Government/Research Councils Initiative on Risk Assessment and Toxicology

# From risk assessment to risk management:

## Dealing with uncertainty

Report of a workshop organised by the Risk Assessment and Toxicology Steering Committee

The Risk Assessment and Toxicology Steering Committee aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Committee takes forward the work of the Government/Research Councils Initiative on Risk Assessment and Toxicology. The Initiative was established in response to a statement in the 1995 UK Government *'Forward Look of Government Funded Science, Engineering and Technology'*, which recognised the inherent limitations of current procedures and committed the Government to pursuing opportunities presented by scientific advances.

The Steering Committee comprises participants from the Department of the Environment, Transport and the Regions, the Department of Health, the Department of Trade and Industry, the Home Office, the Ministry of Agriculture, Fisheries and Food, the Environment Agency, the Health and Safety Executive, the Medicines Control Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Natural Environment Research Council and the Institute for Environment and Health.

The secretariat is based at the Medical Research Council's Institute for Environment and Health.

The Risk Assessment and Toxicology Steering Committee operates as a subgroup of the Interdepartmental Liaison Group on Risk Assessment.

The Interdepartmental Liaison Group on Risk Assessment is an informal committee of officials responsible for policy development and practical application of risk assessment in UK Government departments. The group reports periodically to Ministers on a co-ordinated programme to promote consistency and coherence in risk assessment practices across Government.

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This document is a report arising from a workshop held in Leicester on 10–11 February 1999. Opinions and recommendations are based on those of the participants. Standards derived in the report are hypothetical and have been developed only as illustrations. The Government/Research Councils Initiative on Risk Assessment and Toxicology will consider any recommendations before making its own proposals for future work.

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# Executive summary

A workshop was convened by the Risk Assessment and Toxicology Steering Committee to examine the various influences on approaches for dealing with uncertainty in the toxicological component of chemical risk assessment.

Lack of knowledge about one or more elements of the risk assessment process necessitates the introduction of appropriate uncertainty factors to compensate for the uncertainty. There are a number of influences on the derivation of uncertainty factors, including:

- uncertainties in the quantity and/or quality of the data
- uncertainties in assessing how best to apply the data
- the nature of any adverse effect
- the risk management context within which the risk assessment is used.

The aims of the workshop were:

- to examine how uncertainty factors are established and used
- to make recommendations for improving the transparency about how uncertainty factors are derived and used when decisions are made publicly available.

Risk assessment practices currently used in four risk management contexts – the setting of occupational exposure limits, air quality standards, and consumer and operator standards for pesticides, and the control of food contaminants – were considered.

Five case studies were used to examine current practice, leading to the following recommendations.

- The degree of influence that available risk management options have on risk assessment, and vice versa, should be clearly explained when risk assessments or decisions about risk management are made publicly available.
- Much of the chemical risk assessment performed in the context of UK regulation is about arriving at statements that will contribute to risk management decisions to protect human health. It should be clearly recognised that risk assessment necessarily takes various forms. These include direct estimation of adverse effects at different levels of exposure, estimation of no-effect levels, and assessment on the basis of hazard information only.
- Although uncertainty factors are often presented as single numbers, the scientific and non-scientific influences that contribute to deciding an uncertainty factor should be clearly set out when chemical risk assessments are made publicly available.

# 1 General introduction

## UK Government/Research Councils Initiative on Risk Assessment and Toxicology

A number of UK Government departments have a responsibility for assessing risk to human health from potentially toxic substances that may be found in food, household products, human medicines, the environment or the workplace. Since reliable data from human populations exposed to known levels of a substance are rarely available, except in the case of human medicines and ambient air pollutants, the assessment is often based on data from studies in laboratory animals. Such an approach has to accommodate the uncertainties inherent in extrapolating from animal-derived data to humans and from high to low dose, and in accounting for population variability. The uncertainties in the risk assessment process necessitate the adoption of appropriate uncertainty factors to ensure protection. It is clearly desirable to reduce the uncertainties as far as possible.

The uncertainties inherent in current methodologies are widely recognised, as is the absence of scientific knowledge to define them more precisely. Recent advances in scientific techniques, such as use of novel biomarkers, molecular modelling and computer simulations, and *in vitro* toxicology, may offer new possibilities. Furthermore, the use of such techniques should contribute to the reduction of animal use and/or the refinement and replacement of animal tests, a principle to which Government departments and agencies are committed. Government departments, together with the relevant research councils, have decided to make a co-ordinated drive to pursue these important opportunities. Their commitment was set out in the 1995 UK Government report *'Forward Look of Government Funded Science, Engineering and Technology'* (HMSO, 1995) and resulted in the establishment of the Government/Research Councils Initiative on Risk Assessment and Toxicology in 1996.

The work of the Initiative is being taken forward by the Risk Assessment and Toxicology Steering Committee, which comprises participants from relevant Government departments and Research Councils. The secretariat is provided by Medical Research Council's Institute for Environment and Health. The Initiative aims to stimulate research so that new, improved approaches to the risk assessment of chemicals can be developed. It does not have its own research funds, but provides a focus, co-ordination and positive encouragement for research financed by individual Government departments or research councils (or consortia of these bodies).

The Steering Committee has organised a series of workshops on different aspects of risk assessment. This report is based on a workshop, held in Leicester, UK in February 1999, to examine the influences that determine how uncertainty is dealt with in risk assessment and risk management. The workshop focused on policy issues and was attended mainly by individuals from the Government departments and agencies participating in the Steering Committee.

## Basis for the workshop

### Uncertainty in the risk assessment of chemicals

The report of a review by the Risk Assessment and Toxicology Steering Committee (1999a), *'Risk assessment approaches used by UK Government for evaluating human health effects of chemicals'*, shows that the way in which uncertainties are handled varies between risk assessment schemes. The report also shows that, while a number of different issues are considered in determining uncertainty factors,

the outcome is normally presented as a single value (e.g. acceptable daily intake (ADI), occupational exposure limit (OEL), etc.). This does not cause problems for the comparison of risk assessments for different substances within a particular regulatory scheme or risk management framework, but it can result in apparent inconsistencies when the same substance is considered in different schemes.

The review identified a number of influences on the derivation of uncertainty factors, as follows:

- uncertainties in the data
  - data gaps
  - data quality
- uncertainties in applying the data
  - extrapolation from animals to the human population
  - individual variation within the human population
- the nature of the adverse effect
- the risk management context (framework) within which the risk assessment is used.

The purpose of this present report, based on the workshop, is to examine how these influences affect current practice.

## Aims of the workshop

The aims of the workshop were:

- to examine how uncertainty factors are established and used
- to make recommendations for improving transparency about how uncertainty factors are derived and used, when decisions are made publicly available.

In order to address these aims, summaries of toxicological information on five substances (case studies), anonymised to focus discussion on the general issues, were examined by four working groups, each of which considered how the data would be assessed within a particular risk management context, as follows:

- the setting of occupational exposure limits
- the setting of air quality standards
- the setting of consumer and operator standards for pesticides
- the control of food contaminants.

Each case study was concerned with a different toxicological end-point or issue, to ensure consideration of several possible influences on the choice of an uncertainty factor. The cases were:

- a non-genotoxic carcinogen (substance A)
- a reproductive and developmental toxicant (substance B)
- a respiratory irritant (substance C)
- two substances for which there were significant gaps in the data available for a risk assessment – one with a limited database and no human data (substance D1), and one for which no experimental animal model was available for the qualitative human response (substance D2).

## Workshop report

Section 2 of the report summarises the toxicological issues pertinent to each database, specific questions the groups were asked to address and the responses. The Annex gives the full databases of the five substances considered and more detailed reports of each group's discussion on each substance.

Conclusions and recommendations, based on a synthesis of the working group discussions, are presented in Section 3. The participants in the workshop are listed at the end of the report.

**In this report, standards derived from the databases considered are hypothetical; they have been developed only to illustrate the issues relevant to each case.**

# 2 Influences on the use of uncertainty factors

## 2.1 Introduction

This section provides a synopsis of the major points of discussion, in each of the four working groups, about factors that influence how uncertainty is dealt with (for details see Annex). Points of general agreement, when very similar considerations were apparent in all risk management contexts, are highlighted, as are circumstances in which quite different approaches were adopted. The rationales for similarities and differences in approach are examined further in Section 3.

Each working group was chaired by someone not familiar with the risk assessment scheme considered by that group, while the rapporteur was familiar with the operation of the scheme.

The working groups were required to make some basic assumptions. Each substance was dealt with according to the normal regulatory framework for the assessment scheme under consideration (focusing on the underlying issues), all data were assumed to be of good quality unless stated otherwise, and no new data could be expected. Exposure estimates were not provided; however, the groups were asked to discuss how such information would normally be used. Particular attention was given to ways in which uncertainty factors might be influenced by considerations other than those of a purely scientific nature.

To set the scene, the working group rapporteurs presented, in a preliminary plenary session, the key rationales behind each of the risk assessment schemes under consideration; these are summarised below. Key features of each scheme are outlined in Table 2.1.

**Occupational exposure limits**

The Control of Substances Hazardous to Health (COSHH) Regulations require employers to prevent exposure to hazardous substances. Where this is not reasonably practicable, exposure must be adequately controlled. For those substances that are assigned OELs, these define adequate control under COSHH.

In principle, an OEL ought to be set using data on all the effects on health produced by the substance at different levels of occupational exposure. In practice, however, absence of appropriate data and lack of a clear understanding of the biological processes involved mean that it can be difficult to relate occupational exposure over time to the probability of specific harm, particularly for effects that might develop over long periods of exposure. Alternative approaches are therefore normally adopted.

The conventional approach is to decide whether or not the hazardous properties of the substance have a threshold and, if so, to seek to derive from the available data an overall no-observed-adverse-effect level (NOAEL). Using uncertainty factors, the NOAEL is translated into an OEL – a level of exposure at which, based on current knowledge, it is judged that there is a minimal risk to the health of the workforce. An OEL is, however, only set if the level can be met by the application of good practice and the foreseeable excursions above this level are not expected to be associated with serious health effects. Thus the OEL represents a level of risk considered to be broadly acceptable.

Proposals for OELs are made by an Advisory Committee to the Health and Safety Commission. The Committee comprises appropriate representatives of stakeholders, for example, employers and employees, together with independent experts. Proposals are subject to public

consultation before approval and implementation. This process ensures a consensus approach to judgements about the levels of OELs.

Limits are also set for substances for which a threshold cannot be determined, but these are not considered in this report.

### Air quality standards

A number of conditions apply to the setting of air quality standards. First, a limited number of compounds tend to be considered. Second, current ambient levels of air pollutants are, at least occasionally, associated with effects on health. Third, human data, especially data derived from epidemiological studies, rather than animal data, tend to be used in air quality standard-setting. Epidemiological studies are relatively common in the air pollution field compared to the other areas covered in this report. This is probably because public concern about air pollution is high, prompting support for funding of studies in human populations. Fourth, setting standards is only a part of air quality management, which also includes setting air quality objectives[1]. Whereas standard-setting involves risk assessment, objective-setting involves risk management. Finally, true risk assessment is probably easier when dealing with air pollution than in other areas of regulatory toxicology, because epidemiological studies allow the establishment of coefficients relating ambient concentrations of pollutants to effects on health.

### Pesticides

In the UK, risk assessments for both agricultural pesticides and non-agricultural pesticides (also known as biocides) are performed under regulations which provide for a positive approval scheme, whereby a company wishing to market a new pesticide (the 'Applicant') must satisfy the regulatory authority that the product meets legislative requirements before an approval is granted. Legislation also gives powers to review existing products and revoke approvals if new information indicates that an approval is no longer appropriate. All pesticide products on sale must have an approval. Similar 'positive approval' schemes exist for human drugs, veterinary medicines, food additives and certain cosmetic ingredients. The other areas covered in this report (occupational exposures, air pollution and food contaminants) do not have such powers.

To gain an approval for a pesticide, the Applicant is required to present data or reasoned cases on a number of areas, including a toxicological assessment for human safety. For a new active substance or a compound being reviewed, the toxicological assessment will include metabolism and single and repeat dose toxicity, and investigations of carcinogenicity, genotoxicity, reproductive toxicity and teratogenicity. New formulations are assessed for acute toxicity, irritancy and skin sensitisation. Studies are usually in experimental animals, although human data are available for some pesticides. It is the responsibility of the Applicant to provide the information required by the regulatory authority. If there are any outstanding areas of concern, the regulatory authority can require the Applicant to provide additional information. If acceptable data or reasoned cases are not provided, no approval will be granted.

The approvals scheme for pesticides means that risk assessments are usually performed with an extensive range of supporting information and are backed by powers to refuse approvals or take action to remove an existing product from the market.

The case studies presented here have been assessed from the perspective of an agricultural pesticide. Although the basic process and committee structure is similar for non-agricultural pesticides, the emphasis is different because non-agricultural pesticides are not applied directly to crops or foodstuffs. A human risk assessment for an agricultural pesticide is intended to determine safety to consumers of treated crops, operators applying the products and others who may foreseeably be exposed (e.g. bystanders or workers entering a treated area). The consumer assessment assumes lifetime exposure and involves the derivation of an ADI from the toxicology studies. The assessment of operator exposure is tailored to the likely usage and exposure patterns of the product concerned, and involves the generation of an acceptable-operator-exposure level (AOEL) from the toxicology studies. The derivations of both ADIs and AOELs use uncertainty factors to extrapolate from NOAELs in toxicity studies. These factors are multiplied together and are normally 10 to cover variation in the human population and 10 to extrapolate from other animals to humans. Higher or lower factors can be applied if justified by relevant data. Approval may be granted with the application of additional factors as an interim measure while further data are generated.

[1] As defined in the Air Quality Strategy for England, Scotland, Wales and Northern Ireland: A Consultation Document (published by DETR, 1999) – Standards are the concentrations of pollutants in the atmosphere which can broadly be taken to achieve a certain level of environmental quality. Objectives are policy targets setting out what the Government... intend[s] should be achieved in the light of the air quality standards.

The information supplied for the case studies considered here is less extensive than would normally be required to support approval of a pesticide active ingredient. However, the ADIs and AOELs have been derived, on the basis of the data provided, often applying additional factors to cover deficits in the available database.

A subsequent stage of the assessment, not covered here since the case studies were anonymised, involves a comparison of likely exposure with that considered acceptable. The ADI is compared with estimates of exposure based on data from residue trials and food consumption at the high end of the population range. The AOEL is compared with estimates of exposure based on data from field trials or predictive models. If the exposure estimates are above the applicable ADI or AOEL, action can be taken to refuse, modify or withdraw a particular approval.

**Food–chemical contaminants**

The assessment and management of chemical contaminants in food is complicated because of the many different types of contaminant that can occur; the variety of possible sources of contamination, both 'natural' and 'man-made'; and the various different distributions of contaminants in the food supply. Sometimes the same contaminants can come from different sources; for example, lead can occur at higher than usual levels in certain soils, and can also come from lead in petrol.

Control is mainly by surveillance of relevant parts of the food supply followed by targeted action of various kinds, depending on the problem. There are upper levels set by legislation in a number of cases, but often these are 'long stops' and are normally above the levels that would be desirable in more specific items in the food supply.

Types of food contaminant include:

- inorganic contaminants – e.g. lead, cadmium, mercury
- organic contaminants – e.g. dioxins, polycyclic aromatics
- contaminants from materials in contact with food – e.g. vinyl chloride, phthalates
- natural toxicants arising from contamination of food with toxin-producing fungi/moulds, etc. – e.g. aflatoxin $B_1$
- 'inherent' natural toxicants present as a normal part of food – e.g. phyto-oestrogens, nitrate
- residues of pesticides and veterinary medicines.

The risk assessment process for contaminants is similar to that for food additives. A NOAEL is obtained from animal studies (or human studies if available) from which is derived a level 'of no appreciable risk' such as a tolerable daily intake (TDI). For effects with no threshold, the advice is normally to reduce levels to as low as reasonably achievable (ALARA). Problems are encountered, however, in that data sets are often incomplete, as in many cases the contaminant may arise from a variety of sources. Pesticide and veterinary medicine residues are assessed as part of the approvals process for these chemicals.

It is important to consider the overall context when considering control options. Thus a complete ban on aflatoxin $B_1$ would mean the elimination of certain foods and is not a realistic option. Similarly, natural toxicants have to be considered in the overall food context as they will normally be present in association with nutrients and other beneficial factors.

Where residue levels relate back directly to an addition earlier in the food-chain, as with pesticides and veterinary medicines, control is achieved by setting conditions on use and, in the case of veterinary medicines, by imposing suitable withdrawal periods. Where contamination is from a man-made source, such as lead in petrol, there are, similarly, control options available which target the specific source of the problem.

Generally, the most effective method for limiting exposure to contaminants is to target specific sources that cause exposure to be high. In the case of lead, for example, which can arise from a variety of sources, controls have been placed, over the years, on sources such as lead-soldered cans (now phased out in the UK), the use of lead in wine-bottle caps, and the presence of lead in equipment for drawing beer in public houses.

In many cases, controls may need to operate at different points in the food-chain, and often – as in the case of lead in petrol – these are a matter of more general environmental controls rather than controls in the food-chain itself. Another example is dioxins, where the main route of exposure is food, but where the sources are environmental.

**Table 2.1 Key features of the four risk assessment schemes considered**

| | Occupational exposure limits | Air quality standards | Pesticides | Food contaminants |
|---|---|---|---|---|
| Output | Occupational exposure limit (OEL) | Air quality standard (AQS) | Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) | Tolerable daily intake (TDI) |
| Risk management framework | Define adequate control under the Control of Substances Hazardous to Health Regulations | Objectives in the legislative process, as set out in the National Air Quality Strategy, to be achieved by 2005* – part of air quality management | Control of Pesticide Regulations, Food and Environmental Protection Act, associated statutory instruments and European Commission directives | Considered on a case-by-case basis in accordance with the provisions of the Food Act |
| Data used | Available animal and human data | Human epidemiology data, volunteer studies, animal data | Extensive data package required by regulation | Available animal and human data |
| Population to be protected | Workers | General population | General population and operators | General population |

*The objectives vary between pollutants

## 2.2 Case studies

A summary of the major points of discussion for each case study is presented below. More details, including the reasoning behind the decisions made, can be found in the Annex.

### 2.2.1 Substance A: A non-genotoxic carcinogen

#### *Introduction*

This case study looked at how evidence of the induction of cancer in animals through a proposed non-genotoxic mechanism might affect the selection of uncertainty factors. Toxicity data were provided such that key target tissues (liver and kidney) and a probable mechanism for tumour induction could be identified. Groups were asked to consider, in the presence and absence of the carcinogenicity data, what they saw as the key toxicological issue(s) from a regulatory perspective, and how the presence of a carcinogenic response might influence the choice of uncertainty factors.

#### *Key toxicological concerns in the absence of carcinogenicity data*

The occupational exposure limits, air quality standards and food contaminants groups would all expect to base decisions on the rat liver and kidney toxicity; the air quality standards and food contaminant groups would use as a starting point the NOAEL identified in a 2-year drinking-water study, and the occupational exposure limits group would use the NOAEL identified in a 6-month inhalation study. In contrast, the pesticides group considered that, in view of the accumulation and toxicity profiles, a well conducted chronic/carcinogenicity study would be required for approval of substance A as a pesticide active ingredient.

#### *The influence of the carcinogenicity data on the choice of uncertainty factors*

All the groups agreed that, given the non-genotoxic mechanism of action, a threshold of effect was likely for the observed carcinogenic effects. They would base decisions on the NOAELs chosen above, whether or not there was information on carcinogenicity. Given the additional information from the carcinogenicity study, the pesticides group would now expect to base decisions on the NOAEL identified in the 2-year drinking-water study. Consideration of the carcinogenicity data would cause the occupational exposure limits group to increase the size of the uncertainty factor used, unless additional information could be provided that the NOAEL was robust, the underlying mechanisms were clearly understood, and the health of the exposed workers would be monitored for early signs of adverse effects. On mechanistic grounds (i.e. the substance is not genotoxic), the pesticides and food contaminants groups would not use an additional uncertainty factor. The air quality standards group would consider the ambient concentrations before setting a standard, it being

undesirable that concentrations of any carcinogen, albeit non-genotoxic, should be allowed to rise.

### 2.2.2 Substance B: A reproductive and developmental toxicant

#### *Introduction*

The basis for this case study was concern about effects on reproduction and development. Data were provided on a substance inducing a range of toxic effects in animals, including effects on fertility and development. Groups were asked to consider which of the effects would be of concern, and what would determine the uncertainty factors if no reproductive or developmental toxicity data were available. The groups were then asked to consider their views on these issues in the light of the reproductive and developmental toxicity in animals.

#### *Key toxicological concerns in the absence of reproductive or developmental toxicity data*

The occupational exposure limits, air quality standards and food contaminants groups would all expect to base decisions on the NOAELs identified in 90-day rat drinking-water and oral gavage studies. The pesticides group considered that the absence of appropriate reproductive studies would preclude approval of substance B as a pesticide active ingredient.

#### *The influence of the reproductive or developmental toxicity data on the choice of uncertainty factors*

Concerns about the seriousness of the effects, uncertainty about the mechanisms, and the limited value of health surveillance in this context, would cause the occupational exposure limits group to increase the size of the uncertainty factor, which would be based on an inhalation NOAEL, available from the developmental toxicity studies. The air quality standards group would base decisions on the reproductive toxicity oral data, converted to an inhalation equivalent. However, a standard would not be decided until the ambient concentration was known, it being accepted that it would be inappropriate to allow ambient concentrations to rise. Like the occupational exposure limits group, the pesticides group considered that the presence of developmental effects in three species and the irreversibility and severity of effects indicated that the substance presented a teratogenic hazard to humans; an additional uncertainty factor would therefore be applied. The food contaminants group would not add an additional uncertainty factor unless reproductive toxicity studies failed to permit the identification of a clear threshold. The pesticides and food contaminants groups would expect to base decisions on the NOAEL identified in a rat oral gavage reproductive toxicity study.

### 2.2.3 Substance C: A respiratory irritant

#### *Introduction*

The uncertainty surrounding sensitive subpopulations was the primary issue addressed by this case study. Also considered was the relative value of animal data in the presence of data from human populations, particularly where there are differences between experimental exposure protocols and the pattern of human exposure. Data were provided on a substance which is irritant to the respiratory tract in humans (asthmatics and non-asthmatics) and animals. Each group was asked to consider how information on asthmatics might influence their view on uncertainty factors and whether this was dependent on the severity of any response observed. They were also asked to assess the relative importance to be given to the data from the animal studies.

#### *Relevance of data from animal studies*

The food contaminants group considered that the studies provided little useful information for assessing food contamination risks and that more appropriate studies would be needed before standards could be set.

The other three groups all considered that the animal studies reduced uncertainties, particularly in relation to long-term effects and toxicity at higher doses.

#### *Basis for regulatory standards and role of information on asthmatics*

The occupational exposure limits group considered that, for short-term exposures, a standard could be set on the basis of the NOAEL identified in studies in non-asthmatic volunteers. The bronchial reactivity data that were available were not considered to be of concern, so that an uncertainty factor to protect asthmatics was not needed. If these data had been significant then it would be necessary to apply an uncertainty factor or make recommendations that asthmatics should not be exposed. The air quality standards group would base a standard on the lowest-adverse-effect level (LOAEL) identified in studies on asthmatic subjects. It is likely that an uncertainty factor of 2 would be considered appropriate. This cautious approach was considered justified as the whole population is

exposed, responses in the volunteer studies were variable and there is a need to consider peak as well as longer-term average concentrations. The pesticide group would recommend the use of personal protective equipment to ensure that exposure did not rise above 10% of the LOAEL identified in asthmatic subjects.

### 2.2.4 Substances D1 and D2: Substances with data gaps

#### *Introduction*

These case studies were designed to address the issue of significant but important gaps in the database and the uncertainties this raises. The substance in case study D1 had a reasonable database for all end-points apart from reproductive and developmental toxicity. Groups were asked to consider the key end-points of concern, irrespective of the data gaps, and the uncertainty factors likely to be used for such effects, and then to consider how the lack of information might influence these views. Case study D2 concerned a substance for which a key health effect could be identified in humans qualitatively but not quantitatively. Furthermore, animal models were not available for this end-point but did indicate another possible toxic effect, for which a no-effect level had not been identified. Groups were asked how they would consider the uncertainties regarding both the human and animal data.

#### *The basis for decisions and the account to be taken of data gaps (substance D1 – no human data)*

The occupational exposure limits, air quality standards and food contaminants groups would all base decisions on substance D1 on the NOAEL identified in the 2-year rat inhalation study. The food contaminants group would note the apparent inconsistency with the gavage data. The pesticides group would not consider approval of substance D1 as a pesticide active ingredient without appropriate reproductive and developmental studies.

The lack of data on reproductive and developmental toxicity would not lead the air quality standards or the food contaminant groups to use a larger uncertainty factor. The occupational exposure limits group considered that the toxicological activity of the substance would create at least the potential for reproductive effects to be produced, and considered that the uncertainty factor would therefore be increased.

#### *The effects of the uncertainties in the database on decision-making (substance D2 – human data not modelled in other species)*

The groups agreed that the uncertainties were such that there was no basis for developing standards for D2 from the toxicological data. Consequently the pesticides group would not consider substance D2 for regulatory approval as a pesticide active ingredient. All groups noted that the data were a cause for concern, and risk management advice would be offered to reduce and minimise any exposure.

# 3 Conclusions and recommendations

The anonymised case studies considered by the working groups are intended to focus attention on a number of specific issues, and the discussions presented in the previous section describe the approaches taken in the four risk management contexts considered. Thus hypothetical standards derived by the groups (see Annex) do not necessarily reflect actual conclusions likely to be reached in 'real life' situations Furthermore, in some cases, the substances considered would not be relevant to all the risk management schemes included here. Thus, for example, substance C, a respiratory irritant, would not normally be considered by bodies dealing with food contaminants; and substance D1, with a low vapour pressure, would not be a candidate for consideration for an air quality standard. Nonetheless, the conclusions and recommendations presented here do arise from general considerations about how uncertainty factors would be applied in dealing with a toxicological database.

All four groups worked on the premise that a risk assessment may have to be made in the absence of knowledge about effects in exposed humans (or human populations). If adverse effects subsequently become apparent, as human populations are exposed to a chemical, the risk assessment would be reappraised.

In general, the four groups agreed about the toxicological effects of concern in each of the case studies. All groups identified the same toxic effects as being most important and noted the same key gaps in the data. Thereafter, there were differences in the way data were used, depending on the risk management context. Some of the differences reflected the route of entry into the body that would be of most concern to a given risk assessment scheme, others reflected the different populations at risk. Thus the occupational exposure limits and air quality standards groups, being mainly concerned with inhalation exposure, based decisions, where possible, on NOAELs identified in inhalation studies, while in the pesticides and food contaminants groups, the oral route was of key interest; and, whereas the occupational exposure limits group did not feel that the data set provided for the respiratory tract irritant (substance C) warranted giving particular attention to asthmatics in a working population, the air quality standards group gave particular consideration to asthmatics in the general population.

There was a marked contrast between the pesticides group and the other three in the approach taken to data gaps. The pesticides group would not consider approval of a substance as an active pesticide ingredient in the absence of key studies, requiring, in particular, carcinogenicity and reproductive studies. This reflects the fact that there are minimum data requirements for pesticides approval and the regulatory authorities can demand all the information considered to be necessary before a product can be marketed. A similar approach is taken by other approval schemes, such as those used for veterinary medicines and food additives. In the other contexts considered here, risk management of substances already present in the environment may be based on whatever data are available, without necessarily requesting additional information.

Thus the process of risk assessment as currently practised is influenced by the risk management context within which it operates, and can therefore vary.

**The degree of influence that available risk management options have on risk assessment, and vice versa, should be clearly explained when risk assessments or decisions about risk management are made publicly available.**

It is very rare for chemical risk assessment schemes to attempt to derive direct estimates of adverse effects at different levels of exposure. The discussions of the case studies show how the aim is to use the available data to generate an appropriate output (e.g. a standard or guideline) for use in risk management. The schemes all incorporate varying degrees of caution by applying uncertainty factors to identified starting points (e.g. NOAELs).

Air quality standards are only established for major atmospheric pollutants. Having set the air quality standards, it is possible to estimate the likely magnitude of an adverse effect in a given population. In contrast, for pesticides there is generally no human experience to aid decision-making, except possibly for very limited occupational exposure, and therefore reliance has to be placed on data generated in animals. For substance D2, with very limited data, risk management actions to reduce exposure were proposed on the basis of an assessment of the hazard information alone.

**Much of the chemical risk assessment performed in the context of UK regulation is about arriving at statements that will contribute to risk management decisions to protect human health. It should be clearly recognised that risk assessment necessarily takes various forms. These include direct estimation of adverse effects at different levels of exposure, estimation of no-effect levels, and assessment on the basis of hazard information only.**

Different approaches to the use of uncertainty factors were apparent. The food contaminants and pesticides groups routinely apply the classical $10 \times 10$ approach to account for interspecies and intraspecies variation in response; having applied these factors to the identified starting point (e.g. NOAEL) to establish ADIs, TDIs and AOELs, the usual procedure is to take risk management actions to ensure that human exposures do not exceed these levels.

The air quality standards and occupational exposure limits groups take account of current levels of exposure and feasibility of achieving reduction, respectively. Thus, as exemplified in the discussion of case studies A and B, the air quality standards group operates on the premise that, for substances which can cause serious health effects, for example, reproductive toxicity or cancer, ambient concentrations, as a minimum requirement, should not be allowed to rise. Uncertainty factors would normally be of a similar magnitude to those used for pesticides and food contaminants.

For occupational exposure limits the numerical standards tend to be higher. This is because, in the occupational setting, allowance can be made for the fact that the workforce is generally only exposed for 40 hours per week, that it does not include the most vulnerable members of the population, and that exposures can be monitored and timely remedial steps taken to control exposure further, as necessary. A smaller allowance can therefore be made for uncertainties when setting a standard for occupational exposure than when setting one designed to protect the general public.

Where the adverse effect was carcinogenicity or reproductive toxicity (teratogenicity) there was a suggestion that an additional uncertainty factor might be used to take account of the severity of effects, although the fact that the carcinogen considered (substance A) was non-genotoxic and that there was a plausible mechanism for tumour induction would influence such a decision. In support of the use of such an additional uncertainty factor, it may be argued that an extra margin should be allowed in case a threshold for a severe, irreversible effect were to be incorrectly identified at too high a level; the consequences of such an error might be serious and irreversible.

The usual uncertainty factor of 10 to account for interindividual differences in sensitivity is often intended to reflect the ranges of sensitivities in a population of healthy people. If, for example, the seriously ill are to be included (which should be the case if the whole population is being exposed), a factor of 10 may not be large enough (see also Risk Assessment and Toxicology Steering Committee, 1999b).

Thus there are differences in the approaches to the use of uncertainty factors in the schemes considered here, owing to their different risk management requirements.

As well as toxicological issues, decisions on uncertainty factors may sometimes reflect risk management and social and political factors. Thus, while identification of the lead effect and dealing with uncertainties in the database are technical matters that are handled scientifically, dealing with uncertainties in applying the data involves broader considerations. Additional factors for the seriousness of the effect may also be required.

**Although uncertainty factors are often presented as single numbers, the scientific and non-scientific influences that contribute to deciding an uncertainty factor should be clearly set out when chemical risk assessments are made publicly available.**

# References

HMSO (1995) *Forward Look of Government Funded Science, Engineering and Technology,* London, UK, HMSO

Risk Assessment and Toxicology Steering Committee (1999a) *Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals,* Leicester, UK, MRC Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999b) *Risk Assessment Strategies in Relation to Population Subgroups,* Leicester, UK, MRC Institute for Environment and Health

# Annex

## Case study A: A non-genotoxic carcinogen

### Description

#### *Physicochemical properties*

Substance A is a halogenated hydrocarbon (molecular weight 119) and is a colourless, volatile, non-flammable liquid at room temperature. It has a vapour pressure of 159 mmHg at 20 °C (for comparison, the vapour pressures of water and acetone are 17.5 and 185 mmHg, respectively, at 20 °C), a water solubility of 0.82 g/100 ml at 20 °C, and is miscible with organic solvents. It has an octanol/water partition coefficient (log $K_{ow}$) of 3.

#### *Toxicokinetics*

The substance is well absorbed by the inhalation, oral and dermal routes and, following uptake, is widely distributed around the body. It has been shown to accumulate in fatty tissue on prolonged exposure. The main route of elimination is via the lungs, largely as carbon dioxide following metabolism. Studies in animals and humans have shown that a principal metabolite is produced consistently in all species and that the toxicity of substance A is mediated via this metabolite.

#### *Acute toxicity*

Substance A is of low to moderate acute toxicity following application by the inhalation, oral or dermal routes. Immediate signs of toxicity are due to CNS depressant effects; delayed hepatotoxicity is also seen at higher doses. Such effects have been observed in all species, although they are poorly quantified in humans. The substance (in liquid form) is also highly irritant to the eyes and skin but does not appear to possess these properties in the vapour phase. There is no evidence that substance A is a skin or respiratory tract sensitiser.

#### *Repeat-/continuous-dose toxicity*

The effects of repeated or continuous exposure to substance A in humans are generally poorly documented and qualitative in nature. Toxic jaundice has resulted from occupational exposure at a reported concentration of 400 ppm (2125 mg/m$^3$). In contrast, there is a significant database available from studies in animals. When administered orally by gavage to rats for 90 days, no effects were seen at 30 mg/kg/day but liver and renal toxicity were observed at 150 mg/kg/day. In a long-term (2-year) drinking-water study, rats received substance A at concentrations of 0, 200, 400, 900 or 1800 ppm (equivalent to 0, 20, 40, 90 or 180 mg/kg/day). No effects were seen at 20 or 40 mg/kg but liver and kidney toxicity were observed at the higher dose levels, the severity increasing with dose. Similar findings were obtained in mice that received the same doses in drinking-water over 2 years. In repeated inhalation exposure studies in rats, exposure to 25 ppm (133 mg/m$^3$) or more of substance A for 7 hours/day, 5 days/week for 6 months led to histopathological changes (necrosis, inflammation and hyperplastic changes, the latter indicative of compensatory proliferation) in the livers and kidneys. Inhalation exposure of rats to 25 ppm (133 mg/m$^3$) for 4 hours/day for 6 months did not result in hepatic or renal toxicity.

#### *Genotoxicity*

Substance A has been extensively tested in standard *in vitro* and *in vivo* assays conducted to modern regulatory standards for genotoxic activity and has produced uniformly negative results.

***Carcinogenicity***

No data are available from epidemiological studies in humans. A number of standard rodent (rat and mice) bioassays are available for substance A administered via the inhalation and oral routes of exposure. In these assays, substance A clearly induced tumours (both malignant and benign) in the liver and kidneys, although the effects were more pronounced following oral dosing. Moreover, tumours were only observed at those dose levels that induced other signs of toxicity in these tissues.

***Reproductive toxicity***

Substance A has been investigated in standard reproductive and developmental toxicity assays conducted to modern regulatory standards. The results indicate that the substance is not toxic to the reproductive system and does not induce developmental effects.

**Questions**

In determining the uncertainty factors to be applied, each working group was asked to consider the following additional questions.

- If the carcinogenicity studies had not been performed or the outcome had been clearly negative, what would be the key toxicological issue(s) on which a regulatory decision would be based and what uncertainty factor(s) would be applied?

- Would taking the positive carcinogenicity data into account alter the view on the uncertainty factor(s) to be applied? If so, why and if not, why not?

**Occupational exposure limits**

The high vapour pressure, suggesting easy vapourisation, indicated that inhalation would be a key route of potential exposure.

Had the carcinogenicity data been negative, the key toxicological issues would have been the liver and kidney toxicity on long-term exposure in rats and mice – the observation of jaundice (liver toxicity) in humans indicates that the rodent liver toxicity is clearly relevant to humans. The CNS depression would also have been important, suggesting that short-term, high-level exposure could be a concern. However, it was considered that there were insufficient data provided to take this further forward.

The following approach was used to establish an occupational exposure limit (OEL). The rat no-adverse-effect level (NOAEL) of 25 ppm (133 mg/m$^3$) for 4 hours was assumed to be equivalent to 12.5 ppm (67 mg/m$^3$) for 8 hours. The OEL would be set somewhere below this value. On purely toxicological grounds, in deriving this lower value the use of an uncertainty factor of less than 100 (partitioned according to custom and practice, a factor of 10 to account for interspecies variation in response and 10 to account for intraspecies variation) could be justified because of considerations that: the workforce is generally 'healthy'; the health of the workforce should/can be monitored, and any problems can therefore be detected early and remedial action taken before a toxicological problem becomes serious; compared with other situations, workplace exposure can be more rigorously controlled to any standard set; and the workforce is likely to have been better trained to handle the substance appropriately. In reality, an important factor in establishing an OEL is the degree of control deemed to be achievable in practice. As no information on exposure was given in the documentation, this factor could not be taken into account and it was therefore not possible to determine the value of the OEL or the uncertainty factor that would be involved.

It was considered that the positive carcinogenicity data would justify an increase in the uncertainty factor applied in setting an OEL based on the rat NOAEL unless additional reassurance could be provided that the NOAEL was robust, that the underlying mechanisms involved in the tissue-damaging and carcinogenic processes were clearly understood, and that the health of exposed workers would be monitored for early signs of liver and kidney damage.

**Air quality standards**

The reported studies were considered to provide sufficient evidence for the derivation of NOAELs. From the 2-year study in rats, a NOAEL of 40 mg/kg/day was identified. Application of an uncertainty factor of 100 ($10 \times 10$) produced a value of 0.4 mg/kg/day. From this value (assuming average body weights and inhalation rates) a potential air quality standard (AQS) of 1 mg/m$^3$ was determined. Using the alternative NOAEL of 25 ppm (133 mg/m$^3$) derived from the 4 hours/day inhalation study in rats, adjusting to exposure of 24 hours/day and again applying the uncertainty factor of 100, a potential AQS of 0.25 mg/m$^3$ was derived. The inhalation study was considered to represent the more likely route of exposure and

thus the AQS should be 0.25 mg/m$^3$, measured as a 24-hour average concentration.

The fact that the substance was probably carcinogenic but not likely to be a genotoxic carcinogen indicated that a threshold of effect was likely. Before setting an AQS, therefore, the ambient concentration should be considered, it being undesirable that concentrations of any carcinogen, albeit non-genotoxic, should be allowed to rise.

## Pesticides

The indications of accumulation and the toxicity profile were considered to be such that a well conducted chronic/carcinogenicity study would be required for approval of substance A as a pesticide active ingredient. The evidence of tumours at dose levels above those causing non-neoplastic effects did not affect the overall risk assessment, since the genotoxicity data were negative and there appeared to be a plausible mechanism for tumour production.

A number of areas merit special attention and would need to be considered further as part of an actual evaluation. Reassurance regarding the accumulation in fat and potential for secretion in breast milk might be provided by the lifetime studies and the negative results in the reproduction study. The mechanism of tumour production was probably secondary to tissue damage and associated responses but this would need to be confirmed. No special at-risk groups were identified and none of the effects was considered to merit additional uncertainty factors. The quality of the human database was considered to need further investigation. If the human data were found to be extensive and reliable it might be possible to refine the uncertainty factor for extrapolating from animals to humans. The high volatility might necessitate controls or protective equipment to reduce inhalation exposure in workers. If these were considered necessary, then approval for non-professional (home and garden) use would be unlikely.

### *Derivation of ADI*

The most appropriate NOAEL was considered to be that from the 2-year drinking-water study in rats, 40 mg/kg/day. The NOAEL of 30 mg/kg/day from the 90-day gavage study was not used, the reasoning being that the minimal effect level in the study was 150 mg/kg/day, indicating that the true NOAEL was somewhere between 30 and 150 mg/kg/day – consistent with the value of 40 mg/kg/day from the longer-term study. Applying an uncertainty factor of 100 ($10 \times 10$), the acceptable daily intake (ADI) would be 0.4 mg/kg.

### *Derivation of AOEL*

A systemic acceptable operator exposure level (AOEL) based on oral exposure studies would be the same as the ADI at 0.4 mg/kg/day. The evidence provided no appropriate dermal exposure studies. Given the high volatility of substance A and the extensive database of inhalation studies, it was also considered appropriate to derive a systemic AOEL based on inhalation exposures. Exposure to 25 ppm (133 mg/m$^3$) for 4 hours/day for 6 months was a NOAEL in rats. Conversion to a daily exposure based on rat inhalation for 4 hours ($133 \times 0.18$) gave 24 mg/kg/day. Applying an uncertainty factor of 100 ($10 \times 10$), the AOEL would be 0.24 mg/kg.

The AOEL values were similar for the oral and inhalation routes, as were the effects produced at higher doses. Exposure findings would thus determine the most appropriate scenario.

## Food contaminants

The toxicokinetic studies were considered to provide useful information, that is, that substance A accumulates in fatty tissue, and its toxicity is mediated via a principal metabolite observed in all species, including humans. There was no information to enable identification of possible subgroups. There was a lack of good information about effects in humans. Nevertheless, the report of toxic jaundice arising from occupational exposure was consistent with effects seen in animals.

Repeat-dose studies indicated that substance A is a non-genotoxic carcinogen. The mutagenicity studies had been performed to modern regulatory standards and were reassuringly negative. Tumours had only been observed at dose levels causing overt toxicity. Given the knowledge about the mechanism of toxicity, it was thought likely that an advisory committee on food (e.g. Committee on Toxicity; Committee on Carcinogenicity; Scientific Committee on Food) would consider a threshold approach appropriate. Reproductive toxicity was not of concern. The 2-year drinking-water study in rats provided a NOAEL of 40 mg/kg. This would be used for derivation of a tolerable daily intake (TDI), unless the dose from the inhalation study (25 ppm) was less.

### *Derivation of TDI*

Applying an uncertainty factor of 100 ($10 \times 10$), the TDI would be 0.4 mg/kg.

It was considered that the carcinogenicity study would have limited impact on the regulatory decision, since the compound is not genotoxic and

there is clear evidence of a mechanism of toxicity. Dietary intakes would have to be evaluated and compared with the TDI. If the TDI were to be exceeded by the general population, or by subgroups such as the young or the elderly, advice on risk management options would need to be sought from the Food Advisory Committee.

# Case study B: A reproductive and developmental toxicant

## Description

### *Physicochemical properties*

Substance B is a colourless organic solvent (molecular weight 90) and is a liquid at room temperature. It is highly soluble in water, is miscible with organic solvents, has a log $K_{ow}$ of 0.8 and a low vapour pressure (<0.1 mmHg at 20 °C).

### *Toxicokinetics*

Substance B is readily absorbed following exposure by the inhalation, oral and dermal routes to both the liquid and vapour phases (the latter for inhalation and dermal exposure). Following uptake, it is widely distributed throughout the body. The substance is metabolised to an acetic acid derivative and largely (60–80%) eliminated via the urine. There is no evidence that it accumulates within the body on repeated exposure.

### *Acute toxicity*

The substance is of low acute toxicity following exposure via all routes relevant to human exposure. CNS depression and evidence of damage to blood cells has been observed in animals given high doses and humans accidentally exposed to high doses. It does not possess irritating or sensitising properties.

### *Repeat-/continuous-dose toxicity*

No useful human data are available. Repeated or continuous exposures of experimental animals have indicated that the bone marrow, liver, kidney and testes are target tissues for substance B. In drinking-water studies, rats were exposed for 90 days at doses of 1250–20 000 ppm (equivalent to 110–2240 mg/kg/day). No effects were seen at 1250 ppm. Dose-related anaemia was observed in both sexes at doses of 2500 ppm (205 mg/kg/day) and above. Histopathological signs of liver and kidney toxicity were observed at doses of 5000 ppm (400 mg/kg/day) and above. Signs of testicular damage (atrophy of the seminiferous tubules) were observed at 5000 ppm and above. A similar pattern of response was observed in rats given substance B by gavage for 90 days, with a NOAEL identified at 95 mg/kg/day and histopathological and anaemic changes observed at the next dose (200 mg/kg/day) and above.

### *Genotoxicity*

Substance B has been tested in a full range of *in vitro* and *in vivo* genotoxicity assays conducted to modern regulatory standards and found to produce uniformly negative results.

### *Carcinogenicity*

No data are available from human experience. Standard rat and mouse 2-year bioassays conducted to current regulatory standards were negative.

### *Reproductive toxicity*

No data are available for humans. As indicated above, substance B was found to induce toxicity in the testes of rats (confirmed by reduced fertility in mating studies) but no effects on female fertility have been found in standard reproductive toxicity studies where only females were treated. Developmental toxicity studies have been carried out in the rat, mouse and rabbit. Embryo toxicity (e.g. post-implantation losses) and fetotoxicity (e.g. decreased fetal weight) were induced in all test species by substance B. Furthermore, teratogenic effects, including increased skeletal and cardiovascular malformations, were seen in the rat and rabbit; exencephaly and cleft palate were observed in the mouse. NOAELs have been determined for these effects from some studies. For teratogenic and fetotoxicity, a NOAEL of 50 ppm (200 mg/m$^3$) was determined for both the rat and rabbit following inhalation exposure and 23 mg/kg/day for the rat following oral gavage dosing. Mice were only tested at higher dose levels (>100 mg/kg/day) all of which induced signs of developmental toxicity.

## Questions

In determining the uncertainty factors to be applied, each working group was asked to consider the following additional questions.

- If the reproductive and developmental toxicity studies had not been performed or the outcome had been clearly negative, what would be the key toxicological issue(s) on which a regulatory

decision would be based and what uncertainty factor(s) would be applied?

- What, if any, influence do the results of the reproductive toxicity and developmental toxicity studies have on any uncertainty factor(s) to be applied?

- What, if any, is the influence of the route/method of exposure and the population likely to be exposed?

**Occupational exposure limits**

As the substance has a low vapour pressure, it was thought unlikely that significant airborne concentrations could be created.

Ignoring the reproductive study data, the key toxicological issues were the bone marrow and testicular effects and, to a lesser extent, the liver and kidney effects occurring at higher doses.

A rat oral NOAEL of 95 mg/kg/day (supported by drinking-water studies) was identified. This was extrapolated to predict a rat inhalation NOAEL of 333 mg/m$^3$ for an 8-hour exposure. It was considered that an OEL would be set at a lower value, taking into account the factors described above, but also taking into account an added uncertainty owing to route-to-route extrapolation.

The positive fertility and developmental toxicity results were considered to change the picture in two ways. New effects were seen, particularly the developmental toxicity observed in three species; and for oral dosing, the overall NOAEL was lowered, although the inhalation NOAEL looked similar. Since pregnant women were likely to be exposed, the uncertainty factor should be increased because of the type of effect (irreversible, devastating, also societal horror), the uncertainty about the underlying mechanism, and the fact that health surveillance would be of no value for developmental effects and would probably be impractical for fertility concerns.

**Air quality standards**

Using the approach described for case study A to derive an AQS from studies with different routes of exposure, potential AQSs were derived from three data sets: (a) non-reproductive toxicity studies, 3.5 mg/m$^3$; (b) reproductive toxicity studies using oral dosing, 1 mg/m$^3$; and (c) reproductive toxicity studies using inhalation exposure, 2 mg/m$^3$. From these, 1 mg/m$^3$ was chosen as the AQS. It is arguable that another uncertainty factor might be needed on the grounds that reproductive toxicity is a serious and emotive effect. However, it was thought that this could not be decided until the ambient concentration was known: it being accepted that it would be inappropriate to allow ambient concentrations to rise.

**Pesticides**

Teratology studies would be required for approval of substance B as a pesticide active ingredient. In the absence of such data, an additional factor of 10 would probably be applied to any ADI or AOEL derived for an emergency evaluation. Women could not normally be excluded from working with pesticides, so the developmental effects would need to be considered when performing operator exposure assessments.

A number of areas merited special attention and would need to be considered further as part of an actual evaluation. The presence of developmental effects in three species indicated that the compound would probably present a hazard to the human fetus. The irreversibility and severity of the effects produced by a true 'teratogen' indicated that application of an additional uncertainty factor was appropriate. There would also be societal concerns about effects produced during pregnancy (as with thalidomide). The rarity and severity of the findings, in particular cardiovascular malformations, would need to be determined, as this might influence the additional uncertainty factor. Historical control data might be of value. The steepness of the dose–response curve and the dose level producing a minimal effect would need to be considered as these might influence the additional uncertainty factor. Acceptable exposures derived for workers and consumers were the same (see below). Was one assessment too conservative? Did the other provide adequate protection? The potential for additive exposures from the diet and occupation were not addressed.

***Derivation of ADI***

The most appropriate NOAEL was considered to be that from the gavage teratology study in rats, 23 mg/kg/day. The testicular effects were produced at a dose of 400 mg/kg/day and did not merit special consideration. Applying an uncertainty factor of 500 ($10 \times 10 \times 5$), the ADI would be 0.046 mg/kg.

***Derivation of AOEL***

Inhalation exposure was considered to be minimal under most conditions of use. A systemic AOEL

was derived on the basis of the gavage teratology study in rats (23 mg/kg/day). The derivation was identical to the ADI, 0.046 mg/kg/day.

**Food contaminants**

Substance B appears to be cleared from the body fairly rapidly and so it was considered possible that the 90-day studies could be used to determine a TDI without the application of an additional uncertainty factor to allow for the extrapolation from subchronic to chronic studies. Red blood cell damage had been observed in humans and animals following acute exposure, but information on repeated exposure relied on animal studies. NOAELs of 95 mg/kg/day and 110 mg/kg/day could be derived from drinking-water studies, but the reproductive toxicity studies suggested a lower NOAEL of 23 mg/kg/day from oral dosing. It would be necessary to check that the inhalation exposure does not indicate a lower dose.

***Derivation of TDI***

Applying an uncertainty factor of 100 ($10 \times 10$), the TDI would be 0.2 mg/kg.

If the teratology studies had not permitted identification of a clear threshold, then an additional uncertainty factor of 10 might have been applied.

If the reproductive studies had been negative, then a factor of 100 would have been used on 100 mg/kg/day.

# Case study C: A respiratory irritant

**Description**

***Physicochemical properties***

Substance C is a highly reactive colourless solid (molecular weight 48), yellow liquid or reddish brown gas. It has a boiling point of ~21 °C, a vapour pressure of 767 mmHg at 20 °C, and as a gas it is denser than air (vapour density, 1.58).

***Toxicokinetics***

There is a high degree of absorption of inhaled substance C in the respiratory tract, with the sites of deposition and absorption being dependent on pulmonary ventilation rates. In healthy humans under normal resting conditions, up to 90% of inhaled substance C is absorbed; this increases only slightly (to 92%) at maximal rates of ventilation. Respiratory tract absorption occurs by dissolution of the substance in extracellular and cellular fluids. Subsequent chemical reactions produce metabolites, which are eliminated from the body via the kidneys.

***Acute toxicity***

There are numerous case reports of single accidental exposures to high concentrations (probably in the hundreds of ppm) of substance C, showing severe acute toxicity and death. In these cases, the acute health effects observed involved severe local irritant damage to the eyes and respiratory tract. Animal studies confirm these observations.

The effects of single exposure to lower concentrations of substance C have been extensively investigated in well conducted human volunteer studies, both in non-asthmatic and asthmatic individuals. No clear differences between the responsiveness of non-asthmatics and asthmatics to the effects of substance C on pulmonary function have been identified, either under conditions of rest or exercise, up to a concentration of 4 ppm (8.6 mg/m$^3$). At 5 ppm (11 mg/m$^3$) and above in non-asthmatic subjects, there is weak evidence for an increase in airway resistance with an exposure of many hours duration. Concentrations higher than 4 ppm (8.6 mg/m$^3$) have not been investigated in asthmatic subjects, hence the concentration at which effects on pulmonary function would develop is uncertain. In studies in non-asthmatic subjects, there is no convincing evidence for changes in bronchial reactivity (in response to challenge with methacholine) following exposures to substance C at concentrations of up to 3 ppm (6.4 mg/m$^3$). There is weak evidence for an increase in bronchial reactivity with exposures of several hours duration to 5 ppm (11 mg/m$^3$) and above. In asthmatic subjects, increases in bronchial reactivity have been found in some studies over the concentration range 0.2–0.5 ppm (0.43–1.1 mg/m$^3$), but not in any studies at 0.6, 1 and 3 ppm (1.3, 2.1 and 6.4 mg/m$^3$). Overall, no clear exposure–response relationship can be identified for any effect of substance C on bronchial reactivity in asthmatic subjects.

There is no evidence for the development of sensory irritation, in either non-asthmatic or asthmatic subjects, at concentrations of up to 4 ppm (8.6 mg/m$^3$). Concentrations higher than this have not been investigated in non-asthmatic subjects, hence the threshold for the development of irritant symptoms cannot be identified.

***Repeat-/continuous-dose toxicity***

There is little useful information on the effects of repeated exposure to substance C in humans. The majority of data available suffer from an absence of information on personal exposures and are based on studies where exposure to other airborne substances, both gaseous and particulate, also occurred, such that the possible role of substance C in producing any of the health effects observed could not be reliably identified.

The effects of repeated/continuous inhalation exposure to substance C have been studied in a broad range of animal species; end-points investigated include pathology, pulmonary function and biochemistry. The majority of longer-term exposure studies have involved continuous (24 hours/day, 7 days/week) low-level exposures. It is clear that pathological changes affecting the trachea, main bronchi, bronchioles and alveolar regions occur with continuous exposure to concentrations of 2 ppm (4.3 mg/m$^3$) and above. At concentrations below 2 ppm (4.3 mg/m$^3$) there is a lack of consistency in the findings of the studies available, with several reporting no pathological changes in rats, guinea pigs, monkeys and rabbits with continuous exposure to 1 ppm (2.1 mg/m$^3$). By contrast, there are some studies in rats and mice in which broncho-alveolar changes (dilated airspaces, increases in type II cells, loss of cilia in respiratory bronchioles) have been reported at 0.5 ppm (1.1 mg/m$^3$). Overall, this appears to reflect differences in study methods, with electron microscope and quantitative morphometric techniques identifying changes not observed with traditional light microscopy. A clear NOAEL for histopathological changes to the respiratory tract cannot be identified for continuous low-level exposure. In rats exposed to substance C for 7 hours/day, 5 days/week for 15 weeks, no histopathological changes were evident in the lungs at 1 ppm (2.1 mg/m$^3$), as determined by light microscopy. At 5 ppm (11 mg/m$^3$), and at 1 ppm (2.1 mg/m$^3$) with twice daily peaks at 5 ppm (11 mg/m$^3$), minimal focal histopathological changes were seen in only a few rats from each of these exposure groups ($n$ = 50). In this study, biochemical changes indicative of lung damage were noted at all exposure levels after 3 weeks of exposure, but these had resolved after 15 weeks, apparently owing to adaptive changes leading to some degree of tolerance to further exposure.

***Genotoxicity***

The genotoxic potential of substance C has been investigated *in vitro* and *in vivo* in studies conducted to modern regulatory standards which have, in general, produced negative results. Furthermore, it is considered that any DNA damage produced by exposure to substance C would result from the consequences of cellular oxidative damage caused by the free radical properties of the substance, rather than via a direct mechanism of action. These considerations suggest that the potential for DNA damage resulting from exposure to substance C would not occur until cellular defence mechanisms were overwhelmed (i.e. this would be a threshold phenomenon).

***Carcinogenicity***

There are no useful adequately conducted carcinogenicity studies. However, it is predicted that there would be no development of indirect genotoxic damage caused in the target tissues of the respiratory tract with exposures that are below the threshold for cytotoxicity. Exposures below this threshold would not produce chronic sustained inflammation that could potentially lead to neoplasia. Hence there is unlikely to be an increased risk of tumour development with substance C below the thresholds for chronic cytotoxicity in the respiratory tract tissues.

***Reproductive toxicity***

No human data are available. Animal studies conducted in a number of species have been negative for effects on reproduction and development.

**Questions**

In determining the uncertainty factors to be applied, each working group was asked to consider the following additional questions.

- Considering the database as a whole, do the animal studies increase or reduce the uncertainties in considering the substance, given the human data available?

- How, if at all, should the data on asthmatic subjects influence considerations on uncertainty and any factor(s) that might be used? If the effects in asthmatics had been more marked, what influence, if any, would this have had?

- Given that many of the animal data are based on continuous exposure, would the same uncertainty factor(s) be applied under conditions of intermittent but regular exposure?

### Occupational exposure limits

It was felt that it would be necessary to consider and control both short-term peak exposures and longer-term daily exposure.

Taking into account the effects of short-term peaks, there appeared to be a clear human NOAEL of 4 ppm (8.6 mg/m$^3$); it was considered that the bronchial reactivity data were not of significant concern. The animal studies did not contribute to considerations about short-term exposures. A short-term OEL could be set on the basis of the human data, without the need for an uncertainty factor.

In contrast, the animal data were regarded as crucial when considering the effects of longer-term exposures. An OEL could be set for longer-term, daily exposure by using the rat inhalation NOAEL (for light microscopy findings) of 1 ppm (2.1 mg/m$^3$); the electron microscopy findings for continuous exposure to 0.5 (1.1 mg/m$^3$) ppm were regarded as being of uncertain significance.

On the basis of the available data and given the dismissal of the health significance of the bronchial reactivity results, the fact that asthmatic subjects could be exposed would not justify a change in the approach taken to the application of uncertainty factors. If asthmatics had proved to be markedly more sensitive to the substance than non-asthmatics, then one of two approaches could be justified: either the OEL values could be reduced to levels that would also be protective for asthmatics; or asthmatics could be excluded from the exposed workforce.

It was considered that a smaller uncertainty factor could be used in setting a workplace standard (representing repeated but discontinuous exposure) to take into account the fact that many of the animal data were based on continuous exposure.

### Air quality standards

Examination of the data led to the identification of 0.2 ppm (0.43 mg/m$^3$) as a lowest-observed-adverse effect level (LOAEL) for exposure in asthmatic subjects. It was thought that exposure studies involving asthmatic subjects were unlikely to include the more sensitive asthmatic patients and it was suggested that an uncertainty factor of 2 should be applied to the LOAEL to reach a potential AQS of 0.1 ppm (0.21 mg/m$^3$). The adoption of such a cautious approach was felt to be justified on the grounds that: exposure of the whole population was likely; animal data confirmed toxicity at higher levels; responses were clearly variable, which suggested that a further level of uncertainty should be taken into account; and there was a need to look at peak as well as at longer-term average concentrations.

### Pesticides

Very few gaseous products are used as agricultural pesticides, with uses limited mainly to soil fumigation or protection of stored produce.

The need to determine an ADI for consumer exposure would depend on the levels and chemical nature of any residues in treated produce. If levels were below 10 ppb, consumer exposure could be considered to be minimal and a full package of oral studies might not be required. If residues were above 10 ppb, the current toxicological database was likely to be considered inadequate to support approval.

The precise nature of a formulation based on this product would determine the exact nature of the risk assessment. For the purposes of this exercise it was considered to be a pure chemical.

The lack of effects on reproduction and development, and generally negative genotoxicity data were considered reassuring. The extensive database on humans indicated that it might be possible to apply only a 10-fold uncertainty factor (for intraspecies variability). If the data on asthmatics were robust and asthmatics were shown to be a susceptible population it might be possible to reduce the uncertainty factor below 10.

The reports of respiratory irritancy were a concern and would merit classification and associated safety advice. As it is not usually feasible to monitor or control atmospheres associated with pesticidal use of gases, there would probably be a requirement for respiratory protective equipment (RPE) or engineering controls to minimise inhalation exposure. With such controls in operation, a formal AOEL value might not be set, the aim being to keep exposures as low as reasonably achievable (ALARA). These concerns would probably preclude non-professional uses.

Given the indication of a minimal effect concentration in humans at 0.2 ppm (0.43 mg/m$^3$), engineering controls or RPE should be such that exposure concentrations would be less than 0.02 ppm (0.2/10; 0.043 mg/m$^3$) to cover variability within the working population. Further investigation of the human database might permit upward refinement of this figure.

**Food contaminants**

Substance C is highly reactive and it is therefore possible that dissolution products could enter food. However, it was considered that the studies provided little useful information for assessing food contaminant risks, or for setting a TDI. The Committee on Toxicity view would probably be that there was insufficient evidence to determine a TDI and there would be a request for more appropriate studies to be undertaken. No TDI would be allocated, but it might be noted that there is no evidence that this compound would be of concern via the oral route.

# Case studies D1 and D2: Substances with data gaps

**Description D1: No human data**

***Physicochemical properties***

Substance D1 is a colourless to light yellow organic liquid (molecular weight 111). It has a low vapour pressure (~0.1 mmHg at 20 °C), is miscible with water and is soluble in organic solvents (e.g. acetone, toluene). It has a log $K_{ow}$ of 0.4.

***Toxicokinetics***

No useful information is available on the toxicokinetics of substance D1 in humans. In animals, the toxicokinetics have been extensively characterised in the rat. Information is also available from the dog. Substance D1 is rapidly and extensively absorbed via the oral and inhalation routes in these species and the physicochemical characteristics suggest that it will also readily cross the skin. In the rat, substance D1 is extensively metabolised to form highly polar compounds which are rapidly eliminated, predominantly in the urine.

***Acute toxicity***

There is no information available regarding the acute toxicity of substance D1 in humans. It has been found to be of moderate acute toxicity in experimental species. The liver and kidneys have been identified as target organs and, following oral or inhalation exposure, irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs. Substance D1 does not possess significant skin irritant potential. However, as a liquid it is severely irritant to the eye. It has no sensitising properties.

***Repeat/continuous dose toxicity***

There is little useful information available on the effects of repeated exposure to substance D1 in humans. However, extensive studies have been conducted in rodents. Repeated inhalation of substance D1 by rats and mice resulted in haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx. Fatty changes and degeneration have been observed in the liver. In the nasal cavity, inflammatory changes in the olfactory and respiratory epithelia have been observed. Inflammatory changes were also observed in the larynx after prolonged exposure. A NOAEL of 1 ppm (4.61 mg/m$^3$) has been identified in a 2-year study in the rat. Signs of toxicity in rats inhaling substance D1 vapour at a concentration of 5 ppm (23 mg/m$^3$) for 2 years included clear evidence of nasal cavity inflammation and liver changes. In contrast, when substance D1 is given via the oral route to rats, the dose levels required to induce histopathological changes in the liver are considerably greater than those required by inhalation and the respiratory tract is not a target tissue. A NOAEL of 3.6 mg/kg/day has been identified in a drinking-water study. However, gavage doses of up to 60 mg/kg/day produced no clear histopathological changes in the liver and only slight changes in a few biochemical and haematological parameters. There are no data relating to the effects of repeated dermal exposure to substance D1.

***Genotoxicity***

Substance D1 has been extensively tested in standard *in vitro* and *in vivo* assays conducted to modern regulatory standards for genotoxic activity and has produced uniformly negative results.

***Carcinogenicity***

No data from human experience are available. The substance has been tested in standard 2-year bioassays conducted to modern standards in rodents. Treatment did not produce any increase in tumour formation over controls.

***Reproductive toxicity***

No studies specifically investigating reproductive performance or developmental toxicity have been conducted. There were no indications from histopathological examinations in the repeated dose studies that substance D1 had an adverse effect on the reproductive organs of experimental animals.

**Questions: D1**

In determining the uncertainty factors to be applied, each working group was asked to consider the following additional questions.

- No data are available on reproductive or developmental toxicity. What is the key effect of concern and what uncertainty factor(s) would normally be applied to such effects? How does the lack of information, if at all, influence views on the uncertainty factor that might be applied? If it does have any influence, why is this?

**Occupational exposure limits: D1**

The key effects of concern were considered to be the liver and upper respiratory tract damage. An uncertainty factor would be used to derive an OEL, starting from the rat NOAEL of 1 ppm (4.61 mg/m$^3$) and applying the same considerations as for substance A.

The toxicological activity of the substance was thought to create at least the potential for reproductive effects to be produced, and possibly at dose levels lower than those producing more general systemic toxicity. It was therefore considered that the uncertainty factor should be increased to take account of the lack of information available on the reproductive toxicity potential of the substance.

**Air quality standards: D1**

An AQS of 46 µg/m$^3$ was derived as a result of applying uncertainty factors using the approach outlined for substance A to two NOAEL values: 1 ppm (4.61 mg/m$^3$) from the rat inhalation data (giving 46 µg/m$^3$ as a potential AQS for humans) and 3.6 mg/kg/day from the rat drinking-water study (giving 150 µg/m$^3$ as a potential AQS). The data on laryngeal inflammation were used as a basis for standard-setting.

The lack of data on reproductive toxicity was not thought to justify the addition of another uncertainty factor.

**Pesticides: D1**

The toxicological database presented was considered inadequate to support approval for a new active substance. In the case of an emergency evaluation, an extra 10-fold uncertainty factor would probably be applied in deriving ADI or AOEL values, owing to the absence of any reproduction or developmental studies.

The information presented showed this compound to be a respiratory irritant and as such there would be a need to apply engineering controls or RPE to reduce inhalational exposures. The low vapour pressure and the need to protect against respiratory irritation indicated that inhalation exposure would probably be minimal. For this reason, the production of anaemia following inhalation exposure was not considered to represent a key issue in the risk assessment. The severe eye irritancy and respiratory irritancy might well preclude any approvals for non-professional use. The most significant toxicological findings were considered to be the effects on the liver. As the effects were reported to include 'degeneration', the application of the standard uncertainty factor of 100 ($10 \times 10$) was considered appropriate.

***Derivation of ADI***

The most appropriate NOAEL was considered to be that from the drinking-water study in rats, 3.6 mg/kg/day. Applying an uncertainty factor of 100 ($10 \times 10$), together with an additional factor of 10 to take into account the incomplete database, the ADI would be 0.0036 mg/kg.

***Derivation of AOEL***

It was assumed that the drinking-water study was a lifetime study, so that the most applicable study for deriving a systemic AOEL was the 90-day gavage study. A NOAEL of 60 mg/kg/day was derived. Applying an uncertainty factor of 100 ($10 \times 10$), together with an additional factor of 10 to take into account the incomplete database, the systemic AOEL would be 0.06 mg/kg.

**Food contaminants: D1**

The metabolism and clearance was rapid in animals; there was no information for humans. Repeat-dose studies indicated that the inhalation route was the most sensitive, but this is not relevant for food. A NOAEL of 3.6 mg/kg/day can be derived from drinking-water studies, although the apparent inconsistency with the gavage data was noted. (This might lead to a request that this be examined further).

The mutagenicity and carcinogenicity studies were negative and, although there were no specific reproductive toxicity studies, the toxicokinetics and the repeat dose studies did not suggest a cause for concern.

***Derivation of TDI***

Applying an uncertainty factor of 100 ($10 \times 10$), the TDI would be 0.2 mg/kg.

**Description D2: Human data not modelled in other species**

***Physicochemical properties***

Substance D2 is a colourless solid (molecular weight 128), which sublimes at room temperature. It has a melting point of ~80 °C and a low vapour pressure of ~0.1 mmHg at 20 °C. It is of very low solubility in water (~30 mg/litre) but is appreciably soluble in organic solvents. It has an estimated log $K_{ow}$ of around 3.5.

***Toxicokinetics***

Limited information available for humans indicates that substance D2 is readily absorbed by all routes of exposure. This is confirmed by the available animal data, which show almost complete and rapid absorption. *In vitro* studies in human liver microsomes and human lung preparations indicate that it is metabolised to a dihydrodiol by epoxide hydrolase. Metabolism in rodents is chiefly by cytochrome P450 oxidation, with subsequent glutathione conjugation, and epoxide hydroxylation to a dihydrodiol. Glutathione conjugation does not occur in non-human primates. *In vitro* studies show that the rate of metabolism in mouse lung tissue is approximately 3, 8 and 100 times greater than that observed in lung tissue from hamsters, rats and monkeys, respectively. The urine is the main route of rapid excretion in humans and other species.

***Acute toxicity***

There is no information on the effects of substance D2 following acute inhalation or dermal exposure in humans. Acute oral exposure clearly causes haemolytic anaemia which has resulted in fatalities. Individuals deficient in the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) are more susceptible to these effects. There is little quantitative information available, although severe haemolytic anaemia, which may have proved lethal in the absence of clinical intervention (blood transfusions), was reported in a 16-year-old female who had ingested approximately 6 g of the substance. Studies in animal models (mainly rats, mice and rabbits) have indicated that the toxic effects seen in these species are different from those in humans. Of the species studied, only dogs (in a poorly conducted study) demonstrated haemolytic anaemia. It appears that rodents are not suitable animal models for the acutely toxic human health effect of haemolytic anaemia. Data from animal studies indicate that the substance is only a slight skin and eye irritant and does not possess sensitising properties.

***Repeat-/continuous-dose toxicity***

There are no epidemiological studies on the human health effects of substance D2, and the only human information available derives from a limited number of early case reports which provide no quantitative data on the levels or duration of exposure. The principal human health effect is haemolytic anaemia, which in some cases has been of marked severity following exposure to the vapour by inhalation and to the solid by ingestion. Dermal exposure to the solid and vapour was also likely in these latter cases.

Animal studies reveal species differences in response. Haemolytic anaemia was noted in a dog following oral dosing of 220 mg/kg/day for 7 days but not in rodents, even with high/prolonged exposures. Cataract formation was the principal effect seen in rats and rabbits following oral exposure to 700 and 1000 mg/kg/day respectively in studies lasting 10–180 days, but this effect was not seen in mice with similar exposures. The lack of reliable reports of cataracts in humans, despite the widespread use and high-dose accidental exposure, suggests that cataract formation is unlikely to be a significant health effect in humans.

Marked changes in the olfactory epithelium were noted in a 90-day rat inhalation study at the lowest exposure level of 10 mg/m$^3$. These nasal effects became more marked with increasing levels of exposure. In a 104-week carcinogenicity study in mice, signs of nasal, olfactory and pulmonary inflammation were noted at 50 mg/m$^3$, the lowest exposure concentration used. A NOAEL could not be identified for local respiratory effects from these studies.

General signs of toxicity, including death, were reported in rats and rabbits dosed orally with 700 and 1000 mg/kg/day, respectively. It is apparent that mice are more susceptible than are rats or rabbits following oral treatment, with 100% mortality reported at 500 mg/kg/day in an 8-day study. For systemic effects, a NOAEL of 133 mg/kg/day was identified in a 90-day oral mouse study.

***Genotoxicity***

Substance D2 has given reproducible negative results in a full range of *in vitro* and *in vivo* tests conducted to modern regulatory standards.

***Carcinogenicity***

No conclusions can be drawn from the limited information available in humans. However, the carcinogenic potential of substance D2 has been relatively well investigated in animals. These studies produced negative results with respect to the induction of tumours over and above background levels.

***Reproductive toxicity***

In relation to fertility, there is no information available in humans but animal studies have indicated no effects on this end-point. With respect to developmental toxicity, the only information available in humans comes from cases of haemolytic anaemia in infants born to mothers also suffering haemolytic anaemia following ingestion of unquantified doses of the substance during pregnancy. In rats, fetotoxicity, but not malformations, was observed at doses causing maternal toxicity (450 mg/kg/day). Maternal toxicity was also noted at lower doses without fetotoxicity (150 mg/kg/day). In mice, fetotoxicity was observed at maternally toxic doses (300 mg/kg/day). In rabbits, no developmental effects were seen in one study at a dose causing mild maternal toxicity, or in another study at a dose close to those producing pronounced maternal toxicity. Overall, substance D2 only produces fetotoxicity at maternally toxic doses in animals, and does not produce developmental toxicity at maternally subtoxic doses.

**Questions**

In determining the uncertainty factors to be applied, each working group was asked to consider the following additional questions.

- The key human health effect of concern has been clearly identified in qualitative but not quantitative terms. Animal models either do not show the toxic effects seen in humans or provide only very limited data. How are the uncertainties regarding the lack of human data dealt with? Animals also show other effects, for which, in some cases, no NOAEL has been identified; how are the uncertainties in these data taken into account in establishing a regulatory position?

**Occupational exposure limits: D2**

The situation was considered to merit great concern because of the uncertainty surrounding the obvious but poorly understood interspecies differences; the availability of a LOAEL (with marked effects occurring), rather than a NOAEL, in rats; and the lack of any useful quantitative data for the haemolytic anaemia.

The only approach available to deriving an OEL was to start with the rat NOAEL of 10 mg/m$^3$ and apply a relatively large uncertainty factor, because of the above considerations. Because reasonable practicability of control is also a criterion in setting an OEL, it was not considered possible to propose an appropriate OEL.

**Air quality standards: D2**

Although the substance was known to be toxic in humans, there were no useful quantitative data on effects in humans, and the available animal data did not seem likely to be reliable in predicting such effects. Moreover, the animal reproductive toxicity data and the variability in the animal data were worrying. No NOAEL could be identified, and an AQS could not be set. It was considered that, if exposure was occurring, steps should be taken to reduce or prevent this.

**Pesticides: D2**

The available data were considered to be inadequate and it was therefore not possible to perform any meaningful risk assessment. It was thought extremely unlikely that the database would support use of this product as an agricultural pesticide.

The main concern was that the available toxicokinetic information showed rodents to be inappropriate models for humans. The finding of haemolytic anaemia in dogs and humans indicated that dogs might be a more appropriate model. However, there were no dog studies of a quality appropriate to setting ADI or AOEL values. It was considered that the relevance to humans of the cataracts detected in rats and rabbits after 10 days exposure would need to be investigated further.

If there was pressure to derive some form of ADI, for example, in the event of an emergency, a rough value could be produced. In such instances, the uncertainties surrounding any value would need to be highlighted clearly in some accompanying text. Negative genotoxicity and developmental studies provided some reassurance

***Considerations for deriving a rough estimate for an ADI***

Effects were seen in dogs at 220 mg/kg/day after 7 days. In rats, maternal toxicity was noted at

150 mg/kg/day, indicating increased susceptibility in pregnant animals. A NOAEL of 133 mg/kg/day was reported in mice treated for 90 days and mice were reported to be more sensitive than rats or rabbits.

The mouse NOAEL of 133 mg/kg/day could be used, but its questionable relevance to humans would need to be noted. Applying an uncertainty factor of 100 ($10 \times 10$), together with an additional factor of 10 to take into account the incomplete database, and possibly a further factor of 10 for the irrelevance of the data currently available, the ADI would be ~0.01 mg/kg.

Investigation of the human case reports might provide some additional indications of acceptable or toxic exposure levels.

**Food contaminants: D2**

Although substance D2 was shown to be readily absorbed in all species, there were important species differences in toxicokinetics and toxicity. The critical acute effect appeared to be haemolytic anaemia, seen in dogs and humans but not in rodents. Among humans, the sensitive subpopulation was itself large enough to be of major concern. In repeat-dose studies, haemolytic anaemia was again seen in dogs, but not rodents. Mutagenicity and carcinogenicity studies were negative and it can probably be concluded that these are not a risk for humans, although there were no good human studies available. Reproductive toxicity is linked to maternal toxicity, which in humans is dependent on the haemolytic anaemia.

***Derivation of TDI***

The available data were considered insufficient to set a TDI, but the toxicity studies suggested cause for concern. An advisory committee would almost certainly wish to see a well conducted repeat-dose study and a reproductive study in dogs.

In the absence of this, and with information suggesting dietary exposure, risk management options would need to be considered in conjunction with appropriate stakeholders. It was considered likely that the advice would be for industry to reduce levels as low as reasonably practicable.

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# Risk Assessment and Toxicology Steering Committee publications

cr 1 Developing New Approaches to Assessing Risk to Human Health from Chemicals

cr 2 Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals

cr 3 Risk Assessment Strategies in Relation to Population Subgroups

cr 4 Physiologically-Based Pharmacokinetic Modelling: A Potential Tool for Use in Risk Assessment

cr 5 Exposure Assessment in the Evaluation of Risk to Human Health

cr 6 From Risk Assessment to Risk Management: Dealing with Uncertainty

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