ECETOC

Technical Report No. 77

Skin and Respiratory Sensitisers:

Reference Chemicals Data Bank

European Centre for Ecotoxicology
and Toxicology of Chemicals

Avenue E. Van Nieuwenhuyse 4, (Bte 6)
B-1160 Brussels, Belgium

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ISSN-0773-8072-77

Brussels, August 1999

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CONTENTS

1. INTRODUCTION

BACKGROUND

In susceptible individuals some chemicals cause skin sensitisation (allergic contact dermatitis), whereas others cause sensitisation of the respiratory tract (allergic asthma and/or rhinitis); identified in this report as chemicals with skin or respiratory sensitisation potential, respectively. These allergic diseases represent important occupational and consumer health problems and there is a need for reliable and accurate methods that permit the prospective identification of chemicals with sensitisation potential.

For many years guinea pig tests have formed the basis for toxicological evaluation of skin sensitisation potential. The best known of these are the guinea pig maximisation test and the occluded patch test of Buehler. These two tests, together with the five other guinea pig methods identified in OECD Guideline No. 406, Skin Sensitisation (OECD, 1992), have been reviewed earlier (ECETOC, 1990). The same report also reviewed alternative approaches for prospective testing for skin sensitisation and recommended the murine local lymph node assay (LLNA) and the mouse ear swelling test (MEST) as being the most promising. In parallel, opportunities to develop *in vitro* methods or the use of structure-activity relationships (SAR) were reviewed. The report recommended that further inter-laboratory investigations should be performed to determine the sensitivity and specificity of the LLNA and MEST in comparison with guinea pig tests and to evaluate their reliability.

The situation with respect to sensitisation of the respiratory tract is somewhat different. ECETOC has reviewed the importance to industry of respiratory allergy (ECETOC, 1993). That Monograph described the biological mechanisms underlying respiratory sensitisation and its occurrence in humans and discussed possible approaches for prospective testing. As yet there exist no fully validated or widely applied predictive methods for the identification of the respiratory sensitisation potential of chemicals. Some progress has been made in the development of guinea pig methods in which respiratory reactions can be elicited in previously sensitised animals. To date the only systematic approach in mice has been the mouse IgE test. The ECETOC report recommended further validation of these test methods.

The validation of predictive tests for the measurement of skin and respiratory sensitisation activity (in the context of local, national and international trials) requires an established list of chemicals with well-defined sensitising activity.

To bring the development and evaluation of test methodology a step forward a Task Force with the following terms of reference was established to assist in the selection of relevant chemicals:

- Prepare a list of skin and respiratory sensitisers which may be used for the validation of *in vivo* or *in vitro* toxicological tests; the list should contain chemicals known as human and/or animal sensitisers, and should be supported by published literature or other available sources and be ranked in order of potency.

The purpose of this report is to document those chemicals that are recommended for use as positive and negative controls in the assessment of *new* predictive tests for skin or respiratory sensitisation potential. It must be emphasised that the chemicals identified here have been selected specifically to assess the utility and accuracy of *novel* test methods, and not to confirm the continued sensitivity of existing methods in different laboratories.

2. CRITERIA FOR THE SELECTION OF CHEMICALS

2.1 GENERAL

The objective was to identify chemicals that will facilitate the evaluation and validation of proposed predictive test methods for skin and/or respiratory sensitisation potential. Specifically the aim was to recommend chemicals known to cause, or to lack the ability to cause, skin and/or respiratory sensitisation, and which could be used to probe the sensitivity and selectivity of novel approaches to hazard identification. The processes and criteria used for the selection of chemicals are outlined below.

2.2 CRITERIA AND PROCESSES USED FOR THE SELECTION OF TEST CHEMICALS

Four categories of test chemicals were identified:

- positive controls for respiratory sensitisation;
- negative controls for respiratory sensitisation;
- positive controls for skin sensitisation;
- negative controls for skin sensitisation.

All decisions regarding the inclusion or exclusion of chemicals from one or more of these categories was reached jointly by members of the Task Force using all information available from the published literature and elsewhere. The criteria employed for reaching inclusion or exclusion decisions are listed below.

- Evidence for the existence of sensitising activity, or the lack of sensitising activity, based upon information from one or more of the following sources: sensitisation or lack of sensitisation resulting from occupational or environmental exposure, the results of sensitisation testing in humans and/or the results of sensitisation tests conducted in experimental animals.
- The availability of the chemical from commercial sources in a relatively pure and stable form.
- The availability of the chemical from commercial sources at a relatively low cost.

In addition to those listed above, other criteria were considered during the selection of negative controls for skin and respiratory sensitisation. These were as follows:

- During the selection of negative controls for skin sensitisation, consideration was given to the skin irritancy potential of chemicals to provide a basis for examining the ability of a novel method to distinguish between skin sensitisers and skin irritants.
- During the selection of negative controls for respiratory sensitisation consideration was given to the ability of materials to cause skin sensitisation. The inclusion of known skin sensitisers within the list of chemicals known not to cause sensitisation of the respiratory tract allows evaluation of the ability of the proposed test method for respiratory sensitisation to distinguish between skin and respiratory sensitisers.

The final decisions reached were based on the above criteria and by the unanimous judgement of the experienced toxicologists which comprised the Task Force. It must be emphasised that not all selected chemicals satisfied all the criteria summarised above, but in such instances the view of the Task Force was that the evidence available was sufficient for inclusion in one or more categories. On this basis it is possible to define the chemicals selected as positive controls for either skin sensitisation or respiratory sensitisation as being materials that would register positive in an ideal method for the assessment of sensitising activity. The corollary is that those chemicals identified as negative controls for skin or respiratory sensitisation may be defined as materials which should not elicit positive responses in an ideal method for the evaluation of sensitising activity.

It must be borne in mind, however, that no *ideal* method for the assessment of sensitisation potential exists, or is likely to exist, and as stated above the test chemicals identified in this report should be regarded as a means of probing the sensitivity and selectivity and strengths and weaknesses of novel test procedures. One example may serve to illustrate this point. Among the positive controls selected for skin sensitisation testing is nickel sulphate. Nickel in many countries represents the most common cause of allergic contact dermatitis. Nevertheless, it can not be regarded as a *strong* skin sensitiser. The prevalence of nickel sensitisation in humans undoubtedly results from the extent and duration of exposure, rather than from a high intrinsic allergenic potential. Many sensitive predictive test methods for skin sensitisation have difficulty in detecting nickel salts and responses, if induced, are variable. A failure to elicit positive responses to nickel does not invalidate or necessarily render less useful an otherwise reliable predictive test method, not least because the challenge for toxicological assays is new materials and new chemistry; ‘new’ allergenic metals are not an issue.

The identification of negative controls for skin and respiratory sensitisation warrants some discussion. The selection of such chemicals is no easy task. A very large number of chemicals has been reported in the literature to cause skin sensitisation. Among these are chemicals for which only anecdotal case reports or circumstantial data are available to support their classification as skin allergens. It is

frequently difficult to decide if such materials do in fact possess a potential to cause skin sensitisation in man and whether isolated case reports are of relevance. In the case of respiratory sensitisation in particular, where there is a paucity of information available from studies in experimental animals to support clinical evidence, establishing a lack of activity is difficult. The absence of evidence for sensitisation of the respiratory tract might be due to lack of inherent allergenic activity and/or the fact that susceptible individuals have not experienced appropriate exposure of sufficient magnitude and duration. Notwithstanding these difficulties, a small number of chemicals was selected as negative controls for skin or respiratory sensitisation where, based on the criteria listed above, the judgement of the Task Force was that in an *ideal* method for hazard identification these materials should not elicit a positive response.

As indicated above, among the negative controls for skin sensitisation are materials that have some potential to cause skin irritation, while others are considered to cause neither skin sensitisation nor skin irritation. Some chemicals appear twice in the recommendations; as positive controls for skin sensitisation and as negative controls for respiratory sensitisation. Thus, 2,4-dinitrochlorobenzene (DNCB), eugenol and isoeugenol are all able to induce skin sensitisation, but are considered not to cause sensitisation of the respiratory tract. As indicated above, the value of the inclusion of known skin sensitisers among negative controls for respiratory sensitisation is that it permits examination of whether a proposed test method is able to distinguish between the two forms of chemical allergen, or simply identifies all sensitising chemicals irrespective of whether they cause allergic contact dermatitis or allergic respiratory hypersensitivity.

It should be borne in mind that chemicals selected as positive controls for skin sensitisation and which do not appear as positive controls for respiratory sensitisation cannot necessarily be regarded as lacking the ability to cause respiratory allergy.

Finally, it must be emphasised that the lists of chemicals contained within this report are not exhaustive, nor were such lists intended to be exhaustive. There are many chemical allergens which were not included in the lists of positive and negative controls identified by the Task Force, the objective being to select chemicals that would facilitate evaluation of novel test methods, and not to provide a comprehensive survey of sensitising materials.

2.3 RANKING IN ORDER OF POTENCY

The second objective was to list chemicals, where possible, in rank order of sensitising activity. This was attempted only for skin sensitisation. In using existing data it is frequently difficult to discriminate between prevalence and inherent allergenic potency. As discussed above, as an example, with respect to nickel, a significant risk of skin sensitisation in man may result from high and sustained levels of exposure rather than from potent intrinsic allergenicity. Guinea pig test methods do not provide a

solution to this problem as in such assays activity is measured as a function of the percentage of exposed animals that display a discernible reaction following challenge. Potency, in the context of skin sensitisation, is best considered in terms of the amount of chemical that, under defined conditions, is required to achieve effective sensitisation. This information is often difficult to derive from guinea pig tests where dose-response relationships for the induction of sensitisation are not usually performed or are very limited in scope. Moreover, the induction concentration of test material selected for use in guinea pig methods is dictated usually by the irritant properties of the chemical. There is a greater opportunity to investigate relative potency using the murine local lymph node assay, but few systematic studies are available.

On the basis of these considerations the decision was reached by the Task Force that the available data would not support the formal ranking of skin or respiratory sensitisers with respect to potency. It was nevertheless believed desirable to provide some discrimination between skin sensitisers. The approach taken was to identify strong allergens with an asterisk, these being defined as chemicals which *would be expected routinely to elicit clear positive responses in a predictive test and which would be readily identified as skin sensitisers*. Other chemicals listed as positive controls for skin sensitisation lack an asterisk. These are materials where less vigorous, or even equivocal, activity might be tolerated.

References

ECETOC, 1990. Skin sensitisation testing. Monograph No. 14, March 1990.

ECETOC, 1993. Respiratory allergy. Monograph No. 19, August 1993.

OECD, 1992. OECD guideline for testing of chemicals 406, skin sensitisation, adopted July 1992.

2.4 SELECTED CHEMICALS

Note: Many of the chemicals selected as positive controls for sensitisation are highly reactive. As a consequence care should be taken in preparing and storing dosing solutions.

2.4.1 Respiratory Sensitisers, Positive Controls

- Toluene diisocyanate (TDI)
- Hexamethylene diisocyanate (HDI)
- Ammonium hexachloroplatinate (HCP)
- Diphenylmethane diisocyanate (MDI)
- Trimellitic anhydride (TMA)
- Phthalic anhydride
- Plicatic acid

2.4.2 Respiratory Sensitisers, Negative Controls

- 2,4-Dinitrochlorobenzene (DNCB) †
- Tetramethylthiuram (Thiuram, TMTD)
- Eugenol †
- Isoeugenol †

† Also positive controls for skin sensitisation

2.4.3 Skin Sensitisers, Positive Controls

Substance

- Eugenol ††
- Methyl-chloro-isothiazolinone/methyl-isothiazolinone (MCI/MI) [Kathon CG] *
- Cinnamaldehyde *
- Isoeugenol ††*
- Hexylcinnamaldehyde
- 2-Hydroxyethyl acrylate (HEA)
- Benzocaine
- Diphenylthiourea
- Hydroxycitronellal

- Citral
- Ethylenediamine *
- p-Phenylenediamine *
- Potassium dichromate*
- Nickel sulphate
- Cobalt chloride *
- Glutaraldehyde *
- Formaldehyde *
- 2,4-Dinitrochlorobenzene (DNCB) ††*
- 2-Mercaptobenzothiazole (MBT)
- 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride [Dowicil 200] *
- Toluenediamine bismaleimide (TDB)
- Oxazolone *
- Penicillin G

†† Also identified as negative control for respiratory sensitisation

* Indicates a strong contact allergen that would be expected to elicit routinely clear positive responses in a predictive test for skin sensitisation. It must be emphasised that achieving positive responses with such strong contact allergens should be regarded as a minumum requirement for a novel predictive test method. Positive responses with such chemicals do not of themselves give an indication of the overall sensitivity of the assay method. Indeed, it has been recommended previously (ECETOC Monograph 14, 1990) that strong contact allergens (such as DNCB and p-phenylenediamine) should not be used as standards for verifying the continued sensitivity of established test methods.

2.4.4 Skin Sensitisers, Negative Controls

- Methyl salicylate
- p-Aminobenzoic acid (PABA)
- Sodium lauryl sulphate (SLS)
- Glycerol
- Isopropanol
- Diethyl phthalate (DEP)
- Dimethylformamide (DMF)
- Zinc sulphate

3. ASSESSMENT OF INDIVIDUAL SUBSTANCES

3.1 RESPIRATORY SENSITISATION, POSITIVE CONTROLS

3.1.1 Toluene diisocyanate (TDI)

(Synonyms: 2,4- and 2,6-Tolylene diisocyanate; 4- and 2-methyl-1,3-phenylene diisocyanate)

CAS No. 584-84-9 (2,4-toluene diisocyanate)
91-08-7 (2,6-toluene diisocyanate)

A. Skin sensitisation

A.1 Animal data

TDI gave positive responses using the guinea pig open patch test (Koschier *et al*, 1983). It has also been found to be positive in the mouse ear swelling test (Yasuda *et al*, 1991) and in the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

The major human occupational hazard is one of respiratory allergy. However, there is limited evidence that TDI may have the potential to cause skin sensitisation in man. This includes reports of positive patch tests following occupational exposure to paint and polyurethanes (Huang *et al*, 1991).

B. Respiratory sensitisation

B.1 Animal data

Using various guinea pig models with either inhalation or subcutaneous induction regimes and inhalation or intratracheal challenge with a conjugate, TDI has been found to elicit an immediate-onset pulmonary hypersensitivity response (Karol, 1983, Cibulas *et al*, 1986, Botham *et al*, 1988, Sarlo and Clark, 1992, Aoyama *et al*, 1994). Responses have been found in guinea pigs at sensitisation concentrations of as low as 25-36 ppm (Karol, 1988). TDI has been evaluated also in the mouse IgE test with positive results (Hilton *et al*, 1995).

B.2 Human evidence

TDI exposure occurs widely in the manufacture and use of many plastics, foams, plants and resins. TDI is capable of inducing asthma, although the mechanism of action is still unclear. In humans although the

clinical profile of TDI-induced asthma is consistent with an immunological process, only a proportion of people with isocyanate-induced asthma display a detectable immune response. The ACGIH (1998) has issued a TLV-TWA (8hr) for TDI of 0.005 ppm and a 15 minute TLV-STEL of 0.02 ppm.

Asthma resulting from exposure to TDI has been documented extensively. It has been diagnosed by one or more of the following:

1. decrease in lung function (Butcher *et al*, 1976; 1977, Mapp *et al*, 1986; Pisati *et al*, 1993; Soderlund *et al*, 1993);
2. positive bronchial challenge (Butcher, 1982; Pezzini *et al*, 1984; Park *et al*, 1992);
3. an increase in specific IgE.

The mechanisms whereby TDI causes respiratory allergy is still uncertain. A clear association with TDI specific IgE has been found in some, but not all, cases of TDI asthma diagnosed by bronchoprovocation tests (Soderlund *et al*, 1993). Diagnosing TDI asthma can be confounded by the potential cross-reaction between (di-) isocyanates as frequently occupational exposure can be to more than one isocyanate.

C. Conclusions

TDI is a respiratory allergen in humans and animals. TDI is clearly positive in predictive tests for skin sensitisation, although there is only limited evidence for allergic contact dermatitis in humans.

D. References

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Hilton J, Dearman RJ, Basketter DA and Kimber I, 1995. Identification of chemical respiratory allergens: dose response relationships in the mouse IgE test. Toxicol. Meth. 5, 51.

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Yasuda K, Nozawa G, Goro T, Sasaki N and Ishizu S, 1980. Experimental studies on TDI dermatitis in mice. J. Toxicol. Sci. 5, 11.

3.1.2 Hexamethylene diisocyanate (HDI)

(Synonym: 1,6-Diisocyanatohexane)

CAS No. 822-06-0

A. Skin sensitisation

A.1 Animal data

HDI was found to be positive in mice using the mouse ear swelling test (Gad *et al*, 1986; Thorne *et al*, 1987) and the murine local lymph node assay (Hilton *et al*, 1995).

A.2 Human evidence

Six of 19 operatives from 2 dressmaking mills with work-related dermatitis patch-tested positive to HDI (Wilkinson *et al*, 1991). Six cases of allergic contact dermatitis resulting from exposure to polyurethane chemicals were reported between 1974-1990. Three patients were allergic to different diisocyanates, including HDI (Estlander *et al*, 1992).

B. Respiratory sensitisation

B.1 Animal data

Guinea pigs sensitised to trimeric HDI biuret (Des-N) by repeated intradermal injections or by inhalation exposure displayed immediate and delayed onset of pulmonary reactions following challenge with the hapten (Pauluhn and Eben, 1991).

Two strains of guinea pigs were parenterally immunised with well characterised diisocyanate-protein conjugates. Hapten specific IgE antibodies were detected in the sera of English short hair strain guinea pigs exposed to HDI-HSA (human serum albumin). Antibodies were demonstrated in Hartley strain guinea pigs immunised with HDI-HSA conjugates (Chen and Bernstein, 1982).

HDI is positive in the mouse IgE test (Hilton *et al*, 1995).

B.2 Human evidence

Information on the prevalence of occupational asthma induced by isocyanates in exposed workers is limited to a few cross sectional studies (Vandenplas *et al*, 1993). In the case of HDI there is evidence for occupational respiratory allergy in a proportion of the exposed workforce (Grammer *et al*, 1988;

Greenberg and Fouerman, 1995). The many efforts made to confirm immunological sensitisation to HDI have so far led to variable results. The presence of IgE antibodies against HDI and other isocyanates has been documented in 20-39% of subjects with proven occupational asthma (Cartier *et al*, 1989).

C. Conclusions

Case reports demonstrate that HDI can cause skin sensitisation in humans.

The potential of HDI to cause occupational respiratory diseases has been established and it is probable that HDI provokes the induction of both IgE and IgG specific antibodies. However, the prevalence and the frequency of respiratory disease due to HDI is not clear. HDI elicits allergic respiratory sensitisation in guinea pigs.

D. References

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Wilkinson SM, Cartwright PH, Armitage J and English JS, 1991. Allergic contact dermatitis from 1,6-diisocyanatohexane in an anti-pill finish. Contact Derm. 25, 94.

3.1.3 Ammonium hexachloroplatinate (IV) (Ammonium HCP)

CAS No. 16919-58-7

A. Skin sensitisation

A.1 Animal data

Challenge with ammonium HCP caused enhanced activity in the popliteal lymph node assay in C57/BL/6 mice (Shuppe *et al*, 1992). Ammonium HCP was shown to be a weak positive in the murine local lymph node assay (unpublished).

A.2 Human evidence

None available.

B. Respiratory sensitisation

B.1 Animal data

None available.

B.2 Human evidence

Positive prick test reactions were elicited in three human recipients of sera from 3/6 refinery workers sensitised to ammonium HCP. Antigen mediated histamine release from whole blood of 2 of these 6 workers indicated the likelihood of specific IgE antibody (Pepys *et al*, 1979). In another study, 15/107 workers with a history of platinum-related health problems exhibited positive prick tests to ammonium HCP. Results of RAST analyses for platinum-specific antibodies showed greater levels present in the sera of skin test positive workers as compared with platinum exposed, skin test negative workers or non-exposed control individuals (Biagini *et al*, 1985). Finally, 23/27 platinum refinery workers, exhibiting work related problems, were considered to be allergic to platinum based on a significant drop in specific airway conductance after inhalation of a platinum salt solution. Nineteen of these 23 exhibited a positive skin prick reaction (Marget *et al*, 1991).

C. Conclusions

Ammonium HCP is a skin sensitiser in animals (base on limited data). In humans, there is convincing evidence that ammonium HCP is a respiratory sensitiser.

D. References

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3.1.4 Diphenylmethane diisocyanate (MDI)

(Synonym: 4,4'-Methylenebis(phenyl isocyanate))

CAS No. 101-68-8

A. Skin sensitisation

A.1 Animal data

MDI has been reported to cause skin sensitisation in guinea pigs (Stevens, 1967) and mice (Thorne, 1987) and is positive in the murine local lymph node assay (Dearman *et al*, 1992).

A.2 Human evidence

There are few reported cases of MDI skin sensitisation in humans. Estlander *et al (*1992), reported positive skin reactions in 2 workers following diagnostic patch testing with MDI. The individuals had been exposed to MDI in the workplace, one for 2 months, and the other for 2 weeks.

B. Respiratory sensitisation

B.1 Animal data

In dogs challenged intratracheally with MDI, an increase in pulmonary resistance was noted (Patterson *et al*, 1982). Immediate-type skin reactivity to a MDI-dog serum albumin conjugate was consistent with an IgE response. In mice, MDI treatment resulted in significant increases in total serum IgE (Dearman *et al*, 1992) and MDI is positive in the mouse IgE test (Hilton *et al*, 1995). Guinea pigs previously sensitised to MDI via the dermal route exhibited respiratory reactions following inhalation challenge with MDI (Rattray *et al*, 1994). Guinea pigs sensitised by brief, high level inhalation exposure experienced immediate onset responses upon challenge with MDI that were associated with airway hyper-responsiveness (Pauluhn and Mohr, 1994).

B.2 Human evidence

MDI is capable of causing respiratory allergy in humans occupationally exposed to MDI (Burge *et al*, 1979; Zammit-Tabona *et al*, 1983), although frequently co-exposure to other isocyanates had occurred. MDI was shown to induce an allergic reaction following bronchial provocation testing in workers allergic to HDI (Malo *et al*, 1983), TDI (Innocenti *et al*, 1988), and MDI (Mapp *et al*, 1985), but not to 1,5-naphthylene diisocyanate (Harries *et al*, 1979). However, TDI provocation testing failed to cause a respiratory response in two workers allergic to MDI (Mapp *et al*, 1985).

The evidence for an association between MDI-induced respiratory allergic reactions and specific IgE antibody production is mixed (Zammit-Tabona *et al*, 1983; Tse *et al*, 1985). Not all individuals who react positively to MDI challenge have measurable serum levels of anti-MDI IgE antibodies (Liss *et al*, 1988; Tse *et al*, 1985), while specific IgE antibodies have been detected in workers exposed to MDI in the work place, but who did not respond to MDI challenge (Zammit-Tabona *et al*, 1983).

Nemery and Lenaerts (1993) indicated that mine workers developed respiratory allergic reactions to MDI following dermal exposure.

The ACGIH (1998) has issued a TLV-TWA (8hr) MDI of 0.005 ppm.

C. Conclusions

MDI is a respiratory sensitiser in humans and animals. There are limited data which suggest that MDI may have a potential to cause skin sensitisation in humans and in animals.

D. References

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3.1.5 Trimellitic anhydride (TMA)

(Synonym: 1,2,4-Benzenetricarboxylic-1,2-anhydride)

CAS No. 552-30-7

A. Skin sensitisation

A.1 Animal data

TMA was identified as skin sensitiser in the guinea pig maximisation test. and proved positive in the murine local lymph node assay (Basketter and Scholes, 1992).

A.2 Human evidence

None available.

B. Respiratory sensitisation

B.1 Animal data

Dermal exposure to TMA in the mouse IgE test resulted in a positive response (Dearman *et al*, 1992; Hilton *et al*, 1995).

Guinea pigs were sensitised by intramuscular injection of TMA-protein conjugate combined with Complete Freunds Adjuvant. On inhalation challenge with TMA, immediate-onset respiratory responses occurred (Obata *et al*, 1992). Sensitisation by single or repeated intradermal injections of guinea pigs with TMA and challenge with either free TMA or the protein conjugate resulted in immediate respiratory responses (Botham *et al*, 1989, Hayes 1992, Pauluhn and Eben, 1991). Also sensitisation of guinea pigs by single or repeated inhalation exposures to TMA and subsequent challenge with TMA or TMA-protein conjugate resulted in immediate-onset respiratory responses. There was no evidence of an increased incidence of delayed-onset responses (Pauluhn and Eben, 1991).

B.2 Human evidence

Both IgE and IgG antibodies have been described in workers exposed to TMA. According to Patterson *et al* (1979) and Zeiss *et al* (1980) inhalation exposure to TMA appears to be a significant stimulus for the systemic immune response. The temporal and quantitative relationships between increases in airway responsiveness and late asthmatic reactions provoked by inhalation challenge were studied in workers.

Significant increases in histamine responsiveness were present following challenge exposure which subsequently provoked a definite late asthmatic reaction (Graneek *et al*, 1988).

The ACGIH (1998) has issued a Ceiling Limit for TMA of 0.04 mg/m^3.

C. Conclusions

TMA is a respiratory sensitiser in humans and animals. TMA is a potential human and animal skin sensitiser.

D. References

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3.1.6 Phthalic anhydride

CAS No. 85-44-9

A. Skin sensitisation

A.1 Animal data

In the ear-flank test, topical exposure to phthalic anhydride induced skin sensitisation in guinea pigs (Stevens, 1967). Phthalic anhydride is a sensitiser in the guinea pig maximisation test (Kimber *et al*, 1994). Phthalic anhydride is positive in the murine local lymph node assay (Kimber *et al*, 1994), but negative in a mouse ear sensitisation assay (Descotes, 1988). Only a weak response was induced in the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

Despite wide industrial use and evidence of occupational respiratory hypersensitivity, phthalic anhydride has been found only rarely to cause allergic contact dermatitis in humans (Venables, 1989).

B. Respiratory sensitisation

B.1 Animal data

Phthalic anhydride caused sensitisation of the respiratory tract in guinea pigs following either inhalation (Sarlo and Clark, 1992; Sarlo *et al*, 1994) or intradermal (Blaikie *et al*, 1995) exposure .

B.2 Human evidence

Asthma caused by exposure to phthalic anhydride was documented first by Kern in 1939. Several clinical studies have confirmed the immunological basis for respiratory hypersensitivity caused by phthalic anhydride (Maccia, 1976; Topping *et al*, 1986; Grammer *et al*, 1987).

The ACGIH (1998) has issued a TLV-TWA (8hr) for phthalic anhydride of 1ppm.

C. Conclusions

Phthalic anhydride is a human and animal respiratory sensitiser. Predictive test methods indicate that phthalic anhydride has some potential to cause skin sensitisation. This hazard does not, however, appear to result in a significant risk of allergic contact dermatitis in man.

D. References

ACGIH (American Conference of Governmental Industrial Hygienists), 1998. TLVs and BEIs. Threshold limit values for chemical substances and physical agents. Cincinatti, Ohio.

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Descotes J, 1988. Identification of contact allergens: the mouse ear sensitization assay. J. Toxicol.-Cut. and Ocular Toxicol. 7, 263.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

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Stevens MA, 1967. Use of the albino guinea pig to detect the skin-sensitising ability of chemicals. Br. J. Indust. Med. 24, 189.

Topping MD, Venables KM, Luczynska CM, Howe W and Newman Taylor AJ, 1986. Specificity of the human IgE response to inhaled acid anhydrides. J. Allergy Clin. Immunol. 77, 834.

Venables KM, 1989. Low molecular weight chemicals, hypersensitivity and direct toxicity: the acid anhydrides. Br. J. Indust. Med. 46, 222.

3.1.7 Plicatic acid (Western Red Cedar Allergen)

A. Skin sensitisation

A.1 Animal data

None available.

A.2 Human evidence

A single case of occupational allergic contact dermatitis to Western Red Cedar (the source of plicatic acid) has been reported (Bleumink *et al*, 1973). It is unclear, however, whether the causative allergen in this case was actually plicatic acid.

B. Respiratory sensitisation

B.1 Animal data

Rabbits exposed to plicatic acid-protein conjugates by parenteral administration developed hapten-specific IgE antibody as measured by passive cutaneous anaphylaxis. In such animals subsequent intravenous injection of the conjugate, but not inhalation challenge with the same material, caused rapid shallow breathing and increased airway resistance (Chan *et al*, 1987; Chan-Yeung, 1993). It has been shown also that prolonged sensitisation of guinea pigs to plicatic acid by repeated injection of hapten-protein conjugate is associated with respiratory hypersensitivity following subsequent challenge of animals with the free chemical (Salari *et al*, 1994).

B.2 Human evidence

Plicatic acid is a known cause of human respiratory allergy and induces occupational asthma in a proportion of the exposed workforce. Inhalation challenge of patients with extracts of Western Red Cedar or with plicatic acid results in immediate, late-onset or biphasic asthmatic reactions. Specific IgE antibody is found in some, but not all, patients with plicatic acid asthma (Tse *et al*, 1982; Cartier *et al*, 1986; Chan-Yeung, 1982; 1993).

C. Conclusions

Plicatic acid has uncertain potential to cause skin sensitisation. There is, however, evidence that this chemical is a cause of respiratory sensitisation and occupational asthma.

D. References

Bleumink E, Mitchell JC and Nater JP, 1973. Allergic contact dermatitis from cedar wood (*Thuja plicata*). Br. J. Dermatol. 88, 499.

Cartier A, Chan H, Malo J-L, Pineau L, Tse KS and Chan-Yeung M, 1986. Occupational asthma caused by eastern white cedar (*Thuja occidentalis*) with demonstration that plicatic acid is present in this wood dust and is the causal agent. J. Allergy Clin. Immunol. 77, 639.

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Chan-Yeung M, 1982. Immunologic and nonimmunologic mechanisms in asthma due to Western red cedar (*Thuja plicata*). J. Allergy Clin. Immunol. 70, 32.

Chan-Yeung M, 1993. Western red cedar and other wood dusts. In: Asthma in the Workplace (ed). IL Bernstein, M Chan-Yeung, J-L Malo and DI Bernstein, Marcel Dekker, New York, 503.

Salari H, Howard S, Chan H, Dryden P and Chan-Yeung M, 1994. Involvement of immunologic mechanisms in a guinea pig model of Western red cedar asthma. J. Allergy Clin. Immunol. 93, 877.

Tse KS, Chan H and Chan-Yeung M, 1982. Specific IgE antibodies in workers with occupational asthma due to Western red cedar. Clin. Allergy 12, 249.

3.2 RESPIRATORY SENSITISATION, NEGATIVE CONTROLS

3.2.1 2,4-Dinitrochlorobenzene (DNCB)

(Synonym: 1-Chloro-2,4-dinitrobenzene)

CAS No. 97-00-7

A. Skin sensitisation

A.1 Animal data

DNCB has produced positive responses in a variety of assays including the guinea pig maximisation test and the Buehler test, (Maurer and Hess, 1989; Botham *et al*, 1991).

In the murine local lymph node assay, DNCB has consistently produced positive responses (Kimber and Weisenberger, 1989). DNCB has also proved positive in the mouse ear swelling test (Gad *et al*, 1986; Thorne *et al*, 1991).

A.2 Human evidence

DNCB has been used as a model skin sensitiser in human studies (Rees *et al*, 1990). Determination of allergic skin reactions to DNCB has served as a prognostic test in cancer patients (Roth *et al*, 1975). An outbreak of allergic dermatitis in a tyre factory was traced to DNCB contamination (Zina *et al*, 1987).

B. Respiratory sensitisation

B.1 Animal data

Intradermal injection of DNCB followed by inhalation challenge with either free chemical or DNCB-protein conjugate did not induce respiratory allergy in guinea pigs, as judged by changes in respiratory rate (Botham *et al*, 1989). The animals developed only low titre homocytotropic antibodies. In a subsequent study, DNCB was used as the negative control for respiratory sensitisation (Blaikie *et al*, 1995). Again, high titre DNCB-specific antibodies were not induced in treated animals. Although several guinea pigs gave, on inhalation challenge, pulmonary responses categorised as "severe", it was considered that these were due to irritancy and not sensitisation.

DNCB is negative in the mouse IgE test (Hilton *et al*, 1995).

B.2 Human evidence

The evidence indicates that DNCB is not a respiratory allergen (Botham *et al*, 1989).

C. Conclusions

There is strong evidence that DNCB is a human and animal skin sensitiser. There is convincing evidence for the absence of respiratory sensitisation potential.

D. References

Blaikie L, Morrow T, Wilson AP, Hext P, Hartop PJ, Rattray NJ, Woodcock D and Botham PA, 1995. A two-centre study for the evaluation and validation of the potential of small molecular weight chemicals to cause respiratory allergy. Toxicology 96, 37.

Botham PA, Rattray NJ, Woodcock DR, Walsh ST and Hext PM, 1989. The induction of respiratory allergy in guinea-pigs following intradermal injection of trimellitic anhydride: a comparison with the response to 2,4-dinitrochlorobenzene. Toxicol. Lett. 47, 25.

Botham PA, Basketter DA, Maurer T, Mueller D, Potokar M and Bontinck WJ, 1991. Skin sensitisation - a critical review of predictive test methods in animals and man. Fd. Chem. Toxicol. 29, 275.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Hilton J, Dearman RJ, Basketter DA and Kimber I, 1995. Identification of chemical respiratory allergens: dose-response relationships in the mouse IgE test. Toxicol. Meth. 5, 51.

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Maurer T and Hess R, 1989. The maximisation test for skin sensitisation potential - updating the standard protocol and validation of a modified protocol. Fd. Chem. Toxicol. 27, 807.

Rees JL, Friedmann PS and Matthews JNS, 1990. The influence of area of application on sensitisation by dinitrochlorobenzene. Br. J. Dermatol. 122, 29.

Roth JA, Eilber FR, Nizze JA and Morton DL, 1975. Lack of correlation between skin reactivity to dinitrochlorobenzene and croton oil in patients with cancer. New Engl. J. Med. 293, 388.

Thorne PS, Hawk C, Kaliszewski SD and Guiney PD, 1991. The noninvasive mouse ear swelling assay. 1. Refinements for detecting weak contact sensitisers. Fund. Appl. Toxicol. 17, 790.

Zina AM, Bedello PG, Cane D, Bundino S and Benedetto A, 1987. Dermatitis in a rubber tyre factory. Contact Derm. 17, 17.

3.2.2 Tetramethylthiuram (Thiuram; TMTD)

(Synonyms: bis(Dimethylthiocarbamyl) disulphide; Tetramethylthiuram disulphide; Thiram)

CAS No. 137-26-8

A. Skin sensitisation

A.1 Animal data

TMTD was found to elicit a positive response in the guinea pig maximisation test (Ziegler *et al*, 1972) and in a modified murine local lymph node assay (Ikarashi *et al*, 1993).

A.2 Human evidence

TMTD was a sensitiser in the human maximisation test, with 4/25 subjects giving evidence of a positive reaction (Kligman, 1966).

Thiuram-containing rubber gloves are a well known cause of contact dermatitis (Wilson, 1969). Once sensitised to thiuram, many individuals exhibit a cross sensitivity to gloves containing dithiocarbamate (van Ketel and van den Berg, 1984). In its use as a fungicide and seed protectant, TMTD has been reported to cause allergic contact dermatitis (Shelly, 1964; Rudzki and Napiorkowska, 1980). Peripheral blood mononuclear cells from individuals, who patch tested positive to a thiuram mix, exhibited significant proliferation following incubation *in vitro* with TMTD-HSA (human serum albumin) conjugate (Kimber *et al*, 1991). Contact dermatitis following airborne exposure to thiuram has also been reported (Dooms-Goossens *et al*, 1986).

B. Respiratory sensitisation

B.1 Animal data

None available.

B.2 Human evidence

In its use as a pesticide and as an accelerator and vulcanising agent in rubber processing, over 1300 tons of TMTD were produced in 1981 in the USA alone (IARC, 1991). Routes of occupational exposure include dermal and inhalation. In formulating plants thiuram dust has been detected at levels up to 0.04-0.06mg/m^3 (Maini and Boni, 1986), with no reports of respiratory sensitisation. As mentioned above, airborne exposure to TMTD has resulted in skin, but not respiratory, sensitisation (Dooms-Goossens *et*

al, 1986). Based upon the nature and extent of human exposure, TMTD does not appear to cause respiratory sensitisation.

C. Conclusions

TMTD is a human and animal skin sensitiser. There is no evidence of sensitisation of the respiratory tract in exposed humans.

D. References

Dooms-Goossens AE, Debusschere KM, Gevers DM, Dupre KM, Degreef HJ, Loncke JP and Snauwaert JE, 1986. Contact dermatitis caused by airborne agents. A review and case reports. J. Am. Acad. Dermatol. 15, 1.

IARC, 1991. Thiram. In: IARC monograph on evaluation of carcinogenic risk of chemicals to humans, Vol. 53. IARC, Lyon 403.

Ikarashi Y, Tsuchiya T and Nakamura A, 1993. Evaluation of contact sensitivity of rubber chemicals using the murine local lymph node assay. Contact Derm. 28, 77.

Kimber I, Quirke S, Cumberbatch M, Ashby J, Paton D, Aldridge RD, Hunter JAA and Beck MH, 1991. Lymphocyte transformation and thiuram sensitization. Contact Derm. 23, 164.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitizers. J. Invest. Dermatol. 47, 393.

Maini P and Boni R, 1986. Gas chromatographic determination of dithiocarbamate fungicides in workroom air. Bull. Environ. Contam. Toxicol. 37, 931.

Rudzki E and Napiorkowska T, 1980. Dermatitis caused by the Polish fungicide Sadoplon 75. Contact Derm. 6, 300.

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van Ketel WG and van den Berg WH, 1984. The problem of the sensitisation to dithiocarbamate in thiuram-allergic patients. Dermatological 169, 70.

Wilson HT, 1969. Rubber dermatitis: an investigation of 106 cases of contact dermatitis caused by rubber. Br. J. Dermatol. 81, 175.

Ziegler V, Suess E, Standav H and Hasert K, 1972. Der Meerschweinchen - Maximisations Test zum Nachweis der sensibilisierenden Wirkung wichtiger Industrieprodukte. Aller. Immun. 18, 203.

3.2.3 Eugenol

(Synonym: 4-Allyl-1-hydroxy-2-methoxybenzene)

CAS No. 97-53-0

A. Skin sensitisation

A.1 Animal data

Eugenol elicited positive responses in the guinea pig maximisation test (Koch *et al*, 1971; Maurer *et al*, 1979). It is also positive in the guinea pig optimisation test (Botham *et al*, 1991), the murine local lymph node assay (Gerberick *et al*, 1992) and the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

Eugenol is used routinely for patch tests. In a clinical study of 155 people who complained of dermatitis from using cosmetics, 4/155 individuals patch tested with eugenol were found to be positive (Itoh, 1982). In a clinical study with 18 dental patients who were treated with eugenol-containing preparations, 16 were found to be positive to eugenol in diagnostic patch testing (Koch *et al*, 1971). Other instances of human skin sensitisation to eugenol have been reported (de Groot *et al,* 1994).

B. Respiratory sensitisation

B.1 Animal data

None available.

B.2 Human evidence

There are no clinical reports of respiratory sensitisation to eugenol in man, either in consumers or in an occupational setting, despite many years of use in perfumery. In Kretek cigarettes, where eugenol is the main flavouring agent, there is no evidence of respiratory sensitisation, despite the complications of tobacco-associated disorders (Council on Scientific Affairs, 1988; Guidotti, 1989). The effects possibly attributed to eugenol relate to local toxicity and pneumonitis.

C. Conclusions

Eugenol is a human and animal skin sensitiser. Available evidence indicates that eugenol does not cause sensitisation of the respiratory tract in humans.

D. References

Botham PA, Basketter DA, Maurer T, Mueller D, Potokar M and Bontinck WJ, 1991. Skin sensitisation - a critical review of predictive test methods in animals and man. Fd. Chem. Toxicol. 29, 275.

Council on Scientific Affairs, 1988. Evaluation of the health hazard of clove cigarettes. J. Am. Med. Assoc. 260, 3641.

de Groot AC, Weyland JW and Nater JP, 1994. Unwanted effects of cosmetics and drugs in dermatology, Elsevier, Amsterdam.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Gerberick GF, House RV, Fletcher ER and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. Fundam. Appl. Toxicol. 19, 438.

Guidotti TL, 1989. Critique of the available studies on the toxicity of Kretek smoke and its constituents by routes of entry involving the respiratory tract. Arch. Toxicol. 63, 7.

Itoh M, 1982. Sensitisation potency of some phenolic compounds - with special emphasis on the relationship between chemical structure and allergenicity. J. Dermatol. 9, 223.

Koch G, Magnusson B and Nyquist G, 1971. Contact allergy to medicaments and materials used in dentistry (II). Odontologisk Rev. 22, 275.

Maurer T, Thomann P, Weirich EG and Hess R, 1979. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparison of different methods of cutaneous sensitisation with 'weak' allergens. Contact Derm. 5, 1.

3.2.4 Isoeugenol

(Synonym: Mixture of cis and trans 2-methoxy-4-propenylphenol)

CAS No. 97-54-1

A. Skin sensitisation

A.1 Animal data

Isoeugenol is a skin sensitiser in the guinea pig maximisation test (Maurer *et al*, 1979) and in other guinea pig assays (Itoh, 1982). It is positive in the mouse ear swelling test (Thorne *et al*, 1991) and the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

Isoeugenol is used routinely in the diagnostic patch testing of patients with skin sensitisation induced by cosmetics. In one such study, 8/155 people who complained of dermatitis showed evidence of skin sensitisation when challenged with isoeugenol (Itoh, 1982). Many positive patch test responses to isoeugenol have been published (Thompson *et al*, 1983; de Groot *et al,* 1985).

B. Respiratory sensitisation

B.1 Animal data

None available.

B.2 Human evidence

Despite widespread occupational and consumer exposure there are no reports of allergic respiratory sensitisation to isoeugenol in humans.

C. Conclusions

Isoeugenol is a human and animal skin sensitiser. The available evidence indicates that isoeugenol does not cause sensitisation of the respiratory tract.

D. References

de Groot AC, Liem DH, Nater JP and Van Ketel WG, 1985. Patch test with fragrance materials and preservatives. Contact Derm. 12, 87.

Itoh M, 1982. Sensitisation potency of some phenolic compounds - with special emphasis on the relationship between chemical structure and allergenicity. J. Dermatol. 9, 223.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Maurer T, Thomann P, Weirich EG and Hess R, 1979. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparisons of different methods of cutaneous sensitisation with 'weak' allergens. Contact Derm. 5, 1.

Thompson GR, Booman KA, Dorsky J, Kohrman KA, Rothenstein AS, Schwoeppe EA, Sedlak RI and Steltenkamp RJ, 1983. Isoeugenol: a survey of consumer patch-test sensitisation. Fd. Chem. Toxicol. 6, 735.

Thorne PS, Hawk C, Kaliszewski SD, Guiney PD, 1991. The non-invasive mouse ear swelling assay. II. Testing the contact sensitising potency of fragrances. Fundam. Appl. Toxicol. 17, 807.

3.3 SKIN SENSITISATION, POSITIVE CONTROLS

3.3.1 Eugenol

(Synonym: 4-Allyl-1-hydroxy-2-methoxybenzene)

CAS No. 97-53-0

A. Skin sensitisation

A.1 Animal data

Eugenol elicits positive responses in the guinea pig maximisation test (Koch *et al*, 1971; Maurer *et al*, 1979). It is also positive in the guinea pig optimisation test (Botham *et al*, 1991), the murine local lymph node assay (Gerberick *et al*, 1992) and the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

Eugenol is used routinely for patch tests. In a clinical study of people who complained of dermatitis from using cosmetics, 4/155 individuals patch tested with eugenol were found to be positive (Itoh, 1982). In a clinical study with 18 dental patients who were treated with eugenol-containing preparations, 16 were found to be positive to eugenol in diagnostic patch testing (Koch *et al*, 1971). Other instances of human skin sensitisation to eugenol have been reported (de Groot *et al,* 1994).

B. Conclusions

Eugenol is a human and animal skin sensitiser.

C. References

Botham PA, Basketter DA, Maurer T, Mueller D, Potokar M and Bontinck WJ, 1991. Skin sensitisation - a critical review of predictive test methods in animals and man. Fd. Chem. Toxicol. 29, 4: 275.

de Groot AC, Weyland JW and Nater JP, 1994. Unwanted effects of cosmetics and drugs in dermatology, Elsevier, Amsterdam.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Gerberick GF, House RV, Fletcher ER and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. Fundam. Appl. Toxicol. 19, 438.

Itoh M, 1982. Sensitisation potency of some phenolic compounds - with special emphasis on the relationship between chemical structure and allergenicity. J. Dermatol. 9, 223.

Koch G, Magnusson B and Nyquist G, 1971. Contact allergy to medicaments and materials used in dentistry (II). Odontologisk Rev. 22, 275.

Maurer T, Thomann P, Weirich EG and Hess R, 1979. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparison of different methods of cutaneous sensitisation with 'weak' allergens. Contact Derm. 5, 1.

3.3.2 Methyl-chloro-isothiazolinone/methyl-isothiazolinone (MCI/MI) [Kathon CG]

CAS No. 26172-55-4

A. Skin sensitisation

A.1 Animal data

Kathon CG is positive in the Buehler test (Chan *et al*, 1983) and in the guinea pig maximisation test (Kimber *et al*, 1994). It is positive also in the murine local lymph node assay (Gerberick *et al*, 1992).

A.2 Human evidence

Kathon CG is a widely used preservative and a well-documented human skin sensitiser (de Groot *et al*, 1986, Schuster and Spiro, 1987, Weaver *et al*, 1985, Cardin *et al*, 1986). Patch test results give sensitisation rates of 0.67-16.1% (Aberer *et al*, 1992). In one clinical study 81/1620 patients, recorded a positive patch test response indicative of skin sensitisation (de Groot *et al*, 1988).

B. Conclusions

Kathon CG is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Aberer W, Ziegler V and Anegg B, 1992. Kontaktallergie auf Kathon: Elimination oder Deklaration? Dermatosen 40, 112.

Cardin CW, Weaver JE and Bailey PT, 1986. Dose-response assessments of Kathon biocide. Contact Derm. 15, 10.

Chan PK, Baldwin RC, Parsons RD, Moss JN, Stiratelli R, Smith JM and Hayes AW, 1983. Kathon biocide: manifestation of delayed contact dermatitis in guinea pigs is dependent on the concentrations for induction and challenge. J. Invest. Dermatol. 81, 409.

de Groot AC, Bos JD, Jagtman BA, Bruynzeel DP, van Joost T and Weyland JW, 1986. Contact allergy to preservatives. II. Contact Derm. 15, 218.

de Groot AC, Bruynzeel DP, Van Der Groeff JG and Bos JD, 1988. Routine patch testing with the preservative system Kathon CG. Int. J. Cosmet. Sci. 10, 47.

Gerberick GF, House RV, Fletcher BR and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. Fundam. Appl. Toxicol. 19, 438.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Shuster S and Spiro J, 1987. Measurement of risk of sensitization and its application to Kathon. Contact Derm. 17, 299.

Weaver JE, Cardin CW and Maibach HI, 1985. Dose-response assessments of Kathon biocide. Contact Derm. 12, 141.

3.3.3 Cinnamaldehyde

(Synonym: 3-Phenyl-2-propenal)

CAS No. 104-55-2

A. Skin sensitisation

A.1 Animal data

Positive responses were recorded in the guinea pig maximisation test (Prince and Prince, 1977; Basketter, 1992). and in the Buehler test (Majeti and Suskind, 1976 and 1977; Briggs, 1974). Positive responses were observed also in the murine local lymph node assay (Kimber *et al*, 1994) and the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

There are many reports from the spice industry of positive patch tests with cinnamaldehyde (Collins and Mitchell, 1975). The North American Contact Dermatitis Group reported positive reactions to cinnamaldehyde in 3-4% of 202 patients (Rudner, 1977). Cinnamaldehyde has been found to give positive skin sensitisation reactions in the human maximisation test (Kligman, 1973). In human repeat insult patch tests, cinnamaldehyde induced sensitisation in 5/41 subjects (Danneman *et al*, 1983).

B. Conclusions

Cinnamaldehyde is a human and animal skin sensitiser This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Basketter DA, 1992. Skin sensitisation to cinnamic alcohol: the role of skin metabolism. Acta Derm. Venerol. (Stockh.) 72, 264.

Briggs GB, 1974. Report to Research Institute for Fragrance Materials, 9 August.

Collins FW and Mitchell JC, 1975. Aroma chemicals: reference sources for perfume and flavour ingredients with special reference to cinnamic aldehyde. Contact Derm. 1, 43.

Danneman PJ, Booman KA, Dorsky J, Kohrman KA, Rothenstein AS, Sedlak RI, Steltenkamp RJ and Thompson GR, 1983. Cinnamic aldehyde: a survey of consumer patch-test sensitisation. Fd. Chem. Toxicol. 21, 721.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Kligman AM, 1973. Report to Research Institute for Fragrance Materials.

Majeti VA and Suskind RR, 1976 and 77. The sensitizing activity of three aroma aldehydes and inhibition by specific chemical agents. Reports to Research Institute for Fragrance Materials (16 January 1976; 7 January and 1 November 1977).

Prince HN and Prince TG, 1977. Comparative guinea pig assays for contact hypersensitivity. Cosmet. Toiletr. 92, 53.

Rudner EJ, 1977. North American group results. Contact Derm. 3, 208.

3.3.4 Isoeugenol

(Synonym: Mixture of cis and trans 2-methoxy-4-propenylphenol)

CAS No. 97-54-1

A. Skin sensitisation

A.1 Animal data

Isoeugenol is a skin sensitiser in the guinea pig maximisation test (Maurer *et al*, 1979) and in other guinea pig assays (Itoh, 1982). It is positive also in the mouse ear swelling test (Thorne *et al*, 1991) and the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

Isoeugenol is used routinely in the diagnostic patching testing of patients with skin sensitisation induced by cosmetics. In one such study of people who 8/115 people who complained of dermatitis showed evidence of skin sensitisation when challenged with isoeugenol (Itoh, 1982). Many positive patch test responses to isoeugenol have been published (Thompson *et al*, 1983; de Groot *et al*, 1985).

B. Conclusions

Isoeugenol is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

de Groot AC, Liem DH, Nater JP and Van Ketel WG, 1985. Patch test with fragrance materials and preservatives. Contact Derm. 12, 87.

Itoh M, 1982. Sensitisation potency of some phenolic compounds - with special emphasis on the relationship between chemical structure and allergenicity. J. Dermatol. 9, 223.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Maurer T, Thomann P, Weirich EG and Hess R, 1979. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparisons of different methods of cutaneous sensitisation with 'weak' allergens. Contact Derm. 5, 1.

Thompson GR, Booman KA, Dorsky J, Kohrman KA, Rothenstein AS, Schwoeppe EA, Sedlak RI and Steltenkamp RJ, 1983. Isoeugenol: a survey of consumer patch-test sensitisation. Fd. Chem. Toxicol. 6, 735.

Thorne PS, Hawk C, Kaliszewski SD, Guiney PD, 1991. The non-invasive mouse ear swelling assay. II. Testing the contact sensitizing potency of fragrances. Fundam. Appl. Toxicol. 17, 807.

3.3.5 Hexylcinnamaldehyde

(Synonym: α-Hexylcinnamaldehyde)

CAS No. 101-86-0

A. Skin sensitisation

A.1 Animal data

Hexylcinnamaldehyde is a skin sensitiser in the guinea pig maximisation and Buehler tests and is positive in the murine local lymph node assay (Basketter *et al*, 1993).

A.2 Human evidence

A human maximisation test produced no sensitisation reactions to hexylcinnamaldehyde (Kligman, 1973). Since then there have been reports that hexylcinnamaldehyde has been shown by diagnostic patch testing to be a human skin sensitiser (de Groot *et al*, 1985; de Groot 1988).

B. Conclusions

Hexylcinnamaldehyde is a human and animal skin sensitiser.

C. References

Basketter DA, Selbie E, Scholes EW, Lees D, Kimber I and Botham PA, 1993. Results with OECD recommended positive control sensitisers in the maximisation, Buehler and local lymph node assays. Fd. Chem. Toxicol. 31, 63.

de Groot AC, Liem DH, Nater JP and Van Ketel WG, 1985. Patch tests with fragrance materials and preservatives. Contact Derm. 12, 87.

de Groot AC, 1988. Adverse reactions to cosmetics. University of Groningen. Thesis.

Kligman AM, 1973. Report to Research Institute for Fragrance Materials.

3.3.6 2-Hydroxyethyl acrylate (HEA)

CAS No. 818-61-1

A. Skin sensitisation

A.1 Animal data

HEA has been reported to be positive in both the guinea pig maximisation test and the murine local lymph node assay (Scholes *et al*, 1992).

A.2 Human evidence

Occupational exposure to HEA during the manufacture of soft, disposable contact lenses resulted in skin sensitisation to HEA based on patch test studies (Peters and Andersen, 1986).

B. Conclusions

HEA is an animal skin sensitiser. Little human information is available, but it appears that HEA has also the ability to cause skin sensitisation in humans.

C. References

Peters K and Andersen KE, 1986. Allergic hand dermatitis from 2-hydroxyethylacrylate in contact lenses. Contact Derm. 15, 188.

Scholes EW, Basketter DA, Sarll AE, Kimber I, Evans CD, Miller K., Robbins MC, Harrison PTC and Waite SJ, 1992. The local lymph node assay: results of a final inter-laboratory validation under field conditions. J. Appl. Toxicol. 12, 217.

3.3.7 Benzocaine

(Synonyms: 4-Aminobenzoic acid ethyl ester; Ethyl 4-aminobenzoate)

CAS No. 94-09-7

A. Skin sensitisation

A.1 Animal data

Benzocaine displays a wide range of sensitisation potential in the guinea pig maximisation and Buehler tests (Goodwin *et al*, 1981; Buehler *et al*, 1985; Botham *et al*, 1991). An important factor in detecting benzocaine sensitisation in guinea pigs is the concentrations used for induction and challenge (Maurer *et al*, 1979). In mice, benzocaine has been reported to be a positive in the mouse ear swelling test (Gad, 1988). In the murine local lymph node assay, studies with benzocaine have been inconsistent, with positive (Kimber *et al*, 1989), negative (Gerberick *et al*, 1992) and equivocal (Basketter *et al*, 1993) results reported. This variability has been discussed (Basketter, *et al*, 1995).

A.2 Human evidence

As early as 1976, benzocaine was recognised as one of the eleven most frequently encountered skin sensitisers in Western Europe and North America (Marzulli and Maibach, 1976), with clinical sensitisation rates ranging from 4-5% (Bandeman *et al*, 1972). In 542 patients with suspected allergic contact dermatitis, patch testing revealed the following percentage of patients with positive reactions: nickel (17%), ethylenediamine (9%), formaldehyde (7%), potassium dichromate (6%), thiuram mix (4%), paraphenylenediamine (3%) and benzocaine (1.5%) (Hogan *et al*, 1988).

B. Conclusions

Benzocaine is a human skin sensitiser. In animals, the ability of benzocaine to sensitise has been variable and inconsistent.

C. References

Bandeman HJ, Calnan C, Cronin E, Fregert S, Hjorth N, Magnusson B, Maibach H, Malton K, Meneghini C, Pirila V and Wilkinson D, 1972. Dermatitis from applied medicants. Arch. Dermatol. 106, 335.

Basketter DA, Scholes EW, Wahlquist H and Montelius J, 1995. An evaluation of the suitability of benzocaine as a positive control skin sensitizer. Contact Derm. 33, 28.

Basketter DA, Selbie E, Scholes EW, Lees D, Kimber I and Botham PA, 1993. Results with OECD recommended positive control sensitizers in the maximisation, Buehler and local lymph node assays. Fd. Chem. Toxicol. 31, 63.

Botham PA, Basketter DA, Maurer T, Mueller D, Potokar M and Bontink WJ, 1991. Skin sensitisation - a critical review of predictive test methods in animals and man. Fd. Chem. Toxicol. 29, 275.

Buehler EV, 1965. Delayed contact hypersensitivity in the guinea pig. Arch. Dermatol. 91, 171.

Gad SC, 1988. A scheme for the prediction and ranking of relative potencies of dermal sensitizers based on data from several systems. J. Appl. Toxicol. 8, 361.

Gerberick GF, House RV, Fletcher ER and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. Fund. Appl. Toxicol. 19, 438.

Goodwin BFJ, Crevel RWR and Johnson AW, 1981. A comparison of three guinea-pig sensitization procedures for the detection of 19 reported human contact sensitizers. Contact Derm. 7, 248.

Hogan DJ, Hill M and Lane PR, 1988. Results of routine patch testing of 542 patients in Saskatoon, Canada. Contact Derm. 19, 120.

Kimber I, Hilton J and Weisenberger C, 1989. The murine local lymph node assay for identification of contact allergens: a preliminary evaluation of *in situ* measurement of lymphocyte proliferation. Contact Derm. 21, 215.

Marzulli FN and Maibach HI, 1976. Contact allergy: predictive testing in man. Contact Derm. 2, 1.

Maurer T, Thomann P, Weirich EG and Hess R, 1979. Predictive evaluation in animals of the contact allergic potential of medically important substances. II. Comparison of different methods of cutaneous sensitisation with "weak" allergens. Contact Derm. 5, 1.

3.3.8 Diphenylthiourea

(Synonyms: Thiocarbanilide; 1,3-Diphenyl-2-thiourea)

CAS No. 102-08-9

A. Skin sensitisation

A.1 Animal data

Diphenylthiourea gave a positive response in the guinea pig maximisation test (Fregert *et al*, 1983).

A.2 Human evidence

Diphenylthiourea is reported to be an allergen associated with its use as a rubber vulcanisation accelerator and in PVC adhesive tape (Fregert *et al*, 1982; Foussereau, 1992).

B. Conclusions

Diphenylthiourea is a human and animal skin sensitiser (limited data).

C. References

Foussereau J, 1992. Clothing. In: Textbook of Contact Dermatitis Eds. Rycroft RJG, Menné T, Frosch PJ and Benezra C, Springer-Verlag, Berlin, 510.

Fregert S, Trulson L and Zimerson E, 1982. Contact allergic reactions to diphenylthiourea and phenylisothiocyanate in PVC adhesive tape. Contact Derm. 8, 38.

Fregert S, Dahlqvist I and Trulsson L, 1983. Sensitisation capacity of diphenylthiourea and phenylisothiocyanate. Contact Derm. 10, 16.

3.3.9 Hydroxycitronellal

CAS No. 107-75-5

A. Skin sensitisation

A.1 Animal data

Hydroxycitronellal elicits positive responses in both the guinea pig maximisation test and the murine local lymph node assay (Marzulli and Maguire, 1982; Basketter and Scholes, 1992; Kimber *et al*, 1994).

A.2 Human evidence

Hydroxycitronellal has proven positive in both the human maximisation test (RIFM, 1974) and in the human repeat insult patch test (Ford and Api, 1988). It is one of the 8 substances that comprise the fragrance mix used in the standard patch test battery - in one study it represented 21% of the observed fragrance positives (Fisher, 1986). The clinical literature on skin sensitisation to hydroxycitronellal is summarised by de Groot *et al* (1994).

B. Conclusions

Hydroxycitronellal is a human and animal skin sensitiser.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the local lymph node assay with the guinea pig, maximization test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

de Groot AC, Weyland JW and Nater JP, 1994. Unwanted effects of cosmetics and drugs in dermatology, Elsevier, Amsterdam.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

Ford RA and Api AM, 1988. Allergic contact skin sensitisation potential of hydroxycitronellal in humans. Fd. Chem. Toxicol. 26, 921.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology. 93, 13.

Marzulli F and Maguire H, 1982. Usefulness and limitations of various guinea pig test methods in detecting human skin sensitisers. Validation of guinea pig tests for skin hypersensitivity. Fd. Chem. Toxicol. 20, 67.

RIFM (Research Institute for Fragrance Materials), 1974. Monograph on hydroxycitronellal. Fd. Chem. Toxicol 12, 921.

3.3.10 Citral

(Synonym: 3,7-Dimethyl-2,6-octadienal)

CAS No. 5392-40-5

A. Skin sensitisation

A.1 Animal data

Citral causes skin sensitisation in both the guinea pig maximisation test and the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

There is only limited clinical evidence that citral can cause allergic contact dermatitis in man as the chemical is used only rarely in patch testing and is irritant, thus causing confusion in the interpretation of patch test results (Steltenkamp *et al*, 1980). However, an incidence of up to 32% of positive subjects was recorded in the human maximisation test (reviewed in Steltenkamp *et al*, 1981). In addition, up to 48% of panellists had allergic responses to citral in the human repeat insult patch test (Opdyke, 1979).

B. Conclusions

Citral should be regarded as possessing some skin sensitisation potential on the basis of results from animal models and in human predictive testing. The lack of clear clinical evidence may simply reflect the limited extent of normal human exposure and the difficulties of patch testing with irritant chemicals.

C. References

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Opdyke DLJ, 1979. Monographs of fragrance raw materials: citral. Fd. Cosmet. Toxicol. 17,259.

Steltenkamp RJ, Booman KA, Dorsky J, King TO, Rothenstein AS, Schwoeppe EA, Sedlak RI, Smith THF and Thompson GR, 1980. Citral: a survey of consumer patch test sensitization. Fd. Chem. Toxicol. 18, 413.

Steltenkamp RJ, Booman KA, Dorsky J, Kohrman K, Rothenstein AS, Schwoeppe EA, Sedlak RI and Thompson GR, 1981. SDA fragrance subcommittee report: industry surveys of fragrance sensitization test data. Perfumer and Flavorist 6, 35.

3.3.11 Ethylenediamine

CAS No. 107-15-3

A. Skin sensitisation

A.1 Animal data

Ethylenediamine elicited positive responses in both the guinea pig maximisation test and the murine local lymph node assay (Basketter and Scholes, 1992).

A.2 Human evidence

Ethylenediamine is recognised as a skin allergen in humans (Tass and Weissberg, 1958; Nielson and Jorgensen, 1987; Cronin, 1980; Fisher, 1986). In human patch testing, ethylenediamine is included in the standard series of allergens recommended by the International Contact Dermatitis Group and by the European Environmental and Contact Dermatitis Research Group (ICDRG and EECDRG, 1988).

B. Conclusions

Ethylenediamine is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisers.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the local lymph node assay with the guinea pig maximisation test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

Cronin E, 1980. Contact Dermatitis. Churchill Livingstone, London.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

ICDRG and EECDRG, 1988. Revised European Standard Series. Contact Derm. 19, 391.

Nielsen M and Jorgensen J, 1987. Persistence of contact sensitivity to ethylenediamine. Contact Derm. 16, 275.

Tass J and Weissberg GD, 1958. Allergy to aminophylline. Acta. Allergologica 12, 39.

3.3.12 p-Phenylenediamine

CAS No. 106-50-3

A. Skin sensitisation

A.1 Animal data

p-Phenylenediamine elicits positive responses in both the guinea pig maximisation test and the murine local lymph node assay (reviewed in Kimber *et al*, 1994).

A.2 Human evidence

p-Phenylenediamine gave a 100% positive response in the human maximisation test (Kligman, 1966). Furthermore, it is in the standard screening tray of skin allergens used in human patch testing and is widely reported as a human skin allergen (Cronin, 1980; Fisher, 1986).

B. Conclusions

p-Phenylenediamine is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Cronin E, 1980. Contact Dermatitis, Churchill Livingstone, London.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitizers. J. Invest. Dermatol. 47, 393.

3.3.13 Potassium dichromate

CAS No. 7778-50-9

A. Skin sensitisation

A.1 Animal data

Potassium dichromate is a skin sensitiser in the guinea pig maximisation test. (reviewed in Wahlberg and Boman, 1985). It is also positive in the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

Chromium salts, particularly the hexavelant salts, are common causes of allergic contact dermatitis in humans (reviewed by Burrows, 1983; Rycroft *et al*, 1992). Potassium dichromate is also a highly effective skin sensitiser in the human maximisation test, giving a response rate of 100% (Kligman, 1966).

B. Conclusions

Potassium dichromate is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Burrows D, 1983. Adverse chromate reactions on the skin. In: Chromium: Metabolism and Toxicity, Burrows, D. CRC Press, Boca Raton, eds, 137.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitisers. J. Invest. Dermatol. 47, 393-409.

Rycroft RJG, Menné T, Frosch PJ and Benezra C, 1992. Textbook of Contact Dermatitis. Springer-Verlag, Heidelberg.

Wahlberg JE and Boman A, 1985. Guinea pig maximization test. In: Contact Allergy Predictive Tests in Guinea Pigs, Current Problems in Dermatology, Vol. 14, Andersen KE and Maibach HI (ed), 59, Karger, Basel.

3.3.14 Nickel sulphate

CAS No. 10101-97-0

A. Skin sensitisation

A.1 Animal data

It has proven relatively difficult to demonstrate that ionic nickel is a skin sensitiser in either guinea pig or mouse models (Wahlberg, 1989). However, a positive response rate in the guinea pig maximisation test has been reported by Magnusson and Kligman (1970), and positive results have been obtained in the mouse ear swelling test (Gad *et al,* 1986) and murine local lymph node assay (Gerberick *et al*, 1992).

A.2 Human evidence

Nickel is one of the commonest skin allergens in humans in those countries where sufficient diagnostic patch testing is carried out to allow this assessment to be made (Menné *et al*, 1989; Smit and Coenraads, 1993).

B. Conclusions

Nickel is a human skin sensitiser.

C. References

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Gerberick GF, House RV, Fletcher ER and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. Fundam. Appl. Toxicol. 19, 438.

Magnusson and Kligman, 1970. Allergic Contact Dermatitis in the Guinea Pig, Charles C. Thomas, Springfield.

Menné T, Christopherson J and Green A, 1989. Epidemiology of nickel dermatitis. Nickel and the Skin; Immunology and Toxicology Maibach HI and Menné T, eds., 109, CRC Press, Boca Raton.

Smit HA and Coenraads PJ, 1993. Epidemiology of contact dermatitis. In: Epidemiology of Clinical Allergy. Monographs in Allergy Vol. 31, Burr MI, eds., 29, Karger, Basel.

Wahlberg JE, 1989. Nickel: animal sensitisation assays. In: Nickel and the Skin; Immunology and Toxicology Maibach HI and Menné T, eds., 65, CRC Press, Boca Raton.

3.3.15 Cobalt chloride

CAS No. 7791-13-1

A. Skin sensitisation

A.1 Animal data

Cobalt chloride produced positive responses in the guinea pig maximisation test (Wahlberg and Boman, 1978) and in the modified single injection adjuvant test (Allenby and Basketter, 1989). Guinea pigs sensitised to cobalt chloride gave positive skin reactions when challenged with metallic cobalt (Cavelier *et al*, 1989). Cobalt chloride is positive in the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

In patch tests conducted using a maximisation protocol, cobalt (as sulphate) was classified as a sensitiser (Kligman, 1966). In over 4700 consecutive patients patch tested with an extended standard series of up to 34 chemicals, cobalt chloride was the fifth most common cause of allergic skin reactions, seen in 5.7% of the patients (Shehade *et al*, 1991).

Cobalt causes occupational allergic dermatitis. When 853 Swedish hard metal workers were patch tested with cobalt chloride, 36/39 that gave reproducible positive responses had histories of hand dermatitis (Fischer and Rystedt, 1983). Occupational sensitisation to cobalt, often associated with that to nickel and/or chromium, has also been reported in pottery workers (Pirila, 1953), the cement industry (Pirila and Kajanne, 1965) and the rubber industry (Foussereau and Cavelier, 1988).

B. Conclusions

Cobalt is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Allenby CF and Basketter DA, 1989. Minimum eliciting patch test concentrations of cobalt. Contact. Derm. 20, 185.

Cavelier C, Foussereau J, Gille P and Zissu D, 1989. Allergy to nickel or cobalt; tolerance to nickel and cobalt samples in man and in the guinea pig allergic or sensitised to these metals. Contact. Derm. 21, 72.

Fischer T and Rystedt I, 1983. Cobalt allergy in hard metal workers. Contact. Derm. 9, 115.

Foussereau J and Cavelier C, 1988. Allergic contact dermatitis from cobalt in the rubber industry. Contact. Derm. 19, 217.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitisers. J. Invest. Dermatol. 47, 393.

Pirila V, 1953. Sensitisation to cobalt in pottery workers. Acta Dermatol. Venereol. 33,193.

Pirila V and Kajanne H, 1965. Sensitisation to cobalt and nickel in cement eczema. Acta Dermatol. Venereol. 45, 9.

Shehade SA, Beck MH and Hillier VF, 1991. Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings. Contact. Derm. 24, 119.

Wahlberg JE and Boman A, 1978. Sensitisation and testing of guinea pigs with cobalt chloride. Contact. Derm. 4, 128.

3.3.16 Glutaraldehyde

(Synonym: Glutaric dialdehyde)

CAS No. 111-30-8

A. Skin sensitisation

A.1 Animal data

Glutaraldehyde elicits positive responses in the guinea pig maximisation test (Foussereau *et al*, 1992) and in the Buehler test (Gad *et al*, 1986). Glutaraldehyde is also positive in the mouse ear swelling test (Gad *et al*, 1986; Descotes, 1988) and in the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

In an experimental study, 7/30 male volunteers induced with 5% glutaraldehyde became sensitised, while those induced with 0.1% failed to respond (Marzulli and Maibach, 1974).

There have been numerous reports of skin sensitisation occurring after occupational exposure to glutaraldehyde in hospitals (Nethercott and Holness, 1988; Nethercott *et al*, 1988; Foussereau *et al*, 1992). In addition, a consumer has been reported as having become sensitised to the glutaraldehyde in a hair conditioner (Jaworsky *et al*, 1987).

B. Conclusions

Glutaraldehyde is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Descotes J, 1988. Identification of contact allergens: the mouse ear sensitisation assay. J. Toxicol. Cut. Occul. Toxicol. 7, 263.

Foussereau J, Cavalier C and Zissu D, 1992. L'Allergie de contact professionnelle aux antiseptiques aldehydes en milieu hospitalier. Arch. Mal. Prof. 53, 325.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Jaworsky C, Taylor JS, Evey P and Handel D, 1987. Allergic contact dermatitis to glutaraldehyde in a hair conditioner. Cleve. Clin. J. Med. 54, 443.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Marzulli FN and Maibach HI, 1974. The use of graded concentrations in studying skin sensitisers: experimental contact sensitisation in man. Fd. Cosm. Toxicol. 12, 219.

Nethercott JR and Holness DL, 1988. Contact dermatitis in funeral service workers. Contact Derm. 18, 263.

Nethercott JR, Holness DL and Page E, 1988. Occupational contact dermatitis due to glutaraldehyde in health care workers. Contact Derm. 18, 193.

3.3.17 Formaldehyde

CAS No. 50-00-0

A. Skin sensitisation

A.1 Animal data

Formaldehyde produced positive responses in the guinea pig maximisation test (Basketter and Scholes, 1992), in a modified maximisation test (Maurer and Hess, 1989) and in the Buehler test (Buehler and Griffith, 1975). Formaldehyde is also positive in the murine local lymph node assay (Basketter and Scholes, 1992) and in the mouse ear swelling test (Gad, 1988).

A.2 Human evidence

In patch tests conducted using a maximisation protocol, formaldehyde was classified as a skin sensitiser (Kligman, 1966). In over 4700 consecutive patients patch tested with an extended standard series of up to 34 chemicals, formaldehyde was the ninth most common cause of allergic reactions, seen in 3.0% of the patients (Shehade *et al*, 1991).

Many cases of allergic contact dermatitis have been associated with exposure to formaldehyde. Occupational examples include nurses (Sneddon, 1968), funeral embalmers (Nethercott and Holness, 1988) and newsprint handlers (Black, 1971). Sensitisation has also occurred, for example, as a consequence of wearing formaldehyde-treated clothes (O'Quinn and Kennedy, 1965).

B. Conclusions

Formaldehyde is a human and animal skin sensitiser. This chemical would be expected to elicit positive responses in a predictive test for skin sensitisation.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the local lymph node assay with the guinea pig maximisation test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

Black H, 1971. Contact dermatitis from formaldehyde in newsprint. Contact. Derm. Newsletter 10, 162.

Buehler EV and Griffith JF, 1975. Experimental skin sensitisation in the guinea pig and man. In: Maibach HI, eds., Animal Models in Dermatology, 56, Churchill Livingstone, Edinburgh.

Gad SC, 1988. A scheme for the prediction and ranking of relative potencies of dermal sensitizers based on data from several systems. J. Appl. Toxicol. 8, 361.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitizers. J. Invest. Dermatol. 47, 393.

Maurer T and Hess R, 1989. The maximisation test for skin sensitisation potential - updating the standard protocol and validation of a modified protocol. Fd. Chem. Toxicol. 27, 807.

Nethercott JR and Holness DL, 1988. Contact dermatitis in funeral service workers. Contact Derm. 18, 263.

O'Quinn SE and Kennedy CB, 1965. Contact dermatitis due to formaldehyde in clothing textiles. J. Am. Med. Assoc. 194, 593.

Shehade SA, Beck MH and Hillier VF, 1991. Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings. Contact. Derm. 24, 119.

Sneddon IB, 1968. Dermatitis in an intermittent haemodialysis unit. Br. Med. J. 1, 183.

3.3.18 2,4-Dinitrochlorobenzene (DNCB)

(Synonym: 1-Chloro-2,4-dinitrobenzene)

CAS No. 97-00-7

A. Skin sensitisation

A.1 Animal data

DNCB produced positive responses in a variety of assays including the guinea pig maximisation and Buehler tests (Maurer and Hess, 1989; Botham *et al*, 1991). In the murine local lymph node assay, DNCB has consistently produced positive responses (Kimber and Weisenberger, 1989). DNCB has also proved positive in the mouse ear swelling test (Gad *et al*, 1986; Thorne *et al*, 1991).

A.2 Human evidence

DNCB has been used as a model skin sensitiser in human studies (Rees *et al*, 1990). Determination of allergic skin reactions to DNCB has served as a prognostic test in cancer patients (Roth *et al*, 1975). An outbreak of allergic dermatitis in a tyre factory was traced to DNCB contamination, all workers patch tested gave strong reactions to DNCB (Zina *et al*, 1987).

B. Conclusions

DNCB is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Botham PA, Basketter DA, Maurer T, Mueller D, Potokar M and Bontinck WJ, 1991. Skin sensitisation - a critical review of predictive test methods in animals and man. Fd. Chem. Toxicol. 29, 275.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitising test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Kimber I and Weisenberger C, 1989. A murine local lymph node assay for the identification of contact allergens. Assay development and results of an initial validation study. Arch. Toxicol. 63, 274.

Maurer T and Hess R, 1989. The maximisation test for skin sensitisation potential - updating the standard protocol and validation of a modified protocol. Fd. Chem. Toxicol. 27, 807.

Rees JL, Friedmann PS and Matthews JNS, 1990. The influence of area of application on sensitisation by dinitrochlorobenzene. Br. J. Dermatol. 122, 29.

Roth JA, Eilber FR, Nizze JA and Morton DL, 1975. Lack of correlation between skin reactivity to dinitrochlorobenzene and croton oil in patients with cancer. New Engl. J. Med. 293, 388.

Thorne PS, Hawk C, Kaliszewski SD and Guiney PD, 1991. The noninvasive mouse ear swelling assay. 1. Refinements for detecting weak contact sensitisers. Fundam. Appl. Toxicol. 17, 790.

Zina AM, Bedello PG, Cane D, Bundino S and Benedetto A, 1987. Dermatitis in a rubber tyre factory. Contact Derm. 17, 17.

3.3.19 2-Mercaptobenzothiazole (MBT)

(Synonym : 2-Benzoxazolethiol)

CAS No. 149-30-4

A. Skin sensitisation

A.1 Animal data

MBT elicits positive responses in both the guinea pig maximisation test and the murine local lymph node assay (Basketter and Scholes, 1992; Basketter *et al*, 1993).

A.2 Human evidence

MBT (a rubber accelerator) has been shown to be an important cause of footwear contact dermatitis (Saha *et al*, 1993). MBT is implicated also as an important cause of other forms of occupational contact dermatitis (Fisher, 1986).

B. Conclusions

MBT is a human and animal skin sensitiser.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the local lymph node assay with the guinea pig maximisation test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

Basketter DA, Selbie E, Scholes EW, Lees D, Kimber I and Botham PA, 1993. Results with OECD recommended positive control sensitisers in the maximisation, Buehler and local lymph node assays. Fd. Chem. Toxicol. 31, 63.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

Saha M, Srinivas CR, Shenoy SD, Balachandran C and Acharya S, 1993. Footwear dermatitis. Contact Derm. 28, 260.

3.3.20 1-(3-Chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride [Dowicil 200]

(Synonym: Quaternium 15)

CAS No. 4080-31-3

A. Skin sensitisation

A.1 Animal data

Dowicil 200 has been identified as positive in the guinea pig maximisation test and in the split adjuvant test, but not using the Draize or Buehler methods (Marzulli, 1982).

A.2 Human evidence

Surveys of skin care products revealed that Dowicil 200 was one of the most frequently identified allergic sensitisers (Adams and Maibach, 1985). Reports of clinical sensitisation to Dowicil 200 have been collated (de Groot *et al*, 1994).

B. Conclusions

Dowicil 200 is a human and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References

Adams RM and Maibach HI, 1985. A five-year study of cosmetic reactions. J. Am. Acad. Dermatol. 13, 1062.

de Groot AC, Weyland JW and Nater JP, 1994. Unwanted effects of cosmetics and drugs in dermatology. Elsevier, Amsterdam.

Marzulli F, 1982. Usefulness and limitations of various guinea-pig test methods in detecting human skin sensitisers - validation of guinea-pig tests for skin hypersensitivity. Fd. Chem. Toxicol. 20, 67.

3.3.21 Toluene diamine bismaleimide (TDB)

(Synonyms: Diaminotoluene bismaleimide; N,N'-(4-Methyl-1,3-phenylene)bismaleimide)

CAS No. 6422-83-9

A. Skin sensitisation

A.1 Animal data

TDB has been reported to be positive in both the guinea pig maximisation test and the murine local lymph node assay (Scholes *et al*, 1992).

A.2 Human evidence

There is limited information available on formulated resin matrices, such as TDB. These advanced composite matrix materials are used in the aerospace manufacturing and repair businesses and there are limited data suggesting that TDB has skin sensitising potential (Schwartz, 1989).

B. Conclusions

TDB is a human (limited data) and animal skin sensitiser.

C. References

Scholes EW, Basketter DA, Sarll AE, Kimber I, Evans CD, Miller K, Robbins MC, Harrison PTC and Waite SJ, 1992. The local lymph node assay: results of a final inter-laboratory validation under field conditions. J. Appl. Toxicol. 12, 217.

Schwartz CS, 1989. Toxicity of advanced composite matrix materials. Appl. Ind. Hyg., Special Issue, 23.

3.3.22 Oxazolone

(Synonym: 4-Ethoxymethylene oxazol-5-one)

A. Skin sensitisation

A.1 Animal data

Oxazolone has been used extensively for experimental studies of skin sensitisation and within this context it is regarded as being one of the most potent contact allergens. Oxazolone is positive in all predictive tests in which it has been examined, including the guinea pig maximisation test, the occluded patch test of Beuhler, the murine local lymph node assay and the mouse ear swelling test (Gad *et al*, 1986; Robinson *et al*, 1990; Kimber *et al*, 1994).

A.2 Human evidence

Other than anecdotal reports of accidental skin sensitisation of laboratory workers exposed to oxazolone, there are no data available on allergic contact dermatitis of humans to this chemical.

B. Conclusions

Oxazolone is a human (by inference) and animal skin sensitiser. This chemical would be expected to elicit clear positive responses in predictive tests for skin sensitisation.

C. References

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Kimber I, Dearman RJ, Scholes EW and Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Robinson MK, Fletcher ER, Johnson GR, Wyder WE and Maurer JK, 1990. Value of the cutaneous basophil hypersensitivity (CBH) response for distinguishing weak contact sensitization from irritation reactions in the guinea pig. J. Invest. Dermatol. 94, 636.

3.3.23 Penicillin G

CAS No. 973-53-5 (Ca-salt)
113-98-4 (K-salt)

A. Skin sensitisation

A.1 Animal data

Penicillin G is a sensitiser in the guinea pig maximisation test and is positive in the murine local lymph node assay (Basketter and Scholes, 1992).

A.2 Human evidence

Penicillin G tested positive in the human maximisation test (Kligman, 1966) and has been found, on the basis of patch testing, to cause occupational allergic contact dermatitis (Möller *et al*, 1986).

B. Conclusions

Penicillin G is a human and animal skin sensitiser.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the murine local lymph node assay with the guinea pig maximisation test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

Kligman AM, 1966. The identification of contact allergens by human assay. J. Invest. Dermatol. 47,393.

Möller NE, Nielsen B and Van Wurden K, 1986. Contact dermatitis to semisynthetic penicillins in factory workers. Contact Derm. 14, 307.

3.4 SKIN SENSITISATION, NEGATIVE CONTROLS

3.4.1 Methyl salicylate

CAS No. 119-36-8

A. Skin sensitisation

A.1 Animal data

Methyl salicylate fails to cause skin sensitisation in the guinea pig maximisation test and is usually negative in murine local lymph node assays (Basketter and Scholes, 1992; Montelius *et al*, 1994; Kimber *et al*, 1995).

A.2 Human evidence

Methyl salicylate is negative in the human maximisation test (at a concentration of 8%) (RIFM, 1978). In addition, decades of widespread use of methyl salicylate as a rubefacient in sports rubs and related products at concentrations of > 6%, coupled with no more than a single report of apparent skin allergy in the standard literature, strongly reinforce the view that methyl salicylate is not a skin sensitiser (Rycroft *et al*, 1992; Fisher, 1986, Cronin, 1980).

B. Conclusions

The absence of evidence either from predictive studies in animals and humans or from clinical patch testing in the face of extensive human skin exposure argues that methyl salicylate should be regarded as a non-sensitiser.

C. References

Basketter DA and Scholes EW, 1992. Comparison of the local lymph node assay with the guinea pig maximisation test for the detection of a range of contact allergens. Fd. Chem. Toxicol. 30, 65.

Cronin E, 1980. Contact Dermatitis, Churchill Livingstone, London.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

Kimber I, Hilton J, Dearman RJ, Gerberick GF, Ryan CA, Basketter DA, Scholes EW, House RV, Guy A, Ladics GS and Loveless SE, 1995. An international evaluation of the murine local lymph node assay and comparison of modified procedures. Toxicology 103, 63.

Montelius J, Wahlkvist H, Boman A, Fernström P, Gråbergs L and Wahlberg JE, 1994. Experience with the murine local lymph node assay: Inability to discriminate between allergens and irritants. Acta Derm. Venereol. 74, 22.

RIFM (Research Institute for Fragrance Materials), 1978. Monograph on methyl salicylate. Fd. Chem. Toxicol. 16, 821.

Rycroft RJG, Menné T, Frosch PJ and Benezra C, 1992. Textbook of Contact Dermatitis, Springer-Verlag, Heidelberg.

3.4.2 p-Aminobenzoic acid (PABA)

(Synonym: 4-Aminobenzoic acid)

CAS No. 150-13-0

A. Skin sensitisation

A.1 Animal data

p-Aminobenzoic acid fails to cause skin sensitisation in either the guinea pig maximisation test or the murine local lymph node assay (Kimber *et al*, 1994).

A.2 Human evidence

There was no evidence of skin sensitisation when PABA was tested at 25% in the human maximisation test (Kligman, 1966). Furthermore, despite widespread use in sunscreens at concentrations in the range 1-5%, there are very few reports of allergic contact dermatitis (Cronin, 1980; Fisher, 1986; English *et al*, 1987; Rycroft *et al*, 1992).

B. Conclusions

PABA is not a human or animal skin sensitiser.

C. References

Cronin E, 1980. Contact Dermatitis, Churchill Livingstone, London.

English JSC, White IR and Cronin E, 1987. Sensitivity to sunscreens. Contact Derm. 17, 159.

Fisher AA, 1986. Contact Dermatitis, 3rd ed., Lea and Febiger, Philadelphia.

Kimber I, Dearman RJ, Scholes EW, Basketter DA, 1994. The local lymph node assay: developments and applications. Toxicology 93, 13.

Kligman AM, 1966. The identification of contact allergens by human assay. J. Invest. Dermatol. 47,393.

Rycroft RJG, Menné T, Frosch PJ and Benezra C, 1992. Textbook of Contact Dermatitis, Springer-Verlag, Heidelberg.

3.4.3 Sodium lauryl sulphate (SLS)

(Synonym: Dodecylsulphate, sodium salt)

CAS No. 151-21-3

A. Skin sensitisation

A.1 Animal data

In the guinea pig maximisation test, SLS was negative (Wahlberg and Boman, 1985); it was also negative in the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

Sodium lauryl sulphate is used routinely as an irritation marker in many clinical studies and has even been suggested for use in a maximisation procedure to increase the sensitivity of a patch test method by increasing skin irritation (Kligman and Epstein, 1975). Further supporting evidence for the failure of SLS to cause skin sensitisation is the human maximisation test performed with 25 human volunteers (Kligman, 1966). Notwithstanding the occasional apparent positive patch test to SLS (reviewed by Dooms-Goossens and Blockeel, 1996) this material should be regarded as lacking skin sensitising activity.

B. Conclusions

Sodium lauryl sulphate should be considered to lack skin sensitisation potential.

C. References

Dooms-Goossens A and Blockeel I, 1996. Allergic contact dermatitis and photoallergic contact dermatitis due to soaps and detergents. Clin. Dermatol. 14, 67-76.

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Kligman AM and Epstein W, 1975. Updating the maximisation test for identifying contact allergens. Contact Derm. 1, 231.

Kligman AM, 1966. The identification of contact allergens by human assay. III. The maximisation test: a procedure for screening and rating contact sensitisers. J. Invest. Dermatol., 47, 393.

Wahlberg JE and Boman A, 1985. Guinea pig maximisation test. In: Contact Allergy Predictive Tests in Guinea Pigs. Current Problems in Dermatology Vol. 14, Andersen KE and Maibach HI, eds., 59, Karger, Basel.

3.4.4 Glycerol

CAS No. 56-81-5

A. Skin sensitisation

A.1 Animal data

There are no data in the literature which associate glycerol with skin sensitisation in animals. Glycerol was found to be negative in the murine local lymph node assay (Gerberick *et al*, 1992) and in the mouse ear swelling test (Gad *et al*, 1986).

A.2 Human evidence

Glycerol is found in many skin creams and topical applications. It is used routinely as a vehicle for patch testing. Out of several thousand dermatitis patients who have been patch tested with 50% glycerol, only two have displayed skin reactions following a 24-hour patch test (Hannuksela, 1979). Both patients had regularly used a skin cream containing glycerol.

B. Conclusions

Glycerol is not a human or animal skin sensitiser.

C. References

Gad SC, Dunn BJ, Dobbs DW, Reilly C and Walsh RD, 1986. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84, 93.

Gerberick GF, House RV, Fletcher BR and Ryan CA, 1992. Examination of the local lymph node assay for use in contact sensitisation risk assessment. Fundam. Appl. Toxicol. 19, 438.

Hannuksela M, 1979. Allergic and toxic reactions caused by cream bases in dermatological patients. Int. J. Cosmet. Sci. 1, 257.

3.4.5 Isopropanol (IPA)

(Synonyms: Isopropyl alcohol; 2-Propanol)

CAS No. 67-63-0

A. Skin sensitisation

A.1 Animal data

Isopropanol applied as a 50% aqueous solution to the facial skin of rats for 187 days did not result in sensitisation (Boughton, 1944).

A.2 Human evidence

A few cases of contact dermatitis have been reported following isopropanol use (Ludwig and Hausen, 1977; McInnes, 1973; Wasilewski, 1968), but based upon its widespread use as a skin cleanser and rubbing compound, sensitisation is extremely rare.

B. Conclusion

Due to the lack of evidence for sensitisation, despite widespread dermal exposure, isopropanol is considered not to be a skin sensitiser.

C. References

Boughton LL, 1944. Relative toxicities of ethyl and isopropyl alcohols as determined by long-term rat feeding and external application. J. Am. Pharm. Assoc. 33, 111.

Ludwig E and Hausen BM, 1977. Sensitivity to isopropyl alcohol. Contact Derm. 3, 240.

McInnes A, 1973. Skin reaction to isopropyl alcohol. Br. Med. J. 1, 357.

Wasilewski C, 1968. Allergic contact dermatitis from isopropyl alcohol. Arch. Dermatol. 98, 502.

3.4.6 Diethyl phthalate (DEP)

CAS No. 84-66-2

A. Skin sensitisation

A.1 Animal data

Diethyl phthalate has been tested in guinea pigs in a study comprising concurrent maximisation, open epicutaneous, Draize and Freund's complete adjuvant tests (Klecak *et al*, 1977). Although DEP did not cause sensitisation in any of the 4 tests, confidence in these negative results is undermined by the absence of positive controls. Also, the sensitivity of the strain of guinea pig used in the study is not well-documented (Woodward *et al*, 1986).

A.2 Human evidence

Diethyl phthalate proved negative in patch tests conducted using a maximisation protocol (Greif, 1967).

No information on skin sensitisation resulting from occupational or consumer exposure of humans to DEP is available. In view of the widespread use of phthalate esters, the large tonnages produced and the lack of reports of sensitisation, it can be concluded that the common diesters such as DEP have no appreciable sensitising potential (Woodward *et al*, 1986).

B. Conclusions

DEP is not a human or animal skin sensitiser.

C. References

Greif N, 1967. Cutaneous safety of fragrance material as measured by the maximization test. Amer. Perfum. Cosmet. 82, 54.

Klecak G, Geleick H and Frey JR, 1977. Screening of fragrance materials for allergenicity in the guinea-pig. 1. Comparison of four testing methods. J. Soc. Cosmet. Chem. 28, 53.

Woodward KN, Smith AM, Mariscotti SP and Tomlinson NJ, 1986. Review of the toxicity of the esters of o-phthalic acid (phthalate esters). Health and Safety Executive, Toxicity Review 14, HMSO, London.

3.4.7 Dimethylformamide (DMF)

CAS No. 68-12-2

A. Skin sensitisation

A.1 Animal data

DMF was found not to cause sensitisation following epicutaneous exposure of guinea pigs (Kittila, 1967; DuPont, 1970); indeed it used frequently as a vehicle, in sensitisation studies.

A.2 Human evidence

Despite extensive occupational exposure, there is no evidence that DMF causes sensitisation in the chemical industry workforce (MAK, 1992).

B. Conclusions

DMF is not a human or animal skin sensitiser.

C. References

Kittila RS, 1967. Dimethylformamide Chemical Uses, DuPont, USA.

DuPont de Nemours, 1970. DMF (Dimethylformamide) Product Information.

MAK Gesundheitsschadliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begrundung von MAK-Werten (Maximale Arbeitsplatz-Konzentrationen), 1992. Verlag Chemie, Weinheim.

3.4.8 Zinc sulphate

CAS No. 7733-02-0

A. Skin sensitisation

A.1 Animal data

Zinc sulphate failed to induce a response in a modified murine local lymph node assay (Ikarashi *et al*, 1992).

A.2 Human evidence

A test of an ointment containing 0.5% zinc in 200 patients indicated that the jelly can be used without any risk of allergic skin reactions (Holzmann *et al*, 1988). Zinc salts are used widely in topical medicaments without reported sensitisation. de Groot *et al* (1994) found no reports of skin allergy to zinc sulphate.

B. Conclusion

Zinc sulphate is not a human or animal skin sensitiser.

C. References

de Groot AC, Weyland JW and Nater JP, 1994. Unwanted effects of cosmetics and drugs in dermatology. Elsevier, Amsterdam, 724.

Holzmann H, Muller AA and Wendt G, 1988. Topical treatment of herpes simplex: clinical and human experimental studies of efficacy and tolerance with a combination of zinc sulphate and heparin in a jelly formulation. Aktuelle Dermatologie 14, 64.

Ikarashi Y, Tsuchiya T and Nakamura A, 1992. Detection of contact sensitivity of metal salts using the murine local lymph node assay. Toxicol. Lett. 62, 53.

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D-1999-3001-156