Use of Human Data in Hazard Classification for Irritation and Sensitisation

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CONTENTS

SUMMARY

Reference to the use of human data is made throughout the European legislation relating to the classification and labelling, as well as risk assessment, of substances and preparations. In addition, relevance of animal test results to man is mentioned. However, no guidance is given on what constitutes acceptable human data. The primary purpose of this report is to provide such guidance and to propose how human data may be used in decisions on the classification of irritation and sensitisation effects and when it may be more appropriate than other data.

The provisions in European law for the use of human data are reviewed in Section 2 and Appendix A.

In the context of skin, eye and respiratory irritation, and skin and respiratory sensitisation, the classification of a substance or preparation based on consideration of adequate human data may be different from that based only on animal data. Specific examples are described in Section 3 and Appendix B where the classification of substances and preparations appears to be more soundly based when human data are taken into account. Indeed, human data might lead ultimately to a more accurate risk assessment.

Human data fall into two main classes, observational and experimental. Section 4 lists the various types of data that may be used for classification purposes and gives guidance on factors which influence their quality. Outline protocols for experimental studies on skin irritation and skin sensitisation are presented.

The criteria governing the possible use of such data in the classification process are addressed in Section 5. The Task Force proposes classification criteria based on human data for each endpoint considered (skin, eye and respiratory irritation, skin and respiratory sensitisation).

In the context of this report, human clinical studies may be undertaken where there is a perceived need to develop an improved understanding of irritation and sensitisation effects. For chemicals and preparations where skin contact is unavoidable, human data has the potential to provide the most accurate information in terms of hazard and risk assessment.

Classification and labelling are based currently on the inherent hazard of a chemical substance or preparation. The proposal is made that, in the future, at least labelling should be based on risk assessment and reflect risk rather than hazard. It is suggested that discussions on the global harmonisation of classification and labelling systems should provide the opportunity inter alia to incorporate quality criteria for the use of human data.

The Task Force recommends that human data of good quality should always be taken into account in classification and risk assessment decisions.

1. INTRODUCTION

In the European Union (EU) the classification criteria for health hazards of chemical substances and preparations are based mainly on data from animal tests. Data from human exposure to substances and preparations are recognised as a valuable source of information but little guidance is offered in the European 'chemical legislation' on how to use or, if appropriate, generate such data.

To fill this gap an ECETOC Task Force was set up with the following Terms of Reference:

- Provide illustrative examples where classification of substances and preparations would differ if good human evidence was taken into account;
- develop guidance for the collection and analysis of existing human evidence;
- identify criteria by which human data can be considered for classification (including where they may be more appropriate than animal data).

The main goal of the Task Force was to develop guidance for the use of human data as part of a wider strategy for assessing hazard and risk, whilst acknowledging the undoubted value of animal test data for predicting effects in humans. The primary focus of the Task Force deliberations was in the evaluation of irritation and sensitisation potential since the most objective and reliable human data existed for these endpoints. The Task Force also developed guidance on quality criteria for human volunteer studies so that results from such studies could be considered for classification purposes.

2. HUMAN DATA AND REGULATORY GUIDELINES IN EUROPE

2.1 Current situation

In the EU legislation on chemical substances and preparations there is clear recognition that human data or 'effects on man' are of value and relevance in the identification of hazards. To illustrate the extent to which different European regulations and guidelines take account of human data and prescribe how these data can be used, relevant citations have been included in Appendix A. These relate to excerpts from the 'Dangerous Substances Directive' (DSD) (EC, 1967) and its amendments and technical adaptations to progress, the 'Dangerous Preparations Directive' (DPD) (EC, 1988, 1999) and the Classification and Labelling general requirements for substances and preparations (C&L guide; Annex VI to DSD) (EC, 1991 and subsequent) and the Technical Guidance Document (TGD) in support of the directives and regulations on risk assessment for new notified and for existing substances (EC, 1996a). It is evident from these citations that human data may, and should, be taken into account both in hazard evaluation and in risk assessment. Indeed, with certain exceptions, human information, where available, is given the first priority, with animal toxicity studies and any other supporting information such as data from *in vitro* studies and structure-activity relationship analyses used in a complementary fashion.

Where the human data clearly indicate a material to be a hazard to man, the interpretation is straightforward. In such cases, classification is derived from a consensus based on the weight of the positive evidence, although the criteria have not been defined in all cases (e.g. classification of isocyanates as 'respiratory sensitisers'). However, difficulties can arise where human data indicate a material to be less hazardous than the prediction based on animal data. There is sometimes a reluctance to discount the animal predictions in these cases. On the one hand, such reluctance seems irrational; on the other hand, it is recognised that the use of human data in these deliberations is not straightforward and involves consideration of a number of factors.

To ensure that the principles that are set out in the regulatory guidance are applied consistently, it is essential to develop criteria on the quality and relevance of analytical and descriptive epidemiological studies and case reports. Criteria are also needed for the use of data from studies with human volunteers.

2.2 Regulatory aspects

Currently, classification and labelling for health effects in the EU involves the identification of potential hazards, without specification of the exposure conditions necessary for the hazard to be expressed.

Once classified, the substances or preparations are labelled making use of standardised symbols and Risk (R) and Safety (S) phrases. In the way in which they are presented, R and S phrases contain a general and 'universal' element of risk management, to help the user in taking preventive measures (e.g. **'**Avoid contact with the eyes**'**). However, their choice is based on the inherent hazard of a substance or preparation, not on a specific estimation of the risk. Such an approach may lead to anomalies and inappropriate communication of health information (Basketter *et al*, 1999; Roggeband *et al*, 2001). Risk is determined not only by the inherent effects (hazard) but also by exposure (EC, 1993b; Art. 2).

This causes some confusion in the legislative texts as well as in the public mind about the terms **'**hazard**'** and **'**risk**'** and their significance. This is exacerbated by linguistic complications in using these terms across the EU. It is not surprising that the term **'**Risk phrase**'** is commonly understood as reflecting the result of a risk assessment, whereas according to the EC directives on the classification, packaging and labelling of dangerous substances and preparations, **'**Risk phrases**'** reflect a potential hazard rather than a known risk.

The Task Force accepts that the identification of hazard, the first step in the risk assessment process, should remain the primary basis for classification. Thus, valid human data (see Sections 4 and 5), whether indicative of a greater or lesser risk than animal data, should be considered and normally take precedence over other data. In the second step in the risk assessment process, the identified hazard is evaluated in terms of the relevance of the health effect to man and the exposure level necessary to produce it, in relation to the exposure that might conceivably occur to human beings. The collection of (human) exposure data, as required by the EC 'Risk Assessment' legislation (EC, 1993b, 1994) will enlarge the data base on exposures occurring at the workplace and for the public at large, and this will assist this assessment or evaluation.

It is suggested that, in the future, substances and preparations should be labelled on the basis of the above evaluation rather than on hazard identification only. Suitable Risk phrases should be chosen in order to communicate the potential risk, rather than the theoretical hazard, to the user. Safety phrases to prevent the risks, or suitable advice on first aid, should be used in addition if necessary, but might be sufficient for risk management without Risk phrases where the hazard is of low relevance to man.

Agreements reached (OECD, 1998) and recent discussions (ILO, 2000) on the global harmonisation of classification and labelling systems should provide the opportunity to incorporate quality criteria for the use of human data. This in turn would allow better use of the existing database on effects observed after human exposure, in epidemiological studies, clinical experience (including human volunteer studies) and case reports.

3. CLASSIFICATION DECISIONS BASED ON HUMAN DATA

In the context of skin and eye irritation and skin sensitisation, the classification of a substance or preparation, when based solely on prescribed animal tests, may differ from that which would be derived from relevant human data. Examples are provided in Appendix B where a 'weight of evidence' approach was applied taking into account the available human toxicology database. Differences and similarities between the results of animal testing and data obtained with human volunteers or case reports are illustrated with reference to testing for skin and eye irritancy and skin sensitisation.

As classification for both irritation and sensitisation of the respiratory tract is based essentially on human evidence, it is neither appropriate nor possible to provide comments on the difference in classification based on animal versus human data. Instead a few examples are given, which illustrate how human data can be used for these endpoints (see Annex B2).

3.1 Skin irritation

Comparative testing with rabbits and human volunteers exhibits clear differences in susceptibility to some classes of irritant substances and preparations. Human skin is, in general, less affected. This may be related mainly to physiological differences between species. Human patch tests become important, particularly for substances and preparations at the lower end of the irritation scale. Current predictive tests are designed to detect irritant effects from single exposures. Some chemicals or preparations that are not acutely irritant are known from human experience to produce irritation or other adverse effects on the skin following chronic or repeated exposure. While such effects may not be relevant for classification, they should be reflected in Risk and / or Safety phrases.

3.2 Eye irritation

Quality human eye irritation data are rarely available. However, where such data exist, they should be taken into account.

The existing animal model for eye irritation has been shown to be an adequate predictor for a number of substances and preparations. For detergent and cleaning preparations, cosmetics and their constituent substances, the results obtained with a modified model, the low volume eye test (ASTM, 1985), are more in line with the scores obtained with human volunteers (Roggeband *et al*, 2000). This is further confirmed by experience from accidental exposures. The Draize rabbit eye test has served as a useful tool for assessing eye irritation potential of chemicals and products for many years. However, studies involving the low volume eye test have indicated that the Draize test exaggerates the eye irritancy response reported in humans and results in the over-classification of the irritancy potential of many substances. The most effective public health approach is to have a test that accurately identifies only those products that need to be labelled with an appropriate warning (Lambert *et al*, 1993). One difficulty is that the ASTM test has not been used and thus validated for as many chemicals and preparations as the classical Draize test (Draize *et al*, 1944) on which the EC Annex V test (EC, 1984) was based.

3.3 Respiratory irritation

Human data are the normal basis for the assessment of the irritant hazard to the respiratory system. The C&L guide (EC, 1991; Annex VI, 3.2.6.3) indicates that the decision to use R37 (**'**Irritating to respiratory system**'**) should be based normally on practical observation in humans. High vapour pressure and skin / eye irritancy of a substance or preparation should alert to the need to evaluate for respiratory irritancy potential.

A test that measures the inhaled concentration of a substance necessary to cause a 50% reduction in the respiratory rate in mice (Alarie, 1981) has been used as a predictor of respiratory irritation, but there is no approved test method in Annex V of the DSD (EC, 1984).

It has recently been demonstrated that human volunteer studies can be conducted which may permit the demonstration of the absence of respiratory irritation (Keech *et al*, 2001).

3.4 Skin sensitisation

The examples provided show that the animal models are not always reliable predictors for effects in man. Different animals models sometimes provide conflicting data. Human experience, including clinical case reports, is important in the hazard assessment process and should be considered alongside any available human test data.

3.5 Respiratory sensitisation

There is no well-recognised animal model for predictive testing for the potential to cause respiratory sensitisation. Consequently, human experience, including clinical case reports, is of prime importance in the hazard identification and assessment process.

4. TYPE AND QUALITY OF HUMAN DATA FOR CLASSIFICATION PURPOSES

The Task Force has developed guidance for the type and quality of human evidence appropriate for classification purposes based on the collective scientific experience of Task Force members, using as examples the substances and preparations described in Appendix B.

Human data for classification purposes can be considered to fall within the following broad categories:

Analytical and observational studies

- Analytical epidemiological studies: The frequency (incidence or prevalence) of a health endpoint in an exposed population is compared with the frequency in a reference (presumed to be unexposed) population or the degree of exposure in a population with a health outcome is compared with the degree of exposure in a reference population without the health outcome.
- Descriptive or correlation epidemiology studies: The frequency of a health endpoint is described in populations that differ in ways that may correlate with exposure.
- Observational ('Human experience'): General information from human experience, including case reports and reports of specific health surveillance programmes.

Experimental studies

- Experimental ('Human volunteer studies'): Data from controlled, ethical, clinical studies with human volunteers.

For the health endpoints discussed in this report, it is recognised that the majority of human data will be derived from the observational and experimental categories mentioned above.

4.1 Analytical and observational studies: Sources and validity

4.1.1 Epidemiology

It is widely accepted (Hemminki and Vineis, 1985; CMA, 1991; Baldwin and Hoover, 1991; Zielhuis, 1992) that the validity and quality of an epidemiology study rests on the following criteria (adapted for chemical substances and preparations):

- Proper ethical criteria must be observed;
- the substance or preparation studied should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation;
- exposure to the substance or preparation should be quantified or well-estimated and at a level which is relevant for the population of concern (workers or general public);
- presence of confounding factors should be known;
- control group must be adequate;
- populations observed must be sufficiently large for statistical conclusions to be drawn; proper statistics must be used;
- documentation and records must be adequate.

Various codes of Good Epidemiological Practice have been promulgated and these have recently been reviewed (Jackson, 1999).

4.1.2 Human experience

Information on practical human experience with substances and preparations may come from a variety of sources where a system is in place to detect, monitor and record signals / questions / complaints / incidents:

- Consumer experience and comments, possibly followed up by professionals (e.g. ophthalmologists or dermatologists) (Van Abbe, 1973; Malten *et al*, 1984; Freeberg *et al*, 1986a);
- records from Poison Control Centres (Velvart, 1981);
- national and international home accident surveillance programmes;
- records from forensic medicine, including cases of suicides;
- records of workers' experience and accidents;
- case reports in the general scientific and medical literature.

The collection of data may be retrospective or prospective. Data may be anecdotal or gathered following a defined protocol.

The frequency and the severity of complaints from the general public are also indicators. However, numbers must be read with caution, taking into account such factors as the culture of the country, the variation in the rate of complaints from country to country, and the established fact that the introduction of a 'new' product is generally followed by an increase in the number of complaints compared with the 'old' product, but this rapidly returns to 'background levels' (How *et al*, 1989). In the case of consumer comments, the conditions of exposure leading to the incident are not always known and sometimes are only qualitatively described. Nevertheless, it is possible to derive a significant amount of valuable information from consumer complaints. This is particularly true when the affected person can be asked to visit a qualified physician who can then take appropriate measures to define to what extent the substance or preparation in question was responsible for the observed effects.

Specific prospective or retrospective surveys at Poison Control Centres, national or international surveillance programmes, such as the Home Accident Surveillance System (HASS) in the UK, the Personal Accident Registration System (PORS) in the Netherlands, or the Leisure and Home Accident Surveillance System (ELHASS) at the European level, provide valuable data on frequency and types of accidents, particularly for substances and preparations sold to the general public. These surveys allow the definition of a pattern of response in case of accidental exposure.

4.1.3 Specific health surveillance

More focused than the general human observations described above, is the specific health monitoring of all exposed individuals in a defined worker or general public group:

- Records of worker exposure (ambient air or biological monitoring) and health status (Sarlo *et al*, 1990; Whorton *et al*, 1994);
- medical surveillance to detect early sub-clinical effects in workers (Scailteur and Lauwerys, 1987; Meding and Swanbeck, 1990; Tordoir, 1994);
- consumer tests (monitoring by questionnaire and / or medical surveillance) (How *et al*, 1989; Schmitt, 1994a).

Both negative and positive health data generated at the workplace are particularly useful. These are of most value where suitably qualified professionals are involved and the work conditions (including level of exposure, use of protective equipment, number of individuals and frequency of exposure) are recorded using industrial hygiene methods. Furthermore, medical surveillance may allow detection of biochemical signs at an early stage (e.g. changes in enzymes, DNA adducts) (Tordoir, 1994).

4.1.4 Use for classification

To be valid for classification purposes, records of human experience and of specific surveillance programmes must be such that:

- Frequency of incidents / accidents / effects versus the number of persons exposed, the extent of exposure (magnitude, frequency and duration) can be estimated over a known period of time;
- exposure is described sufficiently and is relevant to classification;
- severity, persistence or absence of health effects is objectively described and evaluated.

When human experience information on a number of similar substances or preparations is used in the classification of a new substance or preparation, designed to be handled and used in the same way, the new product must be sufficiently similar to the others, in terms of chemical composition and physical form, to allow meaningful reference. Such extrapolation requires expert judgement.

4.2 Human volunteer studies (experimental clinical data)

4.2.1 Ethical considerations

Human clinical studies should only be carried out where there is a definite clear probability of obtaining useful information (Butterworth and Mangham, 1987), and can only be performed taking into account relevant ethical considerations. In the context of this report, human clinical studies may be undertaken where there is a perceived need to develop an improved understanding of irritation and sensitisation effects. For chemical and preparations where skin contact is unavoidable human data has the potential to provide the most accurate information in terms of hazard and risk assessment. Ethical considerations and criteria for use of human subjects have been reviewed in detail (Tordoir, 1994). It should be emphasised that any test carried out in human volunteers should conform with the generally accepted ethical principles for biomedical research (Declaration of Helsinki, 1964, last amended 1993) and good clinical practice, including quality assurance and quality control (for description, see EC, 1990; ICH, 1997). These include:

- Ethical review of the protocol by an appropriate independent Ethics Committee;
- fully informed written consent by the participants, who must be volunteers;
- availability of sufficient information on the substances or preparations based on physico-chemical methods and / or existing information from laboratory animals and / or sufficient human experience information on these or similar materials to preclude the occurrence of any significant risk to the volunteers;
- proper medical support;
- discontinuation of the experiment at the discretion of the investigator if he judges that to continue may be harmful;
- volunteers being free to withdraw at any time.

The above principles must be observed for any human test protocol (Schmitt, 1994b).

4.2.2 Protocols for human studies

In Tables 1 and 2, outline protocols are presented for testing a substance or preparation in adults for skin irritation or sensitisation. The results of such tests may contribute to the classification of the product under relevant EU legislation. It should be borne in mind that the skin of children may be more susceptible than that of adults.

Table 1: Skin irritation. Outline human clinical test protocol

Requirements		Comments
Number	Enough to be valid in the context of the protocol	Depending on the nature and the purpose of the study, the number needed may vary (usually 10 to 30)
Sex	Either	It is recommended that the sex ratio (M:F) of the panel should be in the range 0.5-2
Health	Healthy. Where appropriate including atopics, but free of skin disease.	Volunteers should not be taking medication which may interfere with the outcome of the study
Age	≥ 18	
Ethics	Study must be approved by relevant ethical committee	Adequate information should be available to substantiate the safety of the study (e.g. lack of systemic toxicity, corrosive substances/preparations have been eliminated)
Amount and concentration of test material	Undiluted (moistened if necessary) at least 50 mg/cm2	Starting with diluted material and titrating up may provide useful information
Control	If used, positive control giving recognised typical response	Applied in the same manner and amount as the test material, the control patch should give a positive response in a sufficient number of volunteers to permit a proper evaluation
Skin site	Preferably arm or back	Test and control materials should be applied to adjacent skin areas
Patch type	Variable (occluded or semi-occluded)	Many patch types are available e.g. Finn, Hill Top, Van der Bend chambers
Duration	Up to 4 h	Since the intensity of the response may not be known, a progressive protocol (initially short duration of application, perhaps in a sub group of volunteers) may be required
Observation times	24, 48, 72 h and longer if necessary.	
Scoring criteria	Simple scale: 0 no response 1 weak response 2 moderate response 3 strong response 4 severe response	
Evaluation	Against control/standard response or against pre-established scoring criteria	

Table 2: Skin sensitisation. Outline human clinical test protocol

Requirements		Comments
Number	Enough to be valid in the context of the protocol	Usually at least 100 volunteers in an HRIPT[1,2] and 25 in a maximisation study[3]
Sex	Either	It is recommended that the sex ratio (M:F) should be in the range 0.5-2
Health	Healthy. Where appropriate including atopics, but free of skin disease	Volunteers should not be taking medication which may interfere with the outcome of the study
Age	≥ 18	
Ethics	Study must be approved by relevant ethical committee	Adequate information should be available to substantiate the safety of the study (e.g. lack of systemic toxicity, material unlikely to induce skin sensitisation)
Vehicle	Free of allergenic potential and non-irritant	
Placebo	Placebo may be needed, free of allergenic potential	
Control	Irritant control may be used	For example, aqueous high purity sodium lauryl sulphate
Concentration of test material	No more than minimally irritating	This may vary depending on the specific test method
Skin site	Preferably arm or back	Test and control materials should be applied to adjacent skin areas
Patch type	Variable (occluded)	Many patch types are available e.g. Finn, Hill Top, Van Der Bend chambers
Duration	Repeated induction patches (24/48 hours) followed by challenge patch	

1 HRIPT: Human Repeat Insult Patch Test

2 Stotts, 1990

3 Kligman, 1966

Table 2 continued: Skin sensitisation. Outline human clinical test protocol

Requirements		Comments
Observation times	After each induction, and challenge patch (24/48 h and longer if necessary)	
Scoring criteria	Simple scale: 0 no response 1 weak response 2 moderate response 3 strong response 4 severe response	Depending on protocol, with or without oedema, papules, vesicles
Evaluation	Against control/standard response or pre-established criteria 2,3	Responses need to be interpreted with care since it is difficult to distinguish a weak irritant from a weak allergic response; criteria to distinguish include characteristics of the response (e.g. oedema,vesicles). Important criteria to define a positive allergic response are persistence of the response and reproducibility at re-challenge

Human eye irritation (Griffith *et al*, 1980; Ghassemi *et al*, 1993; Roggeband *et al*, 2000) and respiratory irritation testing (Linn *et al*, 1989; Molhave and Pedersen, 1986; Keech *et al*, 2001) may also be conducted under special circumstances. However, due to the limited use of such testing, an outline protocol is considered outside the scope of this report. Human tests to establish sensitisation or allergy by the respiratory route are used for diagnostic purposes (reviewed in ECETOC, 1993).

It should be noted that some human experimental studies are carried out for safety reassurance purposes. In some cases, these may also provide further or different information on the inherent properties of the material and thus may also be useful for classification (Calvin, 1992; Rodriguez *et al*, 1992).

5. HUMAN DATA: PROPOSED CRITERIA FOR CLASSIFICATION

In the light of the experience of Task Force members, classification criteria based on human data are proposed for all endpoints considered in this report, namely:

- Skin irritation / corrosion;
- eye irritation;
- respiratory irritation;
- skin sensitisation;
- respiratory sensitisation.

5.1 Skin irritation/corrosion criteria

5.1.1 Human experience

Irrespective of the results of animal experiments.

- Where there are data from only a small number of exposed people, amongst whom a subset exhibit substantial skin irritation (e.g. objective clinical signs) that lasts several days, or less severe irritation that is long lasting (>3 weeks following a single exposure), the substance or preparation should be classified.
- Where the effect is less substantial, and / or disappears in less than a day, the need for classification should be judged on a case by case basis. Changes in skin hydration or skin blood flow, resulting from exposure and detected by instrumentation, should not, in the absence of objective clinical signs, require classification.
- Where skin contact in a small population under surveillance (e.g. a defined group of workers wearing no gloves or a closely monitored test with consumers) produces no, or only minor, transient, fully reversible irritation, neither classification nor use of R38 (Irritating to skin) is necessary. Note that, in order to exclude more severe reactions in 10% of an exposed population, it would be necessary to observe 29 exposed persons (for 95% confidence) or 44 persons (for 99% confidence).
- Where a large population has skin contact with the substance or the preparation in an uncontrolled way over a considerable period and there is a system in place to pick up adverse reaction reports or complaints and there is no or only minor, transient, fully reversible irritation, in observations covering 100,000 person.years of experience, neither classification nor use of R38 is necessary.

5.1.2 Human volunteer studies

Irrespective of the results of animal experiments.

- Where volunteers exhibit a response that meets the conditions defined below in a properly conducted 4 hour patch test, R38 must be applied. Typically, human studies of skin irritation will comprise from 10 to 30 volunteers. The conditions that need to be fulfilled can be defined by pre-established scores on an irritation scale (as in the case in the EC Annex V rabbit test protocol) (see a. below) or by comparison with an internal standard, chosen to display a typical irritant response (see b. below).

  a. Pre-determine a level of response (based on incidence and / or severity of erythema, oedema, other skin reactions) necessary to trigger classification.

     In this case, where volunteers exhibit a response equal to or higher than the pre-determined response (e.g. erythema score 2, and / or oedema score 2, on scales of 0-4, and / or skin encrustation), classification and the use of R38 is necessary.

  b. Use a positive irritant control substance or preparation:

     - at a concentration well below its limit for classification (e.g. SLS 10%).

     In this case where volunteers exhibit a response clearly higher than the response to the control, classification and the use of R38 is necessary (Dillarstone and Paye, 1994).

     - at a concentration chosen to be at its limit for classification (e.g. SLS 20%).

     In this case where volunteers exhibit a response that is not statistically lower than the response to the positive control, classification and the use of R38 is necessary (Basketter *et al*, 1994).

- Where these conditions are not met, no classification is required.

It should be noted that a reference chemicals data bank for skin irritation has been published (ECETOC, 1995).

5.2 Eye irritation criteria

5.2.1 Human experience

Irrespective of the results of animal experiments.

- Where there are data from only a small number of exposed people, amongst whom a subset exhibit substantial eye irritation (e.g. objective clinical signs) that lasts for several days, or less severe irritation that is long lasting or irreversible, the substance should be classified as irritant and the choice of risk phrase will depend on the severity of the effects.
- Where the effect is less substantial and / or the effect disappears in less than a day, the need for classification should be judged on a case-by-case basis.
- Where eye contact, in a small population under surveillance (e.g. workers who have been exposed to the product in their eye) produces no, or only minor, transient, fully reversible irritation, neither classification nor the use of R36 is necessary. Note that in order to exclude more severe reactions in 10% of an exposed population, it would be necessary to observe 29 exposed persons (for 95% confidence) or 44 persons (for 99% confidence).
- Where there is a mechanism for identifying adverse effects from a population at risk of eye exposure and the evidence is that this causes no or only minor, transient, fully reversible eye irritation in observations covering 100,000 person.years of exposure, neither classification nor the use of R36 is necessary.

5.2.2 Human volunteer studies

These are not normally undertaken for eye irritation classification.

- Where data of appropriate quality exist, they should be taken into account.

5.3 Respiratory irritation criteria

5.3.1 Human experience

Currently, there is no internationally recognised animal protocol that addresses specifically respiratory irritation, although such information may be gained secondary to examination of other toxic endpoints using the inhalation route. Consequently, substances or preparations irritant to the respiratory system are generally identified on the basis of human evidence.

- Where there is well-documented evidence that respiratory exposure produced signs of respiratory distress, dyspnoea, or a non-specific bronchial hyper-reactivity response or an accelerated deterioration in respiratory function, classification with R37 is necessary.

5.4 Skin sensitisation criteria

5.4.1 Human experience

Irrespective of the results of animal experiments.

- Where there are data from only a small number of exposed people, amongst whom a subset exhibit evidence of sensitisation (e.g. objective clinical signs confirmed by patch testing), the substance should be classified with R43.
- Where extensive and prolonged skin exposure has not caused allergic contact dermatitis in a small population (e.g. 100) that is subject to a health surveillance programme which is competent to detect sensitisation should it occur, classification with R43 is not necessary.
- Where a significant number of individuals (e.g. 100,000) have frequent (daily) skin exposure for at least one year and there is a system in place to pick up complaints and adverse reaction reports, and where no or only a few isolated cases of allergic contact dermatitis are observed, no classification with R43 is necessary.

5.4.2 Human volunteer studies

Irrespective of the results of animal experiments.

- Where none of the volunteers (normally at least 100) exhibits a confirmed positive allergic response in a properly conducted HRIPT (Human Repeat Insult Test) (Bannan *et al*, 1991), no classification with R43 is necessary.
- With the human maximisation test (normally with at least 25 volunteers) (Kligman, 1966), a classification threshold higher than a confirmed zero positive response may be necessary, since this is a maximisation procedure. The Task Force recommends that a material is classified R43 if > 5% of the volunteers demonstrate a positive response.

5.5 Respiratory sensitisation criteria

5.5.1 Human experience

Although predictive models are under validation, there is as yet no internationally recognised animal method for identification of respiratory sensitisation. Thus human data are usually evidence for hazard identification.

- Where a statistically and / or biologically significant percentage of those exposed exhibit proven respiratory hypersensitivity (with demonstrated immunological mechanism), even where the proportion of exposed individuals affected is small, the product must be classified and R42 applied.
- Where, in a small population who are subject to a health surveillance programme competent to detect respiratory sensitisation should it occur, extensive and prolonged respiratory exposure, has not caused respiratory sensitisation, no R42 classification is necessary. Note that it would be necessary to have a population of about 300 exposed individuals, all of whom were not sensitised, to exclude a sensitisation rate of 1% with 95% confidence.

- Where a significant number of individuals (e.g. 100,000) have frequent respiratory exposure for at least one year and there is a system in place to pick up complaints and adverse reaction reports, R42 must be applied only when the number of proven cases of rhinitis or asthma in relation to the extent of exposure exceeds that expected from non-specific effects. Observations of idiosyncratic reactions in only a few individuals with hyper-reactive airways are not sufficient to indicate the need for classification.

Respiratory symptoms with no detectable immunological mechanism should normally be considered under a classification heading other than sensitising by inhalation (see also ECETOC, 1993).

RECOMMENDATIONS

The following recommendations are made for the toxicological endpoints (skin, eye and respiratory irritation, skin and respiratory sensitisation) considered in this report:

- Available human data should be utilised in the various steps of the risk assessment process subject to meeting the validity and quality criteria as proposed in Sections 4 and 5.
- Appropriate, valid human data should be considered for classification and labelling purposes and should normally take precedence over other data.
- Retrospective and prospective collection and documentation of human experience information (observational data) may be appropriate in certain sectors of the industry.
- Publication of human data and experimental protocols in the open literature is advocated.

The availability and type of human data will vary greatly depending on the classes of substances and preparations considered. For example, for chemical intermediates there may be none at all, for widely-produced substances, occupational records may be available, for consumer products (preparations) both general public survey and human volunteer studies may co-exist and possibly allow consideration of potency and / or true threshold (no effect level).

In all situations human data must be weighed against other available information to decide on classification.

Where classification of a substance or preparation based on animal data appears to be inappropriate when compared with a more in-depth assessment in which human experience data were applied, the Task Force believes it appropriate to re-open the question of classification. There are a number of well- described examples in various groups of chemicals and preparations that demonstrate, in most cases a 'lower' classification, and in some a 'higher' classification, based on human versus animal data. Using these examples as a basis, criteria for classification have been elaborated based on human data.

According to current legislation, labelling is an 'automatic consequence' of the classification step (hazard identification). The Task Force recommends that in future where effects data (including human data, or analogy with other substances and preparations) allow and where exposure information (including data on conservative scenarios) can be made available, substances and preparations should be labelled on the basis of risk assessment. It is recognised that his may be easier to achieve for consumer products (preparations) than for some other groups of substances and products.

APPENDIX A: HUMAN DATA: CURRENT REGULATORY GUIDELINES IN EUROPE

A.1 Classification: Objective and relation to the risk assessment process

Hazard identification, the first step in the risk assessment process, refers to the inherent capacity of a substance or a preparation to cause adverse effects. When a specific adverse effect has been identified (frequently, but not solely, on the basis of animal test data), it is assigned with a specific classification on the basis of the hazard criteria defined in the Dangerous Substances Directive (DSD), the Dangerous Preparations Directive (DPD) and the classification and labelling (C&L) guide for substances and preparations.

"The object of classification is to identify all the toxicological, physico-chemical and ecotoxicological properties of substances and toxicological and physico-chemical properties of preparations which may constitute a risk during normal handling or use. Having identified any hazardous properties the substance or preparation must than be labelled to indicate the hazard(s) in order to protect the user, the general public and the environment **"** (C&L guide, Art. 1.1) (EC, 1993a).)

" The label takes account of all potential hazards which are likely to be faced in the normal handling and use of dangerous substances and preparations when in the form in which they are placed on the market, but not necessarily in any different form in which they may finally be used**"** (C&L guide, Art. 1.4.) (EC, 1993a).

A.2 Classification: Sources of information including human data

With regard to data collection, "...manufacturers, distributors and importers of dangerous substances ... shall be obliged to carry out an investigation to make themselves aware of the relevant and accessible data which exist concerning the properties of such substances" (C&L guide, Art. 1.5.) (EC, 1993a).

The data may be obtained from a number of different sources, "..for example, the results of previous tests, information required by international rules on the transport of dangerous substances, information taken from reference works and the literature or information derived from practical experience" (C&L guide, Art. 1.6) (EC, 1993a); wherein 'tests' refer mainly but not solely, to animal tests and 'practical experience' to human exposure at the workplace and / or handling of the product by the general public.

For preparations, "Furthermore, where it can be demonstrated that toxicological effects on man differ from those suggested by a toxicological determination (animal test) or a conventional assessment

(calculation method which gives a certain weight to the ingredients of the preparation, depending on their own hazardous properties and on their concentration in the finished preparation), then the preparation shall be classified according to its effects on man, ..." (DPD, Art. 3.3) (EC, 1988). Further explanation is given in DPD, Art. 6.3 (EC, 1999). "Furthermore where it can be demonstrated by epidemiological studies, by scientifically valid case studies...or by statistically backed experience, such as the assessment of data from poison information units or concerning occupational diseases, that toxicological effects on man differ from those suggested by the other methods (animal tests or conventional calculation method) then the preparation shall be classified according its effects on man".

The regulations fail to provide more indications of what constitutes relevant and sufficient **'**practical (human) experience**'** or a proper demonstration of **'**effects on man**'**. Guidance to interpret the following provision is also lacking : **"**If adequate evidence is available to demonstrate in practice that the toxic effect of substances and preparations on man is, or is likely to be, different from that suggested by the experimental results obtained in animal tests or by the application of the conventional method . . ., then such substances and preparations should be classified according to their toxicity in man. However, tests on man should be discouraged and should not normally be used to negate positive animal data" (C&L guide, Art. 3.1.1) (EC, 1993a).

It is specified that "...if clinical studies may be accepted, it is taken as a given that such studies comply with the Helsinki Declaration and the OECD guidelines for Good Clinical Practice" (DPD, Preamble) (EC, 1999).

A.3 Human versus animal data

The data used for the classification of substances and preparations may come from specific animal tests performed according to the protocols defined in Annex V to the DSD. However it is important to note that "When the classification is to be established from experimental results obtained in animal tests the results should have validity for man in that the tests reflect, in an appropriate way, the risks to man" (C&L guide, Art. 3.1.4.).

Similarly, when applying the OECD test methods which are the basis for the EC Annex V protocols quoted above, the investigator is cautioned that extrapolation of the animal results to man requires expert judgement e.g. "Extrapolation of the results of dermal irritancy / corrosivity studies and of eye irritation studies in animals to man is valid only to a limited degree. The albino rabbit is more sensitive than man to irritant or corrosive substances in most cases. The finding of similar results in tests on other animal species may give more weight to extrapolation from animal studies to man" (OECD 404, 1981, 1992; OECD 405, 1987) and also "A skin sensitisation study thus provides an assessment of whether or not a test substance could be a likely sensitiser. Extrapolation of these results to man is valid only to a very limited degree. The only generalisation that can be made is that substances which are strong sensitisers in guinea pigs also cause a substantial number of sensitisation reactions in man, whereas weak sensitisers in guinea pigs may or may not cause reactions in man" (OECD 406, 1981, 1992).

In the general introduction to Annex V of the DSD (Part B. Methods for the determination of toxicity) (EC, 1992) it is stated that: "There are limitations in the extent to which the results of animal and *in vitro* tests can be extrapolated directly to man and this must be borne in mind when tests are evaluated and interpreted. When available evidence of adverse effects in humans may be of relevance in determining the potential effects of chemical substances on the human population." This provision became later "When tests are evaluated and interpreted, limitations in the extent to which the results of animal and *in vitro* studies can be extrapolated directly to man must be considered and therefore, evidence of adverse effects in humans, where available, may be used for confirmation of testing results" (EC, 1996b)

Similar considerations are found in Chapter 3.1 of Part 1 of the Technical Guidance Document (TGD) on risk assessment (EC,1996a): "Generally human data will only be available for existing substances. If both animal data and human data are available, as a general rule, well reported relevant human data for any given endpoint is to be given preference for the risk assessment. However, the potential differences in sensitivity of human studies and studies in animals should be taken into account in the risk assessment on a case-by-case basis. In relation to hazard identification, the relative lack of sensitivity of human data may cause particular difficulty: negative data from studies in humans will not usually be used to override the classification of substances which have been classified on the basis of data from studies in animals in accordance with the criteria given in Directive 93/21/EEC, (Annex VI to Directive 67/548/EEC) unless the classification is based on an effect which clearly would not be expected to occur in humans".

It is recognised in the TGD (Chapter 3.2.2.2) that the assessment of human data requires more elaborate and in-depth critical assessment of the reliability of the data than the assessment of Annex V animal data. The following four different types of human data are considered relevant:

- Analytical epidemiology studies on exposed populations;
- descriptive or correlation epidemiology studies;
- controlled studies in human volunteers;
- case reports.

Criteria for the assessment of these different types of studies are discussed. The difficulty in handling studies with 'negative' results is acknowledged.

A.4 Human data and irritation

The use of data on 'effects on man' is specifically mentioned, in the context of classification as irritant and also in relation to risk assessment. For instance:

> R38 is to be applied to "substances and preparations which cause significant inflammation of the skin, based on practical observation in humans on immediate, prolonged or repeated contact" (C&L guide, Art. 3.2.6.1.) (EC, 1993a).
>
> R36 to "substances or preparations which cause significant ocular lesions, based on practical experience in humans" (C&L guide, Art. 3.2.6.2) (EC, 1993a).
>
> R41 (Risk of serious damage to eyes) to "substances and preparations which cause severe ocular lesions, based on practical experience in humans" (C&L guide, Art. 3.2.6.2.) (EC, 1993a).
>
> R37 to "Substances and preparations which cause serious irritation to the respiratory system based on: ... practical observation in humans "(C&L guide, Art. 3.2.6.3.) (EC, 1996b).

In relation to skin and eye irritancy the provisions given above are in addition to the description of the conditions possibly observed in animal tests performed according to the EC Annex V protocols. In the case of respiratory irritancy the sentence given is the main criterion, apart from the option to use "positive results from appropriate animal tests" with no specified protocol.

According to the TGD (Chapter 3.7.3.2) "Well-documented human data can often provide very useful information on skin and/or respiratory irritation, sometimes for a range of exposure levels. Often, the only useful information on respiratory irritation, which can be a threshold effect in the workplace, is obtained from human experience. The usefulness of all human data on irritation will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. Experience has shown that it is difficult to obtain useful data on substance-induced eye irritation, but data may be available on human ocular responses to certain types of preparations (e.g. Freeberg *et al*, 1986b)".

It is further considered in the TGD (Chapter 3.7.5) that "there may be a significant level of uncertainty in human data" due to " poor reporting, lack of specific information on exposure, subjective or anecdotal reporting of effects, small numbers of subjects…."

A.5 Human data and sensitisation

The use of human data is mentioned in the context of classification for sensitisation by inhalation (R42) and by skin contact (R43) as follows:

"R42 May cause sensitisation by inhalation

Human evidence. Evidence that the substance can induce specific respiratory hypersensitivity will normally be based on human experience. In this context hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

When considering the evidence from human exposure, it is necessary for a decision on classification, to take into account in addition to the evidence from the cases:

- the size of the population exposed
- the extent of exposure

The evidence referred to above could be:

- clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

    - a chemical structure related to substances known to cause respiratory hypersensitivity
    - *in vivo* immunological test (e.g. skin prick test)
    - *in vitro* immunological test (e.g. serological analysis)
    - studies that may indicate other specific but non-immunological mechanisms of action, e.g. repeated low-level irritation, pharmacologically mediated effects
    - data from a positive bronchial challenge test with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction

Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognized that in practice many of the examinations listed above will already have been carried out.

Substances that elicit symptoms of asthma by irritation only in people with bronchial hyperreactivity should not be assigned R42 " (C&L guide, Art. 3.2.7.1) (EC, 1996b).

"**R43 May cause sensitisation with skin contact**

Human evidence - The following evidence (practical experience) is sufficient to classify a substance with R43:

- positive data from appropriate patch testing, normally in more than one dermatological clinic, or
- epidemiological studies showing allergic contact dermaitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or
- positive data from experimental studies in man.

The following is sufficient to classify a substance with R43 when there is supportive evidence:

- isolated episodes of allergic contact dermatitis, or
- epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

Supportive evidence may include:

- data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or
- data from non-standard methods, or
- appropriate structure-activity relationships" (C&L guide, Art. 3.2.7.2) (EC, 1996b).

The TGD acknowledges the availability and usefulness of human data for identifying (absence of) skin and respiratory sensitisation hazards.

"Sometimes case reports or epidemiological studies from human exposure will be available particularly in the case of existing substances. Those which report on cutaneous (allergic dermatitis, eczema) or respiratory (allergic rhinitis, alveolitis, asthma) reactions are of particular significance. Studies indicating negative results should also be evaluated" (Chapter 3.8.2.2).

"Data from dermatologic tests, e.g. Human Repeated Insult Patch test, skin prick test and also from bronchial challenge provocation tests will also sometimes be available. Immunological tests (RAST) may be helpful" (Chapter 3.8.2.2).

"For products for which direct human contact is intended, predictive tests for humans, if already carried out, can be of value in determining the relevance of the sensitisation potential to humans in specific use scenarios" (Chapter 3.8.3.2).

In the assessment of case reports the TGD (Chapter 3.8.3.2) indicates that attention should be paid to the following:

"The number of well-documented cases in relation to the size of the exposed population;

- the existence of two types of populations: individuals previously sensitised and individuals not previously sensitised;
- the type of exposure: e.g. adequate substance identification, multiple exposure, physical state and concentration / quantity of the substance, frequency and duration of exposures;
- reports of sensitisation to substances with structural analogues".

It is concluded that:

"It may be possible to derive reliable non-sensitising concentrations from human studies in specific well-defined conditions" (TGD, Chapter 3.8.4) and that "There may be a significant level of uncertainty in human data on sensitising effects (because of poor reporting, lack of specific information on exposure, small number of subjects, concomitant exposure to other substances)" (TGD, Chapter 3.8.5).

APPENDIX B: EXAMPLES OF CLASSIFICATION DECISIONS BASED ON HUMAN DATA

B.1 Skin irritation/corrosion

B.1.1 Fatty acids and fatty acid blends (C8-C16)

A commercial fatty-acid blend has been classified as corrosive to skin (C, R34) on the basis of the results of a rabbit Draize type test (Draize *et al*, 1944) conducted according to OECD Guideline 404 (OECD, 1992). The blend contained 55% caprylic acid (C8), itself classified as corrosive on a similar basis. The remaining 45% was capric acid (C10), classified as irritant (Xi, R38) based on data from the same test protocol (Basketter, 1994a).

In the *in vitro* corrosivity test, a method which has had the benefit of inter-laboratory validation, the same fatty-acid blend was shown to be corrosive using rat skin, but without effect using human skin. This result was reproduced in five different skin samples including both breast and abdominal skin of Caucasian and black origin (Whittle and Basketter, 1993a). The test methodology using human skin has been validated with recognised positive (i.e. corrosive) and negative controls (Whittle and Basketter, 1993b).

In addition to the above, Stillman *et al* (1975) investigated the effect in humans of repeated patch testing with individual fatty acids of various chain lengths. At the maximum concentration employed (1 Molar, approximately equal to 15% fatty acid for the C8 and the C10 chain lengths), a 24-hour occluded patch on the backs of 10 subjects produced no skin reactions. Furthermore, Wahlberg and Maibach (1980) demonstrated that the undiluted C9 fatty acid, (nonanoic acid), produced no more than an irritant response in 6 female and 7 male subjects following a 48-hour occluded patch treatment.

Similar results were obtained with lauric acid (C12) which caused moderate skin reactions in rabbits,and only slight reactions in humans under conditions of epicutaneous occluded or open application (Henkel, 1988). Classification as Xi, R38 is appropriate according to the test results on rabbit but not on human skin. Palmitic acid (C16) shows no irritant potential when tested on rabbit or on human skin and thus is not classified on the basis of either results (see Table 1).

In a study with 24 volunteers, Basketter *et al* (1997) compared the level of irritation observed after application of undiluted C8-C10 fatty acid or of 20% sodium lauryl sulphate (SLS) under a 4-hour occluded patch. The level of erythema was similar, suggesting that the fatty-acid blend should be classified the same way as 20% SLS, that is as irritant (Xi). The authors suggest that the classification or non-classification of a substance or preparation as skin irritant can be decided upon from a human patch test protocol using a positive (classified as) irritant control (here 20% SLS).

In conclusion, based on experimental studies with human volunteers, C12 fatty acids should not be classified as irritant. Based on the results of the *in vitro* tests and the results of experimental studies with human volunteers, the C8-C10 fatty acid blend should be classified irritant (Xi, R38), but not corrosive This judgement is corroborated by available human experience. There are no reports of skin effects resulting from accidental contact with the commercial C8-C10 fatty-acid blend which would substantiate classification of the mixture as corrosive.

B.1.2 Fatty alcohols (C6-C18)

Fatty alcohols with a short (C6, C8) and a longer (C16, C18, C18') chain cause slight skin reactions in rabbits under occlusive patch (Kästner, 1977; Johnson, 1988; Moore, 1985). In contrast, fatty alcohols with C10, C12 and C14 chains are skin irritants and can cause moderate-strong skin reactions in animal patch testing (Kästner, 1977), as do C12-C18 fatty alcohols (Henkel, 1988). Under approximately the same conditions (occlusive patches, 24-hour or longer contact time) and at the same concentrations (undiluted and 50%), fatty alcohols show no or only mildly irritant reactions on human skin (Kästner, 1977; Johnson 1988; Moore 1985; Henkel, 1988). Moreover, the C12-C18 mixture is also non-irritant to human skin when tested in an open repeated epicutaneous test, using 60 applications within 30 minutes (Henkel, 1988) (Table 3).

Fatty alcohols of chain-lengths C8-C14 are classified as skin irritants (Xi, R38) according to results obtained with the rabbit Draize test (Draize *et al*, 1944) or the OECD Guideline 404 (OECD, 1992). However, according to the results on human skin, none of the tested fatty alcohols requires classification.

Jacobs *et al* (1987) tested several solvents, including undecanol, for their irritant properties to the skin. Using the OECD protocol and the EU criteria for classification, a 'limit concentration' was defined as the highest tested concentration where the mean erythema score in rabbits did not exceed 2. A 25% solution of undecanol was shown to be the 'limit concentration' based on the rabbit test, although a solution of 50% undecanol was found to be non-irritant to human skin. Consequently, the authors proposed using 50% as the classification limit for preparations containing undecanol, in the context of the DPD.

B.1.3 Fatty acid methyl esters (C6-C18)

The findings with fatty acid esters follow a pattern similar to that of the fatty alcohols, namely the effects found in the rabbit are much more severe than those found in humans. A mixture of C6-C10 fatty acid methyl esters was moderately irritant to rabbit skin, but only slightly to human skin (Henkel, 1988). Palmitic acid (C16) methyl ester proved to be a strong irritant to rabbit skin, but was not irritant to human skin. Classification with Xi, R38 was appropriate, based on the rabbit skin reactions, but is unnecessary according to the results on human skin. The oleic acid (C18) methyl ester was slightly irritant in the rabbit test and not irritant in the human test. It is not classified as irritant on the basis of either test (Table 3).

Table 3: Classification based on primary skin irritation tests in rabbit and man*

Chemical	Rabbit*	Man*	Adapted from
Fatty alcohols			
Hexanol (C6)	none	none	Kästner, 1977
Octanol (C8)	Xi; R38	none	Kästner, 1977
Decanol (C10)	Xi; R38	none	Kästner, 1977
Dodecanol (C12)	Xi; R38	none	Kästner, 1977
Tetradecanol (C14)	Xi; R38	none	Kästner, 1977
Cetyl alcohol (C16)	none	none	Kästner, 1977; Johnson, 1988
Octadecanol (C18)	none	none	Kästner, 1977; Moore, 1985
Oleyl alcohol (C16, 18, 18')	none	none	Kästner, 1977; Moore, 1985
Fatty alcohols (C12-C18)	Xi; R38	none	Kästner, 1977; Henkel, 1988
Fatty acids			
Lauric acid (C12)	Xi; R38	none	Henkel, 1988
Palmitic acid (C16)	none	none	Henkel, 1988
Fatty acid methyl esters (ME)			
Fatty acid (C6-C10) ME	Xi; R38	none	Henkel, 1988
Palmitic acid (C16) ME	Xi; R38	none	Henkel, 1988
Oleic acid (C18) ME	none	none	Henkel, 1988

* Using EC classification criteria (EC, 1993a)

B.1.4 Traditional soft soap

Potassium soap is classified as corrosive (C = corrosive, R34 = Causes burns) based on a rabbit OECD test (Potokar *et al*, 1985). However in an occluded 4-hour patch test in humans, 0 / 29 subjects reacted, compared to 9 / 29 who reacted to the 20% SLS positive control (York *et al*, 1996). In addition, decades of human experience with this material confirm that the rabbit-derived classification is misleading. Prior to the marketing of synthetic detergents, generations of housewives used potassium soap to wash clothes. During this hand-wash procedure, intensive skin contact for up to several hours / day with the soap must have been experienced. Such usage of a truly corrosive substance would simply not have been feasible.

B.1.5 Detergent and cleaning products

The skin effects observed for a variety of detergent and cleaning preparations and constituent substances were generally found to be equal or less pronounced in man than in rabbit, (Carter and Griffith, 1965; Nixon *et al*, 1975; Basketter *et al*, 1994), regardless of the duration of exposure (1 or 4 hours) or the type of patch used (Nixon *et al*, 1990).

In the range of products quoted by Carter and Griffith (1965), the product that gave the least reaction in the human test gave the most severe reaction in the rabbit. The results of rabbit and human skin tests led to different classifications (higher or lower) for about one third of the substances and preparations tested by Nixon *et al* (1975, 1990) (Table 4).

Not surprisingly, the human skin test results fit better with the many years of human experience with household detergent and cleaning products. Included in the first column in Table 4 are the risk-phrases obtained for the same products but using the DPD conventional calculation method (CCM) (EC, 1988). The CCM assumes an additive effect for irritant ingredients, which is not borne out by data obtained with mixtures of surfactants, the major components of detergents and cleaning products. This is because antagonism occurs and the irritant potential is related to the combination of the surfactants present in the preparation, and not to their total quantity (Dillarstone and Paye, 1993; Hall-Manning *et al*, 1995).

Towards calibrating the skin irritancy of detergent and cleaning preparations, AISE used a 4-hour semi-occlusive human skin patch test protocol (AISE, 1991a, 2000). The interpretation criteria and classification rules applied were essentially the same as that for the Draize type Annex V rabbit test (EC, 1984). Results with about 80 surfactant-based products were gathered, using this protocol. Contrary to the CCM which indicated that the vast majority of these products required an irritant classification, none required classified on the basis of the human skin irritation test. This finding is again in line with general human experience with these products (AISE, 1991a, 2000).

Table 4: Skin irritancy classification of detergent and cleaning preparations (adapted from Nixon et al, 1975, 1990)

Product	Classification CCM	Rabbit	Human volunteer*
	4h Semi-occluded patch test; readings at 4, 24, 48 h		
Powder detergent A (metasilicate / carbonate / surfactants)	R34	R34	R38
Powder detergent B (silicate / carbonate / surfactants)	R38	none	none
Liquid cleaner A (surfactants / soap / carbonate)	none	R38	none
Liquid cleaner B (soap / pine oil / alcohol)	R38	R38	none
Liquid cleaner C (hypochlorite)	R38	none	R38
	4h occluded patch; readings at 24, 48, 72 h		
Powder detergent C (silicate / surfactants)	R38	none	none
Powder detergent D (silicate / carbonate / surfactants)	R38	R34	none
Dishwashing liquid (surfactants / alcohol)	R38	R38	none
Liquid cleaner / detergent D (surfactants / alcohol)	R38	none	none

* Using EC classification criteria (EC, 1993a).

Dillarstone and Paye (1994) showed that a series of detergents and cleaning products, all classified as irritant based on the calculation method, displayed a level of irritancy in human 4-hour occluded patch tests that was lower than that of an internal standard (10% SLS solution; the internal standard chosen was a non-classified material). On this basis, eight out of nine preparations required no classification. In this series, one preparation was more irritant than the internal standard, (as expected on the basis of its pH and reserve alkalinity; measured according to Young *et al*, 1988) and was thus confirmed as Xi, R38. The authors suggest that a human skin patch test, using an internal standard that displayed a minor level of irritation at a concentration at which it is clearly not classified as irritant (here 10% SLS), can be used as a discriminating method where the conventional calculation method leads to a contentious R38 classification.

B.1.6 Paints

Hignet *et al* (1990) using a 4-hour semi-occluded patch test, showed that the response of human skin to certain paint formulations was usually less severe than that of the rabbit. Three of four preparations would have been classified as irritant (Xi = Irritant, R38) on the basis of the rabbit results compared with one of the four on the basis of the human results. The company's original safety data sheets were modified to give precedence to the human data. There is no clinical evidence suggesting that the use of human data led to inadequate classification.

B.1.7 Other substances and preparations

Data have been published on various other substances which demonstrate that classification based on the rabbit 4-hour patch test does not equate in many instances with that based on human 4-hour patch testing (Nixon *et al*, 1975, 1990; York *et al*, 1996; Griffiths *et al*, 1997; Basketter *et al*, 1997).

There is both over- and under-classification of a wide range of substances and preparations.

B.1.8 Summary

When patch testing was carried out in parallel with the rabbit Annex V test (mainly with preparations such as soaps, detergents, perfumes, cosmetics and their ingredients) the human skin was usually less susceptible to irritation than the rabbit skin. Only a few substances produced more severe responses in man than in the rabbit. Thus, human patch testing, using a protocol similar to the rabbit Annex V skin test, is probably a more reliable model for the prediction of irritation to humans. However, it should not be carried out in an indiscriminate manner.

Patch testing with human volunteers must comply with all internationally recognised ethical and clinical principles (Section 4).

Where ethically possible and justified from the end use of the substance or preparation, and in particular for the classification of chemicals and preparations expected to display a low irritant potential, the Human Patch Test may be considered as a more-reliable basis for classification than the Annex V B5 rabbit test. Rabbit skin tests provide reassurance where no human data are available.

B.2 Eye irritation

B.2.1 Anionic and non-ionic surfactants

CESIO considered rabbit eye irritation studies provided by member companies on a wide range of anionic and non-ionic surfactants. The studies had been performed according to the Annex V B5 test method with observation periods ranging from 24-72 hours up to 21 days. Using the EC classification guidelines (EC, 1986, 1991 in preparation at the time), a number of surfactants gave a score consistent with a R36 'Irritating to eyes' classification. Some studies were terminated at 72 hours, but all animals had not necessarily recovered. In some cases conjunctival, corneal and / or iridial effects persisted beyond 72 hours. There has been debate as to the appropriateness of assigning R41 'Risk of serious damage to eyes' in all these cases (CESIO, 1990). A review of this aspect has been conducted by a separate ECETOC Task Force and its findings and recommendations are presented in Document 37 (ECETOC,1997).

Human data were collated from records of accidental eye exposures occurring in the course of the surfactants manufacturing process. Medical information covering the period from 1972 to 1990 was collected from 22 companies and evaluated. Generally the surfactants were identified using the chemical nomenclature developed by CESIO and the active ingredient content. The number of eye incidents recorded with anionic surfactants was 49, and with non-ionic surfactants, 35. First aid (eye wash) was provided and in a number of cases medication was applied; in more serious cases medical / ophthalmological attention was given. When data on anionic surfactants were pooled, reported cases ranged from conjunctivitis and blurred vision to corneal ulceration. In general terms, anionic surfactants were routinely described by respondents as being irritant to the eye with stated recovery periods of from less than one to 5 days. For non-ionic surfactants, the range of described responses were conjunctivitis, blurred vision and corneal effects. Again, the reported data revealed a general irritant effect to the eye for all reported materials and stated recovery periods ranging from less than one to 14 days (CESIO, 1991).

The available human data confirmed that these materials are irritant to the human eye to various degrees with no reported irreversible effects.

B.2.2 Detergent and cleaning products

These preparations are frequently classified as irritant or severely irritant to the eyes (R36 = Irritating to eyes or R41) on the basis of the conventional calculation method. Most detergent and cleaning products would also be classified as irritant on the basis of the Annex V B5 rabbit eye test (Tables 5 and 6).

Experiments with human volunteers have shown that the human eye is less sensitive than the rabbit eye to irritation by this category of preparations based on surfactants, acids and alkalis (Beckley, 1965; Beckley *et al*, 1969; Freeberg *et al*, 1986b; Ghassemi *et al*, 1993) (Tables 5 and 6). If used for classification purposes, the results of studies in rabbits of a dishwashing liquid (Beckley, 1965), would have led to assignment of Xi, R41 but no classification would be necessary on the basis of the human data.

A modified procedure, the so-called Low Volume Rabbit Eye Test (LVET), was developed and has been adopted as a Standard Method in the USA (ASTM, 1985) because of the poor correlation between the standard rabbit eye test and the response in the human eye. The ASTM test provides for two modifications when compared to the EC Annex V or the Draize test. These relate to the dose (0.01 ml or w/w equivalent) and the site of application (directly on the central surface of the cornea). Compared to direct experience gathered from cases of accidental exposure of consumers and workers to household detergents and cleaning products, the ASTM test produces more severe eye responses in the rabbit. Nevertheless, it is believed to be more accurate, both in terms of severity and duration of effects, than the EC Annex V B5, in predicting the human eye response to this category of preparations (Freeberg *et al*, 1984, 1986a; Walker, 1985; ECETOC, 1988; Lambert *et al*, 1993). For detergent and cleaning preparations the ASTM is considered to be the best available predictor of effects on the human eye.

Though an eye irritation study with human volunteers can be conducted ethically for certain products, such a study cannot be regarded as a routine test. According to the C&L guide "When the classification is to be established from experimental results obtained in animal tests, the results should have validity for man in that the tests reflect in an appropriate way the risks to man" (C&L guide, Art 3.1.4) (EC, 1986 and subsequent), AISE tested about 80 surfactants using the ASTM test to calibrate detergents and cleaning preparations for eye irritancy. Interpretation criteria and classification rules were the same as applied to the Annex V rabbit eye test. On the basis of the DPD CCM or on the basis of the Annex V test, all these products would be classified as Xi, R36 or R41 (AISE, 1991b, 2000). On the basis of the ASTM test only five of these products would be classified (as Xi, R36), corroborating general human experience with these substances (AISE, 1991b, 2000).

Table 5: Animal and human eye response to undiluted dishwashing detergent (adapted from Beckley, 1995)

		Mean Score			
Time of reading	**Tissue†**	**Rabbit** (Draize)	**Dog** (Draize)	**Monkey** (Draize)	**Man**
1 h	Cornea	33.3	40.0	20.0	0
	Iris	10.0	5.0	2.5	0
	Conjunctivae	12.0	4.0	1.0	6-7
24 h	Cornea	33.3	40.0	10.0	0
	Iris	10.0	5.0	0	0
	Conjunctivae	12.0	4.0	0	0
48 h	Cornea	26.7	30.0	5.0	0
	Iris	10.0	5.0	0	0
	Conjunctivae	10.0	4.0	0	0
72 h	Cornea	21.7	30.0	0	0
	Iris	10.0	5.0	0	0
	Conjunctivae	9.3	0	0	0
Classification*		Severe irritant R41	Irritant R36	Non irritant	Non irritant

* Using EC classification criteria (EC, 1991).

† Maximum scores: Cornea 80, Iris 10, Conjunctivae 20.

Table 5a: Correlation of EC Annex V B5 and Draize eye irritation scores §

Tissue	**Annex V B5 R36 scores**	**Equivalent to Draize mean scores**	**Annex V B5 R41 scores**	**Equivalent to Draize mean scores**
Cornea	≥ 2.0 < 3.0	> 20 < 45	> 3	> 45
Iris	≥ 1.0 < 1.5	> 5 < 7.5	≥ 1.5	≥ 7.5
Conjunctivae				
- redness	> 2.5	≥ 9		
- chemosis	> 2.0			

§ The EC Annex V B5 test method is identical to the older 'Draize' (1944) protocol. Both methods are the same in terms of treatment of the animals and observation. Cornea, iris and conjunctiva are separately observed and scored for the effects noted according to defined scales. Maximum scores are: cornea opacity 4; iris 2; conjunctiva: redness 3, chemosis 4 and discharge 3.

The only important difference between the two methods relates to the way in which the scores are used. In the 'Draize' method, the scores recorded for cornea, iris and conjunctiva are multiplied by a factor, related to the relative importance of each part of the eye. These scores are thus: cornea 80; iris 10; conjunctiva 20. The scores for cornea, iris and conjunctiva are summed up to give a final 'eye score' (maximum: 80 + 10 + 20 = 110). The mean score for the 3 or more rabbits observed in the study is the mean of these final 'eye scores'.

In the EC Annex V method, the multiplying factors and this summation are not used, so the maximum scores remain: cornea opacity 4; iris 2; conjunctiva: redness 3, chemosis 4.

Thus the original scores for cornea, iris, conjunctiva available from an old 'Draize' study, can easily be converted into Annex V B5 method scores.

Table 6: Rabbit and human eye responses to household products (adapted from Freeberg et al, 1998b)

	Mean Score			
	Draize protocol		ASTM protocol	
Time of reading (hours)	Rabbit *	Human*	Rabbit*	Human*
Fabric softener (undiluted)				
1	4.3	0.8	4.8	1.8
24	6.5	0	0.3	0
48	3.0	0	0	0
72	0.8	0	0	0
Shampoo (20%)				
1	1	1.1	4.0	6 2
24	7.0	0	0.8	0
48	4.3	0	0	0
72	0.9	0	0	0
Liquid hand soap (10%)				
1	8.0	3.0	4.0	2.5
24	13.9	0	1.8	0
48	4.3	0	0.3	0
72	0.3	0	0.3	0
Liquid laundry detergent (4%)				
1	8.3	4.0	4.5	2.3
24	13.3	0	1.8	0
48	9.0	0	0.5	0
72	1.4	0	0	0

* Using Draize scoring convention, described in footnote to Table 5a

B.2.3 Summary

The information obtained from medical records on accidental exposures in the workplace in the (anionic and non-ionic) surfactant manufacturing industries indicate effects consistent with the results of the Draize test, albeit less severe. For a specific cleaning product, comparative laboratory studies with rabbit, dog, monkey and man show clear distinctions between the species, with man as the least susceptible. The results with the ASTM test are more in line with the human response.

B.3 Skin sensitisation

B.3.1 Sulphanilic acid

Evaluation of the skin sensitisation potential of sulphanilic acid using two test methods in the guinea pig led to conflicting results (Basketter *et al*, 1992). While it was a strong sensitiser in the Guinea Pig Maximisation Test (GPMT) of OECD Test Guideline 406, there was no evidence of sensitisation in the Cumulative Contact Enhancement Test (CCET). In the Local Lymph Node Assay (LLNA), which like the CCET employs only topical application, there was no significant proliferative response to sulphanilic acid in any of four studies. In terms of hazard classification on the basis of 'internationally recognised' animal protocols, sulphanilic acid would be regarded as representing a clear sensitisation hazard since the GPMT result is well above the 30% threshold. It would thus be classified as R43. However, the data from other animal models would not support this conclusion, and would lead to a 'no classification' decision.

Sulphanilic acid has been manufactured in France for more than 20 years, with current production levels exceeding 1000 tonnes / annum. No special containment measures to protect the workforce from skin contact with sulphanilic acid have been in place during that time. Nevertheless, the factory occupational physician reported that there had not been a single instance of skin sensitisation (Basketter *et al*, 1992). In the literature, only two possible cases of skin sensitisation to this compound have been reported.

The report of the occupational physician is anecdotal. However, taking this into account, along with the inconsistent animal data, it is reasonable to question which animal model provides the most appropriate data for classification purposes.

B.3.2 Ethanol

A further example of potentially inappropriate classification based on GPMT data is given by ethanol. This chemical has given a 30% positive response (Basketter, 1994b) that should lead to an R43 classification. There is no doubt that ethanol can act as a human contact allergen in very rare circumstances (reviewed in Fisher, 1983). However, when this is evaluated in the light of the extensive skin contact with leave-on products, such as after shave, used daily by millions of consumers and frequently in contact with damaged skin, ethanol clearly possesses a very low sensitisation potential, not meriting classification.

B.3.3 Linear alkylbenzene sulphonates (LAS)

The LAS anionic surfactants have been tested repeatedly using the GPMT and the Buehler protocols, (OECD test guideline 406). Results of the GPMT usually lead to a classification as R43 while results of the Buehler test provide negative or borderline positive (15%) results, possibly leading to classification. Human skin sensitisation tests with LAS, alone or in detergent products, have proved negative at more realistic concentrations than those used in guinea pig tests. LAS has been used extensively in powder-laundry, liquid-laundry and hand-dish-washing detergents for over 20 years. There have been no reports of allergic contact dermatitis to LAS from occupational or consumer exposure. Specifically, diagnostic patch testing of consumers complaining of skin effects when using preparations containing LAS, failed to demonstrate a contact allergic response to LAS (Robinson *et al*, 1989).

Classifying LAS solely on the basis of the animal test results would be misleading. Human experimental data, together with human experience, do not support classification of LAS as a skin sensitiser.

B.3.4 Benzoisothiazolinones

While some substances are over-classified on the basis of animal data, this is not always the case. This is well illustrated by the benzoisothiazolinone preservatives that failed to elicit significant responses in the GPMT carried out according to the Annex V test method (Basketter, 1994a). However, the chemicals have been implicated in a significant outbreak of allergic contact dermatitis and are now recognised as skin sensitisers in man (reviewed in Botham *et al*, 1991a).

As for all skin sensitisers, it is important to take their potency into account and to define the specific limit concentrations for classification and warning.

B.3.5 Summary

The first three examples show positive results of the GPMT that conflict with the result of other animal test methods including the Buehler test. In each case, adequate human data resolved the conflicting indications and supported less severe classification. In the fourth example however, the importance of human data for authentication of negative animal tests is illustrated.

B.4 Respiratory irritation and sensitisation

B.4.1 General

The classification of a substance or preparation as a respiratory irritant or respiratory sensitiser is based essentially on the existence of sufficient positive human data. Accordingly a detailed commentary on the differences in classification based on animal versus human data is not appropriate.

B.4.2 Formaldehyde

A number of chemicals, including certain isocyanates, anhydrides and platinum salts (ECETOC, 1993), have been identified as respiratory sensitisers on the basis of their clinical effects and demonstrated immunological mechanism. In some cases, however, differentiation between respiratory irritant and respiratory sensitising chemicals can be difficult. Formaldehyde is one such example. This chemical is a known skin sensitiser (Hilton *et al*, 1996) but is also regarded by some as a respiratory allergen (Burge *et al*, 1985); on that basis classification would be R42 as well as R43. It is known that skin and respiratory sensitisers stimulate divergent immunological pathways (Dearman *et al*, 1992). Investigation of the underlying immunological basis of formaldehyde allergy has demonstrated that it is has a cytokine pattern typical of skin sensitisers and not of respiratory sensitisation (Dearman *et al*, 1998). Since formaldehyde does not have a cytokine patter typical of a respiratory sensitiser, it is most likely that the pulmonary effects of formaldehyde are associated with its potential to cause irritation of the respiratory tract. Thus the laboratory evidence supports the view of those who argue that this chemical is in fact a respiratory irritant (Smedley, 1996) rather than a respiratory allergen and should therefore be classified R37 (Irritating to respiratory system) rather than R42.

B.4.3 Summary

In the cases of classification for respiratory irritation and respiratory sensitisation, predictive animal models are not yet internationally recognised. Thus, the availability of human data is essential. The example discussed indicates the need for care in interpreting the available data for each case.

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ECETOC PUBLISHED REPORTS

Monographs

No. Title

No. 1 Good Laboratory Practice
No. 2 A Contribution to Strategy for Identification and Control of Occupational Carcinogens
No. 3 Risk Assessment of Occupational Chemical Carcinogens
No. 4 Hepatocarcinogenesis in Laboratory Rodents: Relevance for Man
No. 5 Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No. 6 Acute Toxicity Tests, LD50 (LC50) Determinations and Alternatives
No. 7 Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
No. 8 Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment (Summary)
No. 9 Assessment of Mutagenicity of Industrial and Plant Protection Chemicals
No. 10 Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man
No. 11 Eye Irritation Testing
No. 12 Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity / teratogenicity)
No. 13 DNA and Protein Adducts: Evaluation of their Use in Exposure Monitoring and Risk Assessment
No. 14 Skin Sensitisation Testing
No. 15 Skin Irritation
No. 16 Early Indicators of Non-Genotoxic Carcinogenesis
No. 17 Hepatic Peroxisome Proliferation
No. 18 Evaluation of the Neurotoxic Potential of Chemicals
No. 19 Respiratory Allergy
No. 20 Percutaneous Absorption
No. 21 Immunotoxicity: Hazard Identification and Risk Characterisation
No. 22 Evaluation of Chemicals for Oculotoxicity
No. 23 Receptor Mediated Mechanisms in Chemical Carcinogenesis
No. 24 Risk Assessment for Carcinogens
No. 25 Practical Concepts for Dose Selection in Chronic Toxicity and Carcinogenicity Studies in Rodents
No. 26 Aquatic Toxicity Testing of Sparingly Soluble Volatile and Unstable Substances
No. 27 Aneuploidy
No. 28 Threshold-Mediated Mutagens - Mutation Research Special Issue
No. 29 Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment
No. 30 Genetic Susceptibility to Environmental Toxicants
No. 31 Guidance on Evaluation of Reproductive Toxicity Data

Technical Reports

No.	Title
No. 1	Assessment of Data on the Effects of Formaldehyde on Humans
No. 2	The Mutagenic and Carcinogenic Potential of Formaldehyde
No. 3	Assessment of Test Methods for Photodegradation of Chemicals in the Environment
No. 4	The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man
No. 5	Toxicity of Ethylene Oxide and its Relevance to Man
No. 6	Formaldehyde Toxicology: An Up-Dating of ECETOC Technical Reports 1 and 2
No. 7	Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere
No. 8	Biodegradation Testing: An Assessment of the Present Status
No. 9	Assessment of Reverse-Phase Chromatographic Methods for Determining Partition Coefficients
No. 10	Considerations Regarding the Extrapolation of Biological Data in Deriving Occupational Exposure Limits
No. 11	Ethylene Oxide Toxicology and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 5
No. 12	The Phototransformation of Chemicals in Water: Results of a Ring-Test
No. 13	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on the Environment
No. 14	The EEC 6th Amendment: A Guide to Risk Evaluation for Effects on Human Health
No. 15	The Use of Physical-Chemical Properties in the 6th Amendment and their Required Precision, Accuracy and Limiting Values
No. 16	A Review of Recent Literature on the Toxicology of Benzene
No. 17	The Toxicology of Glycol Ethers and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 4
No. 18	Harmonisation of Ready Biodegradability Tests
No. 19	An Assessment of Occurrence and Effects of Dialkyl-o-Phthalates in the Environment
No. 20	Biodegradation Tests for Poorly-Soluble Compounds
No. 21	Guide to the Classification of Carcinogens, Mutagens, and Teratogens under the 6th Amendment
No. 22	Classification of Dangerous Substances and Pesticides in the EEC Directives. A Proposed Revision of Criteria for Inhalational Toxicity
No. 23	Evaluation of the Toxicity of Substances to be Assessed for Biodegradability
No. 24	The EEC 6th Amendment: Prolonged Fish Toxicity Tests
No. 25	Evaluation of Fish Tainting
No. 26	The Assessment of Carcinogenic Hazard for Human Beings exposed to Methylene Chloride
No. 27	Nitrate and Drinking Water
No. 28	Evaluation of Anaerobic Biodegradation
No. 29	Concentrations of Industrial Organic Chemicals Measured in the Environment: The Influence of Physico-Chemical Properties, Tonnage and Use Patterns
No. 30	Existing Chemicals: Literature Reviews and Evaluations (Fifth Edition) (No longer available)
No. 31	The Mutagenicity and Carcinogenicity of Vinyl Chloride: A Historical Review and Assessment
No. 32	Methylene Chloride (Dichloromethane): Human Risk Assessment Using Experimental Animal Data
No. 33	Nickel and Nickel Compounds: Review of Toxicology and Epidemiology with Special Reference to Carcinogenesis
No. 34	Methylene Chloride (Dichloromethane): An Overview of Experimental Work Investigating Species Differences in Carcinogenicity and their Relevance to Man
No. 35	Fate, Behaviour and Toxicity of Organic Chemicals Associated with Sediments
No. 36	Biomonitoring of Industrial Effluents
No. 37	Tetrachlorethylene: Assessment of Human Carcinogenic Hazard
No. 38	A Guide to the Classification of Preparations Containing Carcinogens, Mutagens and Teratogens

No. 39 Hazard Assessment of Floating Chemicals After an Accidental Spill at Sea
No. 40 Hazard Assessment of Chemical Contaminants in Soil
No. 41 Human Exposure to N-Nitrosamines, their Effects and a Risk Assessment for N-Nitrosodiethanolamine in Personal Care Products
No. 42 Critical Evaluation of Methods for the Determination of N-Nitrosamines in Personal Care and Household Products
No. 43 Emergency Exposure Indices for Industrial Chemicals
No. 44 Biodegradation Kinetics
No. 45 Nickel, Cobalt and Chromium in Consumer Products: Allergic Contact Dermatitis
No. 46 EC 7th Amendment: Role of Mammalian Toxicokinetic and Metabolic Studies in the Toxicological Assessment of Industrial Chemicals
No. 47 EC 7th Amendment "Toxic to Reproduction": Guidance on Classification
No. 48 Eye Irritation: Reference Chemicals Data Bank (Second Edition)
No. 49 Exposure of Man to Dioxins: A Perspective on Industrial Waste Incineration
No. 50 Estimating Environmental Concentrations of Chemicals using Fate and Exposure Models
No. 51 Environmental Hazard Assessment of Substances
No. 52 Styrene Toxicology Investigation on the Potential for Carcinogenicity
No. 53 DHTDMAC: Aquatic and Terrestrial Hazard Assessment (CAS No. 61789-80-8)
No. 54 Assessment of the Biodegradation of Chemicals in the Marine Environment
No. 55 Pulmonary Toxicity of Polyalkylene Glycols
No. 56 Aquatic Toxicity Data Evaluation
No. 57 Polypropylene Production and Colorectal Cancer
No. 58 Assessment of Non-Occupational Exposure to Chemicals
No. 59 Testing for Worker Protection
No. 60 Trichloroethylene: Assessment of Human Carcinogenic Hazard
No. 61 Environmental Exposure Assessment
No. 62 Ammonia Emissions to Air in Western Europe
No. 63 Reproductive and General Toxicology of some Inorganic Borates and Risk Assessment for Human Beings
No. 64 The Toxicology of Glycol Ethers and its Relevance to Man
No. 65 Formaldehyde and Human Cancer Risks
No. 66 Skin Irritation and Corrosion: Reference Chemicals Data Bank
No. 67 The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and Related Food Webs
No. 68 Assessment Factors in Human Health Risk Assessment
No. 69 Toxicology of Man-Made Organic Fibres
No. 70 Chronic Neurotoxicity of Solvents
No. 71 Inventory of Critical Reviews on Chemicals (Only available to ECETOC members)
No. 72 Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation
No. 73 The Value of Aquatic Model Ecosystem Studies in Ecotoxicology
No. 74 QSARs in the Assessment of the Environmental Fate and Effects of Chemicals
No. 75 Organophosphorus Pesticides and Long-term Effects on the Nervous System
No. 76 Monitoring and Modelling of Industrial Organic Chemicals, with Particular Reference to Aquatic Risk Assessment
No. 77 Skin and Respiratory Sensitisers: Reference Chemicals Data Bank
No. 78 Skin Sensitisation Testing: Methodological Considerations
No. 79 Exposure Factors Sourcebook for European Populations (with Focus on UK Data)
No. 80 Aquatic Toxicity of Mixtures
No. 81 Human Acute Intoxication from Monochloroacetic Acid: Proposals for Therapy
No. 82 Risk Assessment in Marine Environments
No. 83 The Use of T25 Estimates and Alternative Methods in the Regulatory Risk Assessment of Non-threshold Carcinogens in the European Union

Joint Assessment of Commodity Chemicals (JACC) Reports

No.	Title
No. 1	Melamine
No. 2	1,4-Dioxane
No. 3	Methyl Ethyl Ketone
No. 4	Methylene Chloride
No. 5	Vinylidene Chloride
No. 6	Xylenes
No. 7	Ethylbenzene
No. 8	Methyl Isobutyl Ketone
No. 9	Chlorodifluoromethane
No. 10	Isophorone
No. 11	1,2-Dichloro-1,1-Difluoroethane (HFA-132b)
No. 12	1-Chloro-1,2,2,2-Tetrafluoroethane (HFA-124)
No. 13	1,1-Dichloro-2,2,2-Trifluoroethane (HFA-123)
No. 14	1-Chloro-2,2,2-Trifluoromethane (HFA-133a)
No. 15	1-Fluoro 1,1-Dichloroethane (HFA-141B)
No. 16	Dichlorofluoromethane (HCFC-21)
No. 17	1-Chloro-1,1-Difluoroethane (HFA-142b)
No. 18	Vinyl Acetate
No. 19	Dicyclopentadiene (CAS: 77-73-6)
No. 20	Tris-/Bis-/Mono-(2 ethylhexyl) Phosphate
No. 21	Tris-(2-Butoxyethyl)-Phosphate (CAS:78-51-3)
No. 22	Hydrogen Peroxide (CAS: 7722-84-1)
No. 23	Polycarboxylate Polymers as Used in Detergents
No. 24	Pentafluoroethane (HFC-125) (CAS: 354-33-6)
No. 25	1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0)
No. 26	Linear Polydimethylsiloxanes (CAS No. 63148-62-9)
No. 27	n-Butyl Acrylate (CAS No. 141-32-2)
No. 28	Ethyl Acrylate (CAS No. 140-88-5)
No. 29	1,1-Dichloro-1-Fluoroethane (HCFC-141b) (CAS No. 1717-00-6)
No. 30	Methyl Methacrylate (CAS No. 80-62-6)
No. 31	1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)
No. 32	Difluoromethane (HFC-32) (CAS No. 75-10-5)
No. 33	1,1-Dichloro-2,2,2-Trifluoroethane (HCFC-123) (CAS No. 306-83-2)
No. 34	Acrylic Acid (CAS No. 79-10-7)
No. 35	Methacrylic Acid (CAS No. 79-41-4)
No. 36	n-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)
No. 37	Methyl Acrylate (CAS No. 96-33-3)
No. 38	Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)
No. 39	Tetrachloroethylene (CAS No. 127-18-4)
No. 40	Peracetic Acid (CAS No. 79-21-0) and its Equilibrium Solutions

Special Reports

No.	Title
No. 8	HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances
No. 9	Styrene Criteria Document
No. 10	Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1)
No. 11	Ecotoxicology of some Inorganic Borates
No. 12	1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)
No. 13	Occupational Exposure Limits for Hydrocarbon Solvents
No. 14	n-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document
No. 15	Examination of a Proposed Skin Notation Strategy
No. 16	GREAT-ER User Manual

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction