1 ml of TREGDMA (2 mg/ml in ethanol: saline (1:4)) in Freund's Complete Adjuvant (FCA). An additional 0.1 ml injection of TREGDMA in FCA was given into the nape of the neck. A total of 1 mg of TREGDMA was administered. On day 7, open skin tests were conducted with 0.02 ml of TREGDMA (5% in acetone: olive oil (4:1) or the maximum concentration that did not give irritation) on the shaved flank. These open tests were repeated every week for 12 weeks. The authors reported that TREGDMA was not a skin sensitiser using this Polak method. The number of animals used to test TREGDMA is not stated, however, 6–15 animals were used to test other acrylates that did cause sensitisation. The authors found that the Polak method was more sensitive in determining sensitisation to acrylates than their modified Magnusson and Kligman guinea pig maximisation test (Parker & Turk, 1983). TREGDMA was not tested with their modified guinea pig maximisation test.

Björkner (1984) reported that guinea pigs were sensitised with TREGDMA according to the Magnusson and Kligman method by Cavelier *et al*. (1981). Since the Cavelier *et al*. (1981) paper was written in French it was not possible to interpret the results.

Human Evidence

Surveys

Seventeen instructors and 14 students from a dental school were patch tested with TREGDMA and other dental materials at the Department of Dermatology, Osaka Kaisei Hospital, Japan (Oshima *et al*., 1991). All subjects were healthy males (average age 30.8 years) with no history of allergy or contact dermatitis. The authors reported that the concentrations and vehicles of patch test materials were as stated in previous literature. Patch tests were done according to International Contact Dermatitis Research Group (ICDRG) guidelines. Results were read according to the Japanese standard method on days 2 and 3. None of the subjects (i.e. 0%) reacted positive to TREGDMA.

During 1985–1992, 10,280 patients presenting to the dermatological clinic of the University Central Hospital (Finland) were patch tested with the standard series (Epikon Oy, Finland) (Tarvainen, 1995). Some patients were also tested with other series when required. A total of 839 patients were tested with plastics and glues series (Epikon Oy, Finland; Chemotechnique Diagnostics AB, Sweden; Hermal, Trolab, Germany). Given that the composition of the plastics and glues series was changed in 1988, not all patients were tested with all the allergens in the series. Prior to 1988, patches were applied for 1 day but increased to 2 days thereafter. Patch test results were read on days 2, 3 and 4 according to the Finnish Contact Dermatitis Group. Only reactions greater than + were considered positive. Of the 839 patients tested, 52 patients had allergic reactions and 115 had irritant reactions. Fifteen patients with allergic reactions were atopic. Out of 343 patients patch tested with TREGDMA (2% in pet.; Chemotechnique Diagnostics AB), 2 patients (i.e. 0.6%) reacted positive. Both these reactions were clinically relevant (i.e. having a prior history of the patient being exposed to TREGDMA**)**.

Between January 1990 and July 1993, 59 dental technicians and 732 other patients were patch tested with the denture material series at the clinics of the Information Network of Departments of Dermatology (IVDK) (Gebhardt & Geier, 1996). Patch tests were conducted according to the guidelines of the ICDRG and the German

Contact Dermatitis Research Group (DKG). All allergen were obtained from Hermal, Reinbek, Germany. Patches were applied for two days and the results read on two occasions within 3 days. Out of the 59 dental technicians, 27 were diagnosed with allergic contact dermatitis and 10 with irritant contact dermatitis. In 31 dental technicians, their dermatosis was occupational in nature. Out of 41 dental technicians, 2 (i.e. 4.9%) reacted positive (+ reaction) to TREGDMA (2% in pet.). Of the 732 other patients, 137 patients were diagnosed with allergic contact dermatitis and 45 with irritant contact dermatitis. In 64 patients, their dermatosis were occupational in nature. Out of 724 patients, 2 (i.e. 0.3%) reacted positive (1+ & 1++ reaction) to TREGDMA (2% in pet.). Of all 765 patients, only 0.5% of patients reacted positive to TREGDMA.

Between January 1990 and June 1993, 1,184 patients presenting to the Nofer Institute of Occupational Medicine in Poland were patch tested with the Polish standard series (Kiec-Swierczynska, 1996). From July 1993 to December 1994, 435 patients were patch tested with the European standard series (Chemotechnique Diagnostics, Sweden). Twenty-three patients exposed to acrylates were further tested with the methacrylate series (Chemotechnique Diagnostics). Patches were applied for 2 days and results read on days 2 and 3. Reactions ≥ 1+ were considered positive. Of the 1,619 patients, 332 were diagnosed with occupational allergic contact dermatitis. Nine patients were allergic to one or more substances in the methacrylate series with 4 patients reacting positive (3 +++ and 1 + reactions) to TREGDMA (2% in pet.). All 4 reactions were occupational in nature with three of these patients being dentists and the other a dental technician. While 4 out of 23 patients tested with the methacrylate series reacted to TREGDMA (2% in pet.) it must be noted that these patients were pre-selected from 1,619 patients over a 5-year period.

Andersen *et al*. (1996) studied the stability and the homogeneity of some allergens stored at the Allergen Bank in Denmark. These authors also reported some of the statistics relating to the most frequently ordered allergens from the Allergen Bank. The Allergen Bank has been in operation from February 1992 and during the first 23 months, 2,209 allergens were ordered to patch test 386 patients. A total of 164 positive reactions were reported to the Allergen Bank. With 18 orders, TREGDMA was one of the 16 most ordered allergens within this period. Two positive reactions (i.e. 11.1%) to TREGDMA (2% in pet.) were reported to the Allergen Bank. Given that the Allergen Bank did not conduct any of the tests themselves, a patch test protocol was not included.

Munksgaard *et al*. (1996) investigated the causes and prevalence of occupational dermatitis in Danish dentists. In 1993, a group of 3,257 Danish dentists were randomly drawn from the membership registers of the two Danish dental organisations (Dansk Tandlægeforening and Tandlægernes Nye Landsforening). This random selection represented 69.4% of all practicing Danish dentists. A questionnaire was either mailed or personally delivered to each subject. A total of 2,208 dentists responded to the questionnaire. Out of the 834 dentists reporting dermatological reactions, 787 were contacted by telephone. Of the 834 dentists that reported skin reactions, 601 dentists stated that their skin reactions were occupational in nature. 146 dentists thought that their dermatological condition was due to contact with (di)methacrylate-containing materials. Fifteen dentists (of 2,208 dentists; i.e. 0.68%) reported that they were clinically diagnosed with (di)methacrylate allergy. In 13

dentists, the dermatological condition was due to methylmethacrylate (MMA), 2-hydroxyethylmethacrylate (HEMA), di-ethyleneglycol-dimethacrylate and TREGDMA. The actual number of dermatological cases caused by TREGDMA is not stated.

Santosh *et al*. (1999) reported patch test results from 31 patients tested with 12 dental allergens (Chemotechnique Diagnostics AB, Sweden). The patients (19 males and 12 females) were tested at the Department of Skin & STD of the Kasturba Medical College & Hospital, Manipal, India between January 1990 and July 1998. Thirty patients had an allergic aetiology with lesions of the buccal mucosa and/or of the lips. Patch tests were read on day 2 according to the ICDRG recommendations. Reactions greater than or equal to 1+ were considered positive. Of the 31 patients, 2 (i.e. 6.5%) reacted positive to TREGDMA (conc. and vehicle not stated). Severity of these reactions was not stated. It must be noted that these 31 cases occurred over 8.5 years. The total number of patients seen at the clinic was not stated.

A retrospective study analysed 14,000 patch test results obtained between January 1983 and March 1998 at the dermatological clinic of Hope Hospital (UK) (Tucker & Beck, 1999). Records of those patients patch tested with (meth)acrylates (Chemotechnique Diagnostics AB, Sweden) were further analysed. Patches were applied for 2 days and reading taken on days 2 and 4. Of 343 patients patch tested, 21 patients (i.e. 6.1%) reacted positive to TREGDMA (2% in pet.). It is uncertain whether these reactions were clinically relevant. Severity of these reactions was not stated. These cases have been collected over a 15-year period.

Between 1 January 1978 and 31 December 1999, 13,833 patients presenting to the Department of Dermatology at the Katholieke Universiteit Leuven (Belgium) were patch tested with various trays of allergens (Geukens & Goosens, 2001). Patches were applied for 2 days and results read on days 2 and 3 or 4. Contact allergy to one or more substances was found in 7,369 patients (i.e. 53.3 %). Fifty-four patients had a positive reaction to 1 or more methacrylates. In 31 patients, the positive reactions to methacrylates were occupational in nature. Only 6 patients had positive reactions to TREGDMA (2% in pet.). None of these reactions were occupational in nature. It is not certain whether all 13,833 patients were patch tested with TREGDMA (2% in pet.).

Kiec-Swierczyńska and Krecisz (2002) studied the incidence of allergic contact dermatitis in dentists and dental nurses. Between 1990 and 2000, 79 dentists (72 female and 7 male) and 46 dental nurses (male) with suspected contact dermatitis were patch tested with the European standard series, dental screenings series and additional allergens at the Nofer Institute of Occupational Medicine, Poland. Some patients were additionally patch tested with the rubber additives, fragrances, plastic and glues, (meth)acrylates and the epoxy series (Chemotechnique Diagnostics AB, Sweden). Patches were applied and read according to the guidelines of the ICDRG. Of 79 dentists patch tested, 12 reacted positive to TREGDMA (2% in pet.). Of the 46 dental nurses, none reacted positive to TREGDMA (2% in pet.). In patients, the incidence of TREGDMA-induced sensitisation is 9.6% (i.e. 12 out of 125 patients). These reactions are likely to be clinically relevant as TREGDMA is used to fill carious defects in teeth.

Patch tests were done on patients presenting to the Department of Dermatology of Toho University (Japan) with atopic dermatitis, contact dermatitis, lichen planus and other form of dermatitis (Washizaki, 2003). Between January 1996 and December 2000, 334 patients were patch tested with 11 dental materials. Patch tests were read at 72 hours according to ICDRG guidelines. Reactions greater than "+" were considered positive. Of the 334 patients tested, 0.8% of patients reacted positive to TREGDMA (2%; vehicle not stated). Only the abstract of this paper was available in English.

Case Reports

A 71-year old dentist presented to the Department of Dermatology of the University of Milan (Italy) with dermatitis of the fingers (Riva *et al*., 1984). The dentist was patch tested with ICDRG standard series, 1% methyl methacrylate, 0.5% benzoyl peroxide (Hollister-Stier) and dental materials Concise® and Silar®. The vehicles were not stated. The patches were applied for 48 hours. The patient reacted positive only to Concise® and Silar®. No positive reactions were observed in 10 control subjects. The authors speculated that the patient was allergic to TREGDMA even though the patient was not tested for TREGDMA-induced sensitisation.

Condé-Salazar *et al*. (1988) reported six cases of occupational allergic contact dermatitis induced by acrylates in sealants. Two mechanics and 4 workers on a car assembly line presented with pruritic papulo-vesicular lesions on their fingertips. The patients were patch tested with the Grupo Español de Investigación Dermatitis de Contacto (GEIDC) standard series and acrylate series at the Instituto Nacional de Medicina y Seguridad del Trabajo, Spain. They were also patch tested with the sealants themselves. The patients were patch tested according to the GEIDC recommendations. The patches were applied for 48 hours and read on days 2, 3 and 4. While all patients reacted positive to sealants only one patient reacted to TREGDMA (1% in pet.; ++ reaction). The patient was also allergic to the other acrylates such as ethyl methacrylate monomer (10% in pet.; + reaction) and hydroxyethyl methacrylate (2% in pet.; +++ reaction). This patient was 1 of 80 workers (i.e. 1.3%) using the sealant in a car assembly line. The factory had a 1,400 work-force.

Kanerva *et al*. (1989) reported 7 cases of allergic contact dermatitis to dental composite resin products. All cases were occupational in nature with 6 being dental nurses and the other a dentist. Three patients had a personal history of atopy and 2 others had a family history of atopy. All seven patients (female) had eczema on the hand and fingers. The patients were patch tested at the dermatological clinic of the Institute of Occupational Health, Finland. Patches were applied for 24 hours and 3 readings were taken according to the recommendations of the Finnish Contact Dermatitis Group. Of the five patients patch tested with TREGDMA (2% in pet.) the dentist and two other dental nurses reacted positive (2+, 3+ and 4+ reactions, respectively). With these patients showing positive reactions to several other (meth)acrylates (eg. 2-hydroxyethyl methacrylate and 2-hydroxypropyl methacrylate) and epoxy resin the authors speculated regarding possible cross-sensitisation.

A 67-year old woman with dermatitis of both ears and nose presented to the Department of Dermato-Venereology at the University Hospital Rotterdam (The Netherlands) (Dutree-Meulenberg *et al*., 1991). She was wearing "hearing glasses"

(i.e. hearing aid glued to both sides of the spectacle frame) repaired with an acrylate resin called Sonopal. Within a day of the repair she had severe itching and acute weeping eczema. The patient was patch tested with the European standard series and the materials used in the manufacture of the "hearing glasses". No other detail was presented on the test protocol. The patient reacted positive to cobalt chloride (1% in pet.; ++ reaction), formaldehyde (1% in aq.; ++), scrapings of spectacle (as is; ++), scrapings of hearing aid (as is; ++), scrapings of hearing aid adaptor (as is; +++) and Sonopal (50% in pet.; +++). Following the patch tests, the "hearing glasses" were coated with Sillac (S)-glass coating. However, she again developed acute weeping dermatitis 4 weeks later. When patch tested again the patient reacted positive to Sillac (S)-glass coating (as is; +++), ethylene glycol dimethacrylate (2% in pet.; ++), diethylene glycol diacrylate (0.1% in pet.; ++), triethylene glycol diacrylate (0.1% in pet.; ++), urethane diacrylate (0.1% in pet.; ++) and TREGDMA (2% in pet.; +). Once "hearing glasses" were replaced completely, the patient was free of symptoms.

A 39-year woman presented to the Department of Dermatology at the Gentofte Hospital (Denmark) with oedema, erythema and ulceration of the mucosa of the upper lip (Agner & Menné, 1994). The symptoms occurred 24–48 hours after a visit to the dentist. A similar reaction occurred after a visit to the dentist 2 years earlier. The dental work involved maleic acid, 2-hydroxyethyl methacrylate (HEMA) and 2,2 bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)propane (BIS-GMA). When patch tested, a 3+ reaction to HEMA (conc. and vehicle not stated) and a 2+ reaction to TREGDMA (conc. and vehicle not stated) were observed. The authors speculated that the positive reaction to TREGDMA was probably due to cross-sensitisation with HEMA.

Five women with photobond acrylic nails presented to the Dermatologic and Pediatric Allergy Clinic at the Wilhelminen Hospital (Austria) as they were suffering from pruritic and painful perionychial and subonychial dermatitis (Hemmer *et al.*, 1996). The patients suffered from their conditions for several months. The dermatitis exacerbated when the artificial nails were renewed. One patient was occupationally exposed to acrylic nails as she worked as a manicurist. Patients were patch tested with a standard series, a special (meth)acrylate series, and other photoinitiators, inhibitors and aldehydes. Patch test readings were done on days 2 and 3 according to the recommendations of the ICDRG. None of the patients reacted positive to the photoinitiators, inhibitors and aldehydes. However, strong positive reactions (≥ ++ reactions) were observed in 4 out of 5 patients patch tested with TREGDMA (2% in pet.). All five patients reacted positive to 2-hydroxyethyl methacrylate (0.6% in pet.), 2-hydroxypropyl methacrylate (0.6% in pet.), ethyleneglycol dimethacrylate (2% in pet.) and urethane diacrylate (0.1% in pet.).

Kanerva *et al*. (1996) reported a case study where a 60-year old female dentist was allergic to several acrylates. She had worked as a dentist for 32 years and has worked with dental acrylics. She was patch tested at the Finnish Institute of Occupational Health, Finland. The results were read on days 2, 3 and 4. The test method was not reported any further. Patch tests to the European standard series, rubber chemical series, antimicrobial series and dental series were negative. However, she reacted positive to butyl acrylate (0.1%; 2+), ethyl acrylate (0.1%; 2+), methyl methacrylate (2%; 1+), ethyl methacrylate (2%; 2+), 2-hydroxyethyl methacrylate (2%; 3+), 2-hydroxypropyl methacrylate (2%; 2+), ethylene glycol dimethacrylate (2%; 2+),

tetrahydrofurfuryl methacrylate (2%; 1+) and TREGDMA (2%; 2+; vehicle not stated) in the (meth)acrylate series (Chemotechnique Diagnostics, Sweden). She also reacted positive (2+) to the dental products All-Bond 2 Pre-Bond Resin and Dentin Enamel Bonding Resin (1%; Bisco Dental Products, Illinois).

Estlander *et al*. (1996) reported 3 cases of skin sensitisation to methacrylates. One dental laboratory worker and a hearing aid laboratory assistant developed conjunctivitis in addition to fingertip dermatitis. The patients underwent patch testing with the European standard series, dental series and (meth)acrylate series (Chemotechnique Diagnostics AB, Sweden). The patch testing was done at the Finnish Institute of Occupational Health, Helsinki. The patients were also prick tested with a series of environmental allergens (Allergologisk Laboratorium A/S, Denmark), latex allergens, methylmethacrylate and 2-hydroxyethylmethacrylate. The investigation also included an ophthalmologist's examination. Conjunctival scrapings showed that both patients had lymphocytic reaction and activated eosinophils. The dental laboratory worker was atopic and was prick test positive to grass pollen, mugwort and house-dust mite. Although her family had atopic dermatitis the prick tests suggested that the hearing aid laboratory assistant was non-atopic. When patch tested, the dental laboratory worker gave a 3+ reaction and the hearing aid laboratory worker gave a 1+ reaction to TREGDMA (2% in pet.). Both patients reacted positive to several other (meth)acrylates. The third case was not discussed at all.

A 37-year old printer with a 4-year history of hand and periorbital dermatitis was patch tested at the Department of Dermatology, Queen's Medical centre, UK (Bong & English, 2000). The patch test methodology was not presented. The patient reacted positive to UV-cured varnish, 2-hydroxymethyl methacrylate, BIS-GMA and TREGDMA (concentration, vehicle and severity of the reaction were not stated). The patient later suffered from severe facial dermatitis after visiting a dental surgery. This was in spite of the dentist not using any compounds containing (meth)acrylate. The authors speculated that airborne exposure to acrylates at the dental surgery might have induced the allergic reaction.

Other Studies

None.

Occupational Health Database Entries

Occupational Dermatology Research and Education Centre (ODREC), Melbourne, 2003

ODREC report 4 positive reactions for this chemical out of 1,500 workers (0.3%) referred to ODREC for assessment.

Centre for Occupational and Environmental Health, University of Manchester, 1998-2002

The EPIDERM occupational skin surveillance database contains 4 cases for phenol resin out of a total of 6,067 cases. The Occupational Physicians Reporting Activity (OPRA) database contains no cases for this chemical out of a total of 838 skin cases, (0%), out of a total of 5,546 cases on the OPRA database.

Recommendation for Classification

Comment

Triethyleneglycol dimethacrylate and other multifunctional methacrylates have wide industrial uses (Björkner, 1984; Conde-Salazar *et al.*, 1988; Hemmer *et al.*, 1996; Geukens & Goosens, 2001). The above studies indicate that TREGDMA is used in dental composite resin products, sealants and artificial nails.

Björkner (1984) studied the sensitising capacity of triethyleneglycol dimethacrylate in guinea pigs. In the Magnusson and Kligman guinea pig maximisation test, only 1 out of 15 animals (i.e. 6.6%) were sensitised by TREGDMA (in pet.). To be considered a sensitiser the NOHSC Approved Criteria requires a positive response in at least 30% of the animals using an adjuvant type test method. Hence, results of this study suggest that TREGDMA is not a skin sensitiser. Using a non-standard adjuvant type test method, Parker and Turk (1983) also showed that TREGDMA is not a skin sensitiser in guinea pigs. The authors suggested that the Polak method utilised in this study is more sensitive in determining sensitisation to acrylates than their modified Magnusson and Kligman guinea pig maximisation test (Parker & Turk, 1983). Björkner (1984) reported that in an earlier study Cavelier *et al*. (1981) managed to sensitise guinea pigs with TREGDMA according to the Magnusson and Kligman method. However, it was not possible to confirm the results of this paper.

While several dermatological clinics have reported that TREGDMA causes sensitisation, a number of studies with patient numbers ranging from 31 to 765 indicated that the incidence is quite low (0–0.8%) (Oshima *et al.*, 1991; Tarvainen, 1995; Gebhardt & Geier, 1996; Washizaki, 2003). Santosh *et al*. (1999), Tucker and Beck (1999), and Kiec-Swierczynska and Krecisz (2002) reported a higher incidence of TREGDMA-induced sensitisation of 6.1-9.6%. However these are limited studies with small numbers of patients (31, 343 and 125 respectively). In the Santosh *et al*. (1999) study, only 2 patients were sensitised by TREGDMA over an 8.5-year period. Tucker and Beck (1999) found 21 positive cases over a 15 years period, and these were out of a pool of 14,000 patch test results. Similarly, Kiec-Swierczyńska and Krecisz (2002) found 12 positive cases over a 10-year period. As in the case of Tucker and Beck (1999), it seems that many of these studies had pre-selected their subjects from a much larger pool of patients with contact dermatitis. Hence, inflating incidence rates. Considering that TREGDMA is used in several industries, the number of reported positive cases are relatively small. Given that TREGDMA is found in several industries and in materials with a high human exposure potential ie. artificial nails and dental materials, there is a significant potential for human exposure to this chemical. In the case of artificial nails, only four cases of skin sensitisation to TREGDMA were reported.

While there is some suggestion of cross-sensitisation with other methacrylates such as 2-hydroxyethyl methacrylate and 2-hydroxypropyl methacrylate (Kanerva *et al.*, 1989; Agner & Menne, 1994), this has not been conclusively shown.

The weight of evidence suggests that the sensitisation rate for triethyleneglycol dimethacrylate is insufficient to satisfy the guidelines for skin sensitisation under NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

Conclusion

Data available for the assessment do not meet the criteria for classification as a hazardous substance with respect to Sensitisation by Skin Contact according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (1999).

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Appendix – Call for Information

Call For Information On Sensitiser Chemicals

NICNAS has been commissioned by the National Occupational Health and Safety Commission (NOHSC) to conduct an assessment of certain chemicals with clinical reports of occupational sensitisation.

The assessment will determine whether data for these chemicals are sufficient to meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* for skin sensitisation and on this basis whether the chemicals should be listed as hazardous substances with the risk phrase R43.

Presently, there are a number of chemicals reported by the Occupational Dermatology Research and Education Centre (ODREC) as common allergens in ODREC clinics that are not classified as sensitisers in the NOHSC *List of Designated Hazardous Substances*. Following an initial screening to exclude mixtures and non-industrial chemicals, NICNAS has determined that a detailed call for information and assessment are warranted for 20 individual chemicals that appear to have a clinical history of occupational dermal sensitisation.

NICNAS is seeking unpublished sensitisation toxicity data and information on any adverse incidents regarding sensitisation by skin contact associated with the following chemicals:

Common Name	AICS Chemical Name	CAS
Glyceryl monothioglycolate (GMTG)	Acetic acid, mercapto-, monoester with 1,2,3-propanetriol	30618-84-9
Coconut diethanolamide (Coco. DEA)	Amides, coco, N,N-bis(hydroxyethyl)	68603-42-9
Cobalt chloride	Cobalt(II) chloride, hexahydrate	7791-13-1
Germall II (Diazolidinylurea)	Urea, N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis(hydroxymethyl)-	78491-02-8
Dowicil 200 (Quaternium 15)	3,5,7-Triaza-1-azoniatricyclo[3.3.1.13,7]decane, 1-(3-chloro-2-propenyl)-, chloride	4080-31-3
Germall 115 (Imidazolidinylurea)	Urea, N,N''-methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-	39236-46-9
Wool alcohols (lanolin)	Alcohols, lanolin	8027-33-6

Cl+Me-isothiazolinone (Kathon CG)	3(2H)-Isothiazolone, 2-(chloromethyl)-	21277-94-1
2-Nitro-4-phenylenediamine	1,4-Benzenediamine, 2-nitro-	5307-14-2
N-Cyclohexylbenzothiazyl sulphenamide	1,4-Benzenediamine, N,N'-bis(1,4-dimethylpentyl)-	3081-14-9
Zinc dimethyldithiocarbamate (Ziram)	Zinc, bis(dimethylcarbamodithioato-S,S')-, (T-4)-	137-30-4
Amerchol	Alcohols, lanolin	8027-33-6
Basic Red 46	C.I. Basic Red 46	12221-69-1
Benzalkonium chloride	Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides	8001-54-5
Phenol formaldehyde resin (P-F-R-2)	Phenol, polymer with formaldehyde	9003-35-4
Toluenesulfonamide formaldehyde resin	Benzenesulfonamide, 4-methyl-, polymer with formaldehyde	25035-71-6
4-tert-Butylphenol formaldehyde resin (PTBP)	Formaldehyde, polymer with 4-(1,1-dimethylethyl)phenol	25085-50-1
Abietic acid	1-Phenanthrenecarboxylic acid, 1,2,3,4,4a,4b,5,6,10,10a-decahydro-1,4a-dimethyl-7-(1-methylethyl)-, [1R-(1a,4ab,4ba,10aa)]-	514-10-3
Sodium metabisulfite	Disulfurous acid, disodium salt	7681-57-4
Triethyleneglycol dimethacrylate	2-Propenoic acid, 2-methyl-, 1,2-ethanediylbis(oxy-2,1-ethanediyl) ester	109-16-0

Only skin sensitisation data are sought for these chemicals for assessment against the NOHSC Approved Criteria for this single endpoint.

Data should be submitted by 5 December 2003 to Dr Graham Harvey tel: (02) 8577 8851, fax: (02) 8577 8888, or email: graham.harvey@nicnas.gov.au. from whom further information can also be obtained.