SKIN AND RESPIRATORY SENSITISERS:
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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

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 minimum 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

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


Skin and Respiratory Sensitisers - Reference Chemicals Data Bank


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


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 (based on limited data). In humans, there is convincing evidence that ammonium HCP is a respiratory sensitiser.

D. References


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 workplace, 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 sensitisier 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

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


Pauluhn J and Mohr U, 1994. Assessment of respiratory hypersensitivity in guinea pigs sensitised to diphenylmethane-4,4'-diisocyonate (MDI) and challenged with MDI, acetylcholine or MDI-albumin conjugate. Toxicology 92, 53.


3.1.5  Trimellitic anhydride (TMA)

   (Synonym: 1,2,4-Benzene-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/m³.

C. Conclusions

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

D. References

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


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.


Kern RA, 1939. Asthma and allergic rhinitis due to sensitization to phthalic anhydride. Report of a case. J. Allergy 10, 164.


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


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 (Blakie 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 \textit{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


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/m³ (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
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


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


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

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


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


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.


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


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


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


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


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 sensitisier 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 sensitisier. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References


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.

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


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


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


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.


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


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 sensitisir (limited data).

C. References


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

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


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


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


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


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


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


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


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.


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 sensitisier. This chemical would be expected to elicit clear positive responses in a predictive test for skin sensitisation.

C. References


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


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.


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


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


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


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 sensitisser.

C. References


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


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


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


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


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


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


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.


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


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.


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


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