Government/Research Councils Initiative on Risk Assessment and Toxicology

Risk assessment strategies in relation to population subgroups

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.

This document is a report of a workshop held in Leicester on 24–25 April 1997. Opinions and recommendations expressed are those of the participants. The Government/Research Councils Initiative on Risk Assessment and Toxicology's Steering Committee will consider the recommendations further 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 risk assessment strategies in relation to population subgroups. The aims of the workshop were to:

- examine the relevance of the scientific basis of current extrapolation procedures used in chemical risk assessment and the way in which they account for population variability;
- suggest how these procedures could be improved;
- consider whether special risk assessment provision should be made for certain population subgroups; and
- make recommendations regarding the research required in order to obtain better underlying information and to develop improved methods of risk assessment.

In order to promote examination of current values for uncertainty factors used in risk assessment, to see whether they are valid for the general population and whether they can be refined, the following recommendations were made.

- Further research is needed to increase knowledge on the response of specific subpopulations to toxicological insult, in order to determine whether, on the basis of scientific evidence, additional uncertainty factors may be needed to allow for the presence of such subgroups in a population.
- Further work should be undertaken on interindividual variations in toxicokinetic and toxicodynamic parameters, in particular on the inherent variability within the human population due to genetic factors affecting the metabolism of chemicals. In particular, *in vitro* screens should be developed further to determine the metabolic pathways for chemicals and their regulation in humans, in order to estimate the size of population subgroups that have a genetic deficiency in metabolism.
- Further information is needed on the interaction of nutritional status, nutrition and response to chemicals.
- Research is needed on variations in immune response and on the importance of immunotoxicological end-points, in order to increase understanding of immunologically mediated susceptibility and how this might be addressed in risk assessment.

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, the assessment is generally based on animal data. Such an approach has to accommodate the uncertainties inherent in extrapolating from animals to humans, from high to low dose and from one population to another. 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 a possible and to secure optimal use of resources.

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, *in vitro* toxicology, molecular modelling and computer simulations, may offer new possibilities. Furthermore, the use of such techniques should contribute to the reduction of animal use and 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 and is co-ordinated from the Medical Research Council's Institute for Environment and Health. The Initiative aims to stimulate research so that new, improved approaches to chemicals risk assessment 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, with the aim of bringing together regulatory toxicologists, policy-makers from government and experts from academic institutions and industry to develop research specifications.

The first such workshop was held in Leicester, UK in April 1997 to examine how effective current risk assessment practice is at protecting vulnerable groups within the population and provides the basis of this present report.

Basis for the workshop

Two sets of criteria for controlling risks, based on cost–benefit and on equity, have been defined (Interdepartmental Liaison Group on Risk Assessment, 1996).

In establishing *cost–benefit criteria*, the benefits (e.g. lives saved, life–years extended) that will result from a particular course of action for reducing risks are

determined and compared with the costs of achieving them. The approach to valuing such benefits is to try and establish how much the recipients of the risk are willing to pay to achieve a particular level of benefit.

Equity-based criteria arise from the premise that all individuals have the absolute right to a certain level of protection. In practice, a limit is fixed to represent the maximum level of risk to which any individual can be exposed. If the risk estimate derived from the risk assessment is above the limit, the risk is held to be intolerable whatever benefits may be associated with the exposure.

An earlier report on risk assessment (Royal Society Study Group, 1983) suggested a type of regulatory process and control strategy which has subsequently become known as the 'tolerability of risk'. The scheme was set out as:

- an upper limit of risk which should not be exceeded for any individual;
- further control, so far as is reasonably practicable, making allowance if possible for aversions to higher levels of risk or detriment; and
- a cut-off in the deployment of resources below some level of exposure or detriment judged to be trivial.

Frequently, the results of conventional toxicological studies are extrapolated to obtain an exposure level which represents a negligible or 'broadly acceptable' risk to health. This extrapolation is conducted using the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL), together with uncertainty factors*. This approach is based on the assumption that the incidence and the severity of toxic effects increase with increasing dose. For standards based exclusively on equity, this is sufficient to allow a standard to be set. However, when there is a benefit accruing from the use of a substance but the risk of ill health as a consequence of exposures during that use is not negligible, it may be necessary to strike a balance of risk against benefit when managing the risks. For genotoxic carcinogenicity and other toxic effects, where it is currently assumed that there is no threshold for the effect, a similar balance has to be struck. In this case the concept used in UK standard-setting, that exposures to genotoxic carcinogens should be reduced as far as is reasonably practicable, requires a balancing of the risk and the costs of the risk management procedures.

The use of uncertainty factors for extrapolation from a NOAEL or a LOAEL to an equity-based exposure standard has been the convention in most UK and European standard-setting for more than 20 years. Values for uncertainty factors were first described in the 1950s, at a time when risk assessment was largely deterministic. They were pragmatic values aimed at setting standards which prevent ill health occurring in virtually the entire population. (The current basis for the use of these factors is covered in Section 2.3 of this report.) At present, there is no rigorous scientific justification for these particular uncertainty factors and they are subjected to modification in the light of expert judgement.

In the absence of clear evidence to the contrary, it is often difficult to refute claims that, when risks have to be examined in conjunction with benefits, current standards are both conservative and inappropriate. It has been suggested that societal judgements concerning the acceptability of given levels of risk have implicitly affected the size of the uncertainty factors used. A recent report, *The Setting of Safety Standards* (HM Treasury, 1996) commented that:

> ...it is unsatisfactory for public (and other) prejudices to be smuggled into policy through apparently technical decision formulae, by means of, for example, numerical factors imposed subjectively by technical experts to reflect supposed ethical or societal concerns.

However, opposing claims maintain that the standards (often derived from studies on groups of healthy adult rodents) no longer adequately protect some groups within the population. One reason given is the better understanding nowadays of the factors resulting in human disease and of the variation in human susceptibility to disease induced by chemicals. Another concerns the greater use of animals specially bred to reduce interindividual variation in experimental data. These may be coupled with extremes of variability in exposure. Recent US legislation has proposed that risk assessments should be directed towards specific groups, for example, children, as well as the general public.

* Although the word 'safe' has been used in the context of risk assessment, its use has been avoided, as far as possible, in this document. Similarly, although the term 'safety factor' is commonly used, the term 'uncertainty factor' has been used in this document to avoid any possible misunderstanding.

Aims of the workshop

A better understanding of the extrapolations made in chemical risk assessment, their effectiveness in establishing realistic standards and their relevance to specific subgroups in the population is needed in order to refine current practice and also to develop strategies for improving risk assessment for standard-setting. Some groups may be at risk throughout life because of genetic or immunological factors. Others may be vulnerable only at certain times in life, such as during pregnancy, in childhood or when elderly. It is important to determine whether special risk assessments need to be carried out for any or all of these groups or whether a single method of risk assessment can be derived that will provide protection for all of them. The workshop therefore had four main aims:

- to examine the relevance and scientific basis of current extrapolation procedures and the ways in which they account for population variability;
- to suggest how these procedures could be improved;
- to consider whether special risk assessment provision should be made for certain population subgroups; and
- to make recommendations regarding the research required in order to obtain better underlying information and to develop improved methods of risk assessment.

Workshop report

Papers presented at the workshop to provide a background for the ensuing discussions are reproduced in Sections 2 and 3 of the report. Section 4 sets out the conclusions and recommendations arising from the workshop. The participants in the workshop are listed at the end of the report.

References

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

HM Treasury (1996) *The Setting of Safety Standards*, London, UK, HM Treasury

Interdepartmental Liaison Group on Risk Assessment (1996) *Use of Risk Assessment within Government Departments*, Sudbury, UK, HSE Books

Royal Society Study Group (1983) *Risk Assessment*, London, UK, Royal Society

2 Current extrapolation procedures and population variability

2.1 Current dietary exposure assessment methodology

N Rees

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The intake of a chemical present in food (dietary exposure) is estimated by combining chemical (residue) data, which provide information on the occurrence and concentration of contaminants of interest in foods, with consumption data, which provide information on the quantity of each food consumed by an individual consumer or by the total population. Several methods for doing this have been developed in the UK. The method selected will depend on the information that is available and the level of accuracy and detail required. More detailed analyses will obviously be more time-consuming and costly. A hierarchical approach is used (Rees & Tennant, 1993) and this usually means a stepwise progression from relatively simple, crude methods to the very sophisticated.

It is also important to consider the nature of the hazard, that is whether the chemical in question has an acute toxic effect or produces a toxicological reaction with long-term exposure. Dietary exposure is usually assessed against safety limits which have been established on the basis of toxicological tests of the chemical in question in animals and which include uncertainty factors to compensate for the extrapolation of the results to humans. These limits are expressed on a body-weight basis.

As exposure assessment methodology has developed, more emphasis has been placed on protecting 'critical' or 'non-average' groups of individuals. These groups may be more susceptible to the specific toxic effects of a food chemical, or may consume greater quantities, or regularly consume foods with higher concentrations of the food chemical than the general population. The most accurate estimates of exposure require reliable food consumption data obtained through dietary food surveys of individual consumers or targeted food consumption surveys of subgroups of the population such as infants, pre-school children, schoolchildren, diabetics and vegetarians.

In the UK a number of different dietary surveys have been used to assess the food consumption patterns of the population subgroups of concern. The Dietary and Nutritional Survey of British Adults (Gregory *et al.*, 1990) provides individual food consumption data and is usually considered first. A representative sample of British adults aged between 16 and 65 years took part in the survey which was conducted throughout the year to take account of seasonal variation. Information on all the food and drink consumed by each individual over 7 days was collected and recorded using a 'weighed diary' method. The consumption data derived from this study are used in the UK to estimate the dietary intakes of food chemicals by the 'average' and the 'high-level' (defined as the 97.5^{th} percentile) consumer.

It is possible to have localised pockets of contaminated food, so that consumers living in a particular area may be at risk of higher intakes than average. Similarly a chemical may accumulate in only a few foods — for example, mercury tends to accumulate in fish — and regular consumers of those foods may have higher intakes. Special care is taken identify possible 'critical' groups and, where possible, intake assessments are focused on them.

It has also been recognised that young children have higher nutritional requirements, on a body-weight basis, than adults and may be a subgroup of concern in relation to exposure. Children can have

energy, protein and liquid requirements up to 3, 2.5 and 5 times higher than adults respectively. Their pattern of consumption is different and young children can eat individual foods, particularly dairy products, soft drinks and some fruit and vegetables, in quantities up to 16 times higher than adults, when expressed on a body-weight basis. The Dietary and Nutritional Survey of children aged 1½ and 4½ years (Gregory *et al.*, 1995) can be used in the same way as the adult survey mentioned above to estimate exposure in this age group.

Intakes by young children of additives and contaminants are usually considered on a case-by-case basis. For example, the sweetener saccharin and the environmental contaminant dioxin were considered in two recent risk assessments (Lawrie, 1998). In each case the intakes by young children were found to be higher than the rest of the population, but a different risk management option was selected for each compound. High intakes of dioxin were found in breast fed infants. The considerable benefits associated with breast feeding and the relatively short period of exposure were weighed against the knowledge that dioxin has a long elimination half-life and no action was considered necessary to reduce the intake from this source. Higher saccharin intakes were found in pre-school children than the general population with the largest contributor being dilutable squashes. The saccharin levels exceeded the acceptable daily intake but did not substantially erode the inherent uncertainty factors. In this case action was taken by advising consumers, through voluntary labelling and leaflets, to add extra water to squashes (Lawrie, 1998).

Intakes by young children of pesticide residues are assessed regularly. Additional information about how this is done can be found in the Pesticide Safety Directorate's *Registration Handbook* (Health and Safety Executive/Pesticides Safety Directorate, 1998)*.

A number of general principles have been identified which aim to promote a more systematic approach to assessing the exposure of population subgroups and these are listed below:

- foods that are more highly consumed by different subpopulations should be determined;
- these foods should be adequately represented in surveillance activities; and
- a greater knowledge about the adverse health effects associated with the toxicity of chemicals should be sought.

* This can also be downloaded from http://www.maff.gov.uk/aboutmaf/agency/psd/software.htm

References

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Gregory J, Collins D, Davies P, Hughes J & Clarke P (1995) *National Diet and Nutrition Survey: Children Aged 1½ and 4½ Years*, London, UK, HMSO

Health and Safety Executive/Pesticides Safety Directorate (1998) *The Registration Handbook* (Part 3/A3/Appendix 1c), available from Information Office, Pesticide Safety Directorate, Mallard House, King's Pool, 3 Peasholme Green, York YO1 7PX

Lawrie CA (1998) Different dietary patterns in relation to age and the consequences for intake of food chemicals. *Food Addit Contam, 15 (suppl)*, 75–81

Rees NMA & Tennant DR (1993) Estimating consumer intakes of food chemical contaminants. In: Watson DR, ed, *Safety of Chemicals in Food*, Chichester, UK, Ellis Horwood, pp 157–181

2.2 Environmental applications

Based on the presentation by P Hinchcliffe

Department of the Environment, Transport and the Regions, London, UK

In assessing the risk to human health from environmental pollutants, decisions must be made on a case by case basis using the best available scientific evidence. The overall aim is to protect the most sensitive individuals in the population. Data are already available on the effects of some environmental pollutants in sensitive population subgroups. In the absence of data, risk assessment should be based on the 'precautionary principle' which states:

> Where there are significant risks of damage to the environment the Government will be prepared to take precautionary action to limit the use of potentially dangerous pollutants, even where the scientific knowledge is not conclusive, if the likely balance of costs and benefits justifies it.

The Department of the Environment provides a guide giving advice on how to conduct risk assessments for environmental protection (Department of the Environment, 1995), which is currently in the process of review.

2.2.1 Pollutants in air

Generally, the approaches used in assessing risks to human health are based on the use of uncertainty factors. There are a number of examples where these uncertainty factors have been adjusted to allow for particularly sensitive subgroups within the population. These are given in Table 2.2.1.

2.2.2 Contaminated land

The contaminated land exposure assessment model (CLEA) has been developed to calculate a range of exposures, expressed as average daily intakes for pollutants present in contaminated land, together with an assessment of the probability of occurrence of these intakes. The model takes into account exposure route (ingestion, skin contact, inhalation), the type of site (listed in Table 2.2.2) and the ages of exposed individuals. Exposure is calculated for individual years of life for the first 15 years, and then as an adult group (those aged between 16 and 59) and an elderly group (those aged 60–70). It also allows for certain factors (summarised in Table 2.2.2) that may affect uptake. An allowance for background exposure is included in the model.

The mean daily intake (MDI) from food, water and air and the tolerable daily intake (TDI) are obtained from published literature. By subtracting the MDI from the TDI an 'intake assignable to other sources' can be derived, which can be compared with the estimate of the average daily intake and the range of intakes obtained from the CLEA model. A 'contaminated land guidance value' is thus obtained.

One difficulty with the model is that it is unable to allow for differential uptake for different pollutants.

2.2.3 Pollutants in water

Some examples of the approaches used and the data available for estimating total intake of pollutants from water are given in Table 2.2.3. Different key groups were identified for the four chemicals presented in the table, and different assumptions were made about the contribution of water consumption to the total intake of each chemical.

Table 2.2.1 Examples of population subgroup sensitivity to pollutants in air

Pollutant	Effect	Population subgroup	Additional uncertainty factor*
Ozone (50 ppb, 8 hours)	Airway inflammation and impairment of ventilatory capacity	Particularly sensitive individuals (10% of the population)	–
Sulphur dioxide (100 ppb, 15 minutes)	Irritation and possibly narrowing of the airways	Severe asthmatics	2
Carbon monoxide (10 ppm, 8 hours)	Changes in electro-cardiogram on exercise	People with angina and coronary heart disease	~1.4
Nitrogen dioxide (150 ppb, 1 hour)	Changes in responsiveness of the lung	Asthmatics and those with chronic lung disease	1.3

* Over that conventionally employed for a general population

Table 2.2.2 Information used in Contaminated Land Exposure Assessment (CLEA)

Characterisation of site	Receptor characteristics
Residential with garden	Body height
Residential without garden	Body weight
Allotments	Active respiration rate
Parks, playing fields, open spaces	Passive respiration rate
Commercial/industrial	Exposed skin area
	Vegetable consumption rate
	Fraction of vegetables homegrown
	Ingestion rate of contaminated soil

Table 2.2.3 Examples of the data available on the contribution of pollutants in water to total intake

Contaminant	Susceptible group	Contribution to total intake
Lead	Infants, children, pregnant women	50% of PTWI in bottle-fed babies
Cyanide	All	20% of TDI
Cadmium	All	10% of PTWI
Nitrate	Bottle-fed babies	High

PTWI, provisional tolerable weekly intake; TDI, tolerable daily intake

For lead in water, infants, children and pregnant women have been identified as population subgroups known to be 'at special risk'. The Joint Expert Committee on Food Additives (JECFA) has established a provisional tolerable weekly intake (PTWI) of 25 µg/kg body weight for infants and children (based on 3.5 µg/kg body weight/day). The guideline for drinking water of 10 µg/l is based on the assumption of a 50% allocation to drinking water for a 5 kg baby consuming 0.75 litres of water per day.

Although there is some evidence for an association between dietary nitrate and cancer, the evidence does not provide a basis for a guideline. The guideline is based on another biological effect, methaemoglobinaemia, caused by the nitrite formed as a consequence of gut microfloral metabolism. These bacteria are particularly abundant in babies as a consequence of the higher pH in their gastrointestinal tract. Bottle fed babies aged up to 3 months have a high intake of drinking water per kilogram of body weight and are therefore considered the most susceptible group. The guideline of 50 mg/l (as nitrate) in drinking water is based on epidemiological evidence on methaemoglobin formation.

2.2.4 Conclusion

This paper illustrates that current practice in the Department of the Environment, Transport and the Regions includes a consideration of potential subgroups of the population at special risk and exemplifies some of the approaches that are currently being used to address this issue.

Reference

Department of the Environment (1995) *A Guide to Risk Assessment and Risk Management for Environmental Protection*, London, UK, HMSO

2.3 Human variability and risk assessment/safety assurance

AG Renwick

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Risk assessment and safety assurance (the determination of intakes or exposures associated with negligible risk, such as the acceptable daily intake (ADI) or TDI) are usually based on the NOAEL for the critical effect in animals divided by a safety or uncertainty factor, which is usually 100. The 100-fold factor comprises two 10-fold factors: one to take into account the extrapolation from animals to humans (interspecies); the other to account for human variability (intraspecies). Since animal studies frequently involve small groups (typically $n = 50$) of inbred homogeneous rats, the NOAEL defines the dose without effect in the 'average rat'. In consequence, the interspecies factor of 10 has to allow for interindividual variability in the test animals. Each of the 10-fold factors also has to allow for differences in both toxicokinetics and toxicodynamics (Renwick, 1991). Subdivision of the 10-fold factor into two parts would permit the use of specific compound-related data rather than a universal default uncertainty factor. Such a subdivision should be made whenever relevant toxicokinetic or toxicodynamic data are available. If the toxicokinetic and toxicodynamic characteristics are known in humans, then the risk assessment should be based on the human not the animal data. If the variability of toxicokinetic and toxicodynamic data in humans is known then the risk assessment could be based on sensitive humans without the use of an uncertainty factor.

A similar degree of interindividual variability was found for both kinetics and dynamics (mostly of therapeutic drugs), in an initial review of human and animal data (Renwick, 1993). However, it was suggested that there would be more variability in kinetics than dynamics when factors such as age and disease are taken into account, because changes in liver and kidney function would affect most chemicals, whereas, dynamic changes would be specific to the mechanism of toxicity affected (Renwick, 1993). A review by an International Programme on Chemical Safety Working Group (WHO, 1994) did not accept this view and proposed an even split of the 10-fold (10^1) factor for human variability into two 3.16-fold factors ($10^{0.5}$).

In practice, there have been very few cases where it has been possible to replace a default uncertainty factor by compound-related data because basic toxicity testing rarely provides adequate human data. However, the subdivision of the 10-fold factor provides a useful tool for exploring the adequacy of this factor. For example, in a recent International Life Sciences Institute-Europe workshop on average daily intake and children, it was recognised that the higher clearance in children would compensate (at least in part) for greater sensitivity of developing organ systems (Renwick, 1998). The kinetic differences between children and adults have been well defined, but the meeting failed to quantify differences in target organ sensitivity.

In the context of risk assessment and safety assurance, most NOAELS are based on chronic studies in animals and, rarely, in humans. The critical toxicokinetic parameters are bioavailability and clearance, since these will determine the steady-state plasma concentrations and steady-state body load. Values for these parameters in animals given the NOAEL and humans given the potential daily intake are of particular importance. The critical toxicodynamic estimates relate to the target organ sensitivity to the presence of the chemical in the circulation. These can be estimated by pharmacokinetic–pharmaodynamic modelling of response or using *in vitro* data.

For data showing a normal distribution it is impossible for a uncertainty factor of 3.16, 10 or any number less than infinity to cover every single individual in a population. Regulators and politicians should therefore recognise that the usual safety assurance procedures to derive estimates such as the ADI or TDI (defined as an intake without appreciable health risk - WHO, 1987, 1994) do not provide a guarantee of complete protection for all individuals. The database used by Renwick (1993) has recently been enhanced considerably and the variability in kinetics and dynamics compared. Data on the split between kinetics and dynamics support an equal split of the normal 10-fold factor into 3.16×3.16 for kinetics and dynamics. The expanded database has been analysed (using the Z-score) to determine the proportion of the population not covered by a factor of 3.16 (above the mean), allowing that the factor of 3.16 has to allow for only those subjects more at high 'risk' than the average and not the 50% of the population at lower risk than the average. The analyses (Renwick & Lazarus, 1998) indicate that the composite 10-fold factor (3.16×3.16) is adequate except for subgroups which show major differences in kinetics or dynamics compared with the population mean (e.g. polymorphic oxidation reactions).

References

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WHO (1994) *Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits* (International Programme on Chemical Safety, Environmental Health Criteria, 170), Geneva, Switzerland, World Health Organization

2.4 Interindividual variability in xenobiotic metabolism and the consequences for response

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The activity of the enzymes responsible for the detoxification and activation of drugs and other foreign compounds in humans shows wide interindividual variation. The idea that differences between individuals in the way that they respond to drugs could be inherited was put forward almost exactly 40 years ago, and several traits controlled by a single gene and associated with a defective ability to metabolise drugs have since been identified (Daly, 1995). The genetic polymorphisms of drug metabolising enzymes that have received particular clinical attention are those related to the carbon oxidation of drugs by cytochrome P450 (CYP) 2D6 and CYP2C19, acetylation by *N*-acetyltransferase, *S*-methylation by thiopurine methyltransferase and ester hydrolysis by pseudocholinesterase. The pharmacokinetic, pharmacodynamic and clinical consequences of polymorphic drug metabolism are best exemplified by the genetic polymorphism of CYP2D6 (Lennard, 1993; Tucker, 1994). Individuals who are homozygous for an autosomal recessive trait affecting the CYP2D6 gene are termed poor metabolisers. They constitute 7–10% of Caucasians, but there are considerable differences in the prevalence of the poor metaboliser phenotype between ethnic groups. The remainder of the population are designated as extensive metabolisers. Activity of CYP2D6 in extensive metabolisers also shows wide interindividual variability and a subgroup of genetically 'ultra-rapid' metabolisers has been identified; these individuals have among the highest CYP2D6 activities in the population.

Routine methods have been developed for phenotyping and genotyping populations with respect not only to CYP2D6 but also to other polymorphic enzymes (Gonzalez & Idle, 1994). CYP2D6 phenotyping tests, using probe drugs such as debrisoquine, are accurate predictors of the plasma concentration of a number of CYP2D6 substrates, for example, desipramine.

To a varying extent, CYP2D6 polymorphism controls the metabolism of a growing list of drugs, many of which are in widespread clinical use, and include anti-depressants, anti-psychotics, anti-hypertensives and anti-anginal agents as well as several beta-blocking drugs. Controlled studies have revealed large phenotypic differences in the pharmacokinetics and pharmacodynamics of many of these drugs. For example, for a given dose of the beta-blocking drug metoprolol, poor metabolisers develop plasma drug concentrations that are six times higher than those of extensive metabolisers, and this is associated with a more intense and prolonged pharmacological effect in the former group (Lennard, 1993). The metabolites of metoprolol are inactive pharmacologically but other drugs metabolised by CYP2D6 produce active metabolites for example propafenone. In these cases the pharmacodynamic consequences of the polymorphism are less clear. There are also examples of drugs that are converted by CYP2D6 to a quantitatively minor but much more active metabolite, for example codeine. Finally, the two phenotypes might suffer differential toxicity from some drugs, for example, methylenedioxymethamphetamine ('ecstasy').

For many of the drugs whose metabolism is affected in this way, the clinical consequences of phenotypic differences in pharmacokinetic and pharmacodynamic characteristics have not been rigorously evaluated. In most cases the available evidence for toxicity in poor metabolisers is based on unsubstantiated reports in small numbers of healthy volunteers or patients. However, a very clear example of how polymorphic CYP2D6 metabolism determines individual risk of adverse effects is shown with the anti-anginal drug perhexilene (Tucker, 1994). Patients who experience perhexilene-induced peripheral neuropathy achieve higher blood concentrations of the drug than those not suffering this adverse effect. It was reported that 50% of patients developing peripheral neuropathy while taking perhexilene were poor metabolisers and subsequently it was shown that they had a 24-hour plasma perhexilene concentration that was on average six times higher than that of extensive metabolisers.

Drug interactions mediated by inhibition of CYP2D6 activity have important pharmacokinetic consequences and may be of clinical significance (Lennard, 1993). For example, extensive metabolisers are at particular risk of toxicity when taking a selective serotonin-reuptake inhibitor in combination with a tricyclic antidepressant. Fluoxetine and other selective serotonin-reuptake inhibitors are potent inhibitors of CYP2D6 and their use has been associated with a number of reports of large increases in the plasma concentration of tricyclic anti-depressants and severe cardiotoxicity. Such interaction could have

been predicted and thus avoided with prior knowledge of the CYP isoforms involved.

In view of the perceived role of cytochrome P450 in the aetiology of chemically-induced disease, the possible relationships between CYP2D6 phenotype or genotype as well as those of other polymorphic enzymes and disease susceptibility have been studied in a variety of conditions. Most effort has centred on lung cancer and Parkinson's disease, but results have been conflicting. Some studies have shown a small decreased risk of developing lung cancer in poor metabolisers compared with extensive metabolisers but other studies have not confirmed this. Similarly, the data are confusing as to whether poor metabolisers are more susceptible than extensive metabolisers to developing Parkinson's disease. A recent meta-analysis of the published literature has shown that poor metabolisers have a small but significantly reduced risk of developing lung cancer (Rostami-Hodjegan *et al.*, 1998). For Parkinson's disease they had a small increased susceptibility which was of borderline significance. The authors discuss the difficulties and merit of investigating the contribution of a single factor to multifunctional diseases.

There are few examples suggesting the influence of genetic factors on the disposal of environmental chemicals or food constituents/additives and the consequences for toxicity. Population and family studies performed 30 years ago led to the idea that the ability to excrete beetroot pigments is under the control of a single gene and that this phenomenon called beeturia is inherited as an autosomal recessive trait. Recent studies confirmed the wide interindividual variation in the urine excretion of beetroot pigments but did not provide evidence that this process is under polymorphic control (Watts *et al.*, 1993). Several studies have indicated that about 40% of the population produce malodorous urine after eating asparagus, a trait that was suggested to be inherited in an autosomal recessive fashion. There are also anecdotal reports of the passing of bright yellow urine after eating piccalilli and other foods containing turmeric, of which the yellow pigment curcumin is a constituent. Although none of these phenomena have toxicological significance, the findings indicate that genetic studies of the disposal and potential toxicity of other food constituents are merited.

Examples are emerging of the ability of food constituents to inhibit, potently the activity of some cytochrome P450 enzymes. Thus, interactions resulting in toxicity have been reported among patients taking grapefruit juice in combination with drugs such as nifedipine (used for lowering blood pressure), cyclosporine (used to prevent rejection of transplanted organs) and terfenadine (an antihistamine that can cause abnormal heart rhythms; Ameer & Weintraub, 1997). These interactions arise through the inhibition of CYP3A4-mediated metabolism; a recent study has shown that a constituent of red wine (but not white wine) has a similar effect (Chan *et al.*, 1998). Further work is needed to determine how widespread interactions between foods and drug metabolising enzymes might be.

In conclusion, genetically variable metabolism is an important source of interindividual differences in drug response, and genetic polymorphisms of drug-metabolising enzymes can have important clinical consequences. However, in many instances there is a need for controlled prospective studies to determine clinical significance. Accordingly, routine phenotyping and genotyping, to identify poor metabolisers who may be at risk of toxicity, before beginning drug treatment cannot be justified at present. It is likely that environmental chemicals and food constituents are also subject to metabolism by polymorphic enzymes. However, estimates of risk in genetically vulnerable groups will only be possible once any suspected toxic effects of specific compounds have been properly characterised and the relevant data on their metabolism are available. Human liver *in-vitro* screens for characterising metabolism are readily accessible (e.g. Parkinson, 1996) and should prove useful in chemical risk assessment.

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2.5 Differences between males and females and the consequences for risk assessment and regulation

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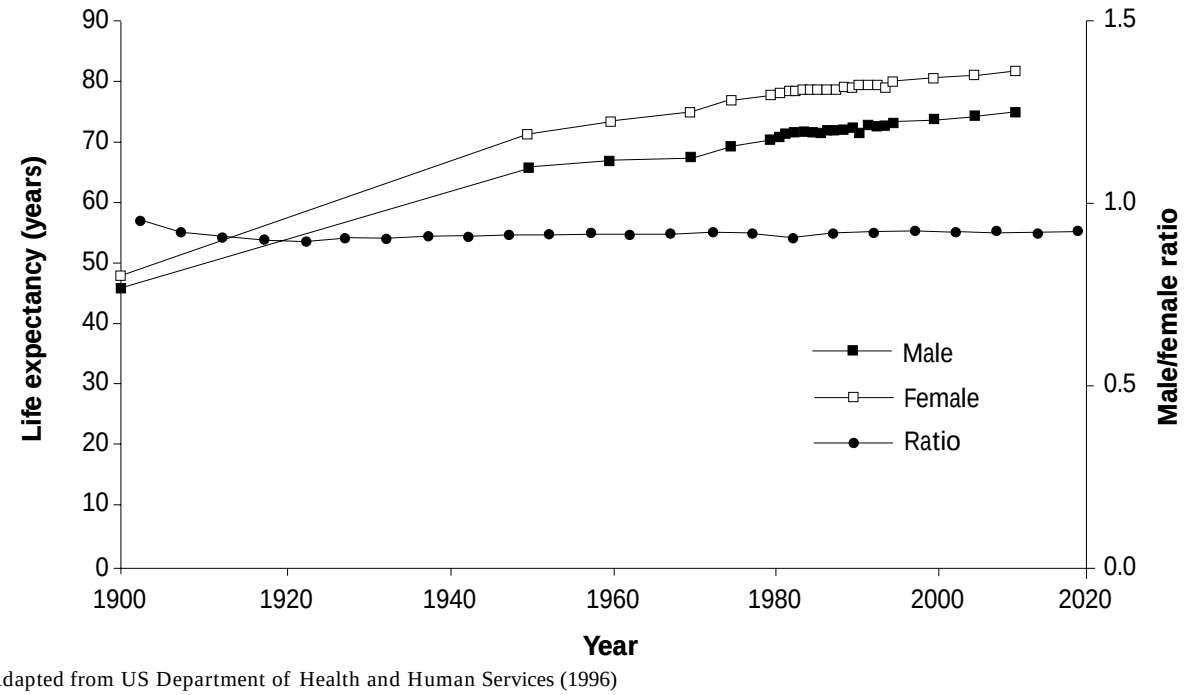
2.5.1 Introduction

While there are many differences between men and women (pregnant and non-pregnant), some of which are based on individual variations in body size and composition (Hattis, 1996a,b; Hattis & Minkowitz, 1996; Renwick & Hattis, 1996), and some of which are true differences between the sexes (Calabrese, 1986), it is not clear how these differences should influence occupational or environmental health regulations (Stellman, 1998). It is clear in developed countries that men and women have substantial differences in longevity and life-expectancy at birth, with men dying younger than women, although of similar causes (Figure 2.5.1; US Department of Health and Human Services, 1996). Despite these differences, evaluations of differential exposures or responses to those exposures are seldom carried out. For example, the US National Cancer Institute (Pottern *et al.*, 1994) recently evaluated the data available from occupational health studies to determine the impact on women. The authors found that women were often excluded from occupational studies; where they were included, their data were often not analysed or were analysed using less robust analytical methods – suggesting a bias towards men in the design of important occupational health studies. A similar bias has been observed in the design of clinical trials (Institute of Medicine, Committee on the Ethical and Legal Issues relating to the Inclusion of Women in Clinical Studies, 1994). Analysis of toxicological data suggests that there are more than 200 toxicants for which important differences between males and females in the expression of toxicity have been observed in experimental animals (Calabrese, 1985). Studies that permit analysis of the effects on men and women have also shown significant differences. For example, women appear more likely than men to develop lung and oral cancers as a consequence of smoking, whether cumulative tar or pack–years is used as a measure of dose (Figure 2.5.2; based on data from Muscat *et al*, 1996). Such differences are also of consequence for some psychoactive drugs (Yonkers *et al.*, 1992, 1993; Yonkers & Hamilton,1995).

2.5.2 Exposure factors

Men and women differ in many lifestyle factors, including dietary patterns and how they spend their time (American Industrial Health Foundation, 1994; EPA, 1996). For some of these factors, for

Figure 2.5.1 Life expectancy at birth in the USA



Adapted from US Department of Health and Human Services (1996)

example dietary intake, it appears that the mean or higher characteristic for consumption (such as the 97th percentile) will be adequate for the majority of women in the population (Figures 2.5.3 and 2.5.4; based on data from American Industrial Health Foundation, 1994 and EPA, 1996). It is important to note, however, that this may not apply to children (National Research Council, 1993) or minority subgroups whose dietary pattern can be very different from that of the majority of adults in the population (see Section 2.1).

2.5.3 Toxicokinetic factors

In considering differences between the sexes it is important to take into account body composition and other physiological parameters. By influencing the absorption, distribution, metabolism and elimination of xenobiotics, these parameters may have a profound influence on toxicity (Silvaggio & Mattison, 1994).

Figure 2.5.2 Adjusted odds ratio for smoking and cancer

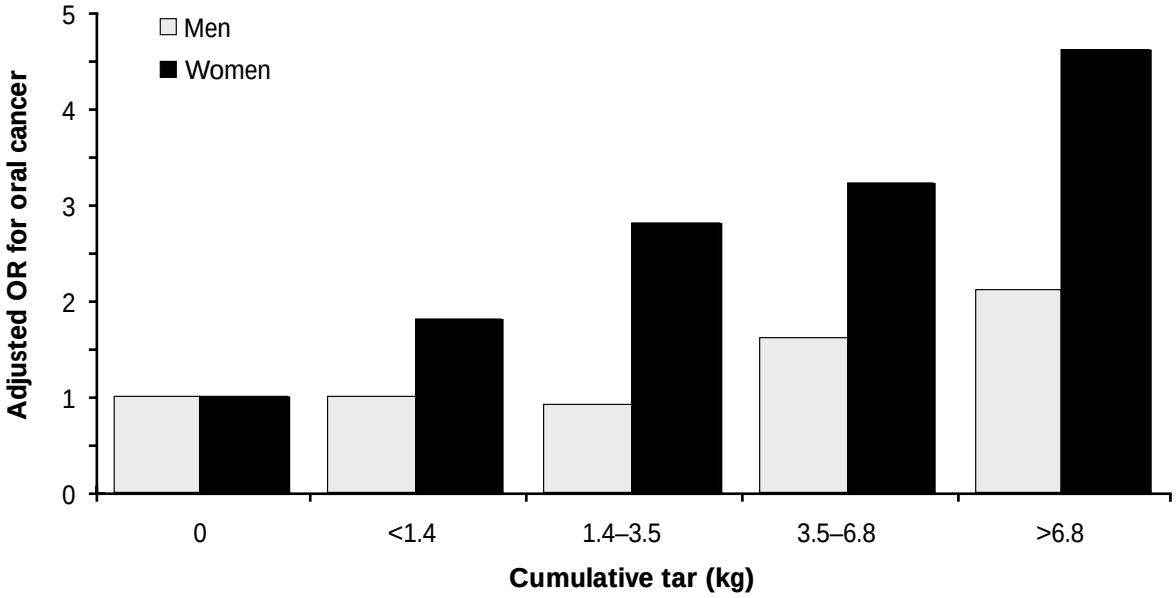


Figure 2.5.3 Total liquid intake in adults aged 18–55 years

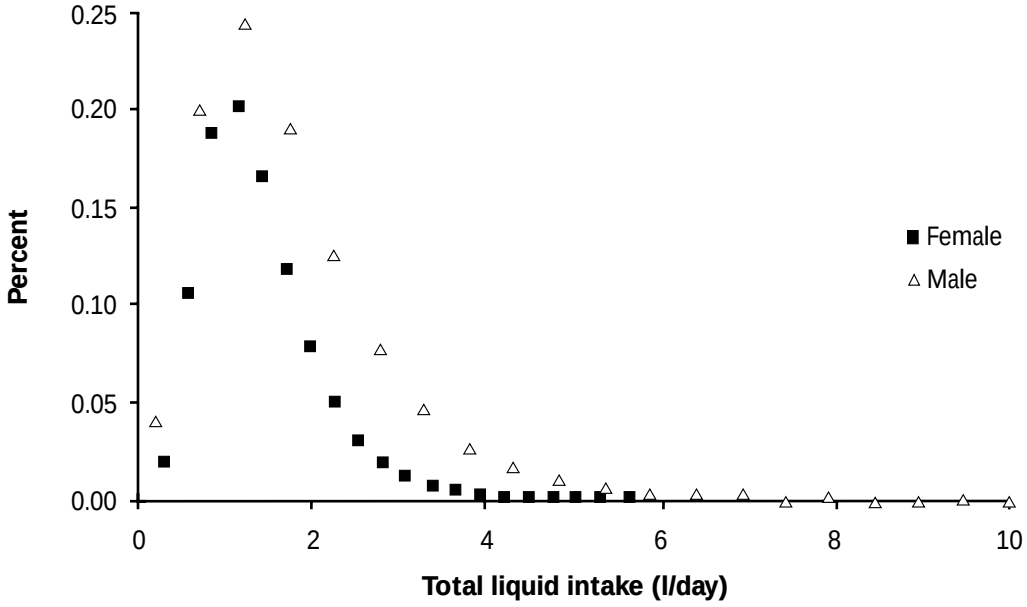
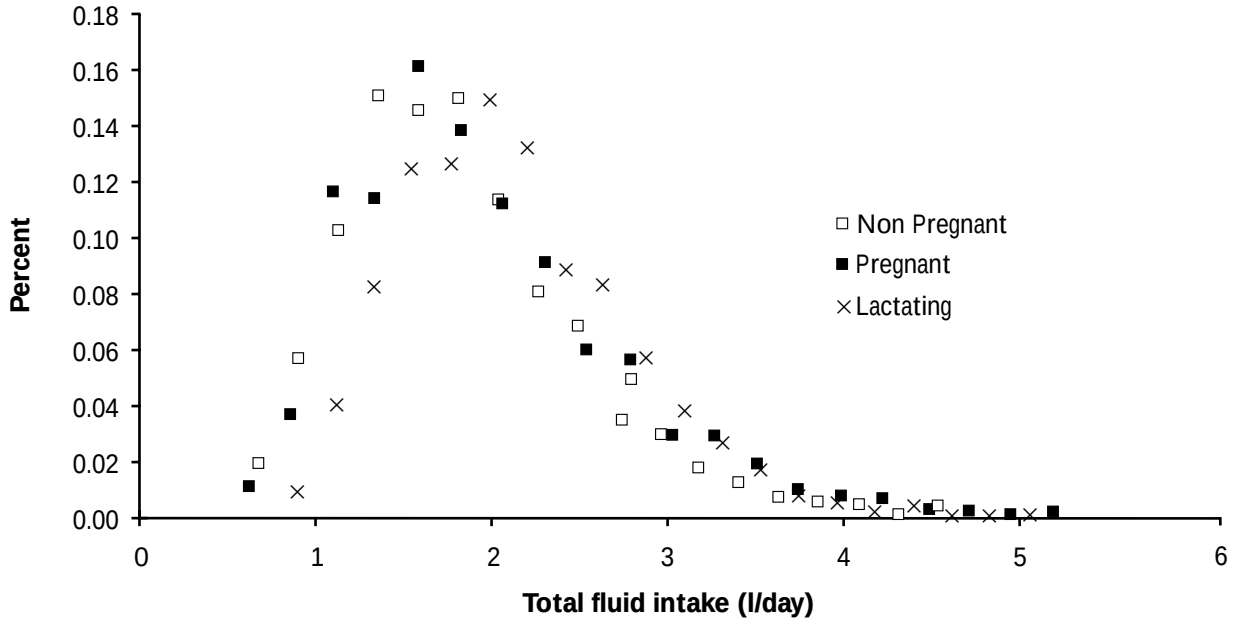


Figure 2.5.4 Total fluid intake of women aged 15–49 years



Absorption of xenobiotics may occur from the gastrointestinal tract, through the skin or from the respiratory tract. Factors influencing absorption are summarised in Table 2.5.1.

Distribution is the process by which a xenobiotic is translocated from the site of absorption or metabolism to tissues and organs throughout the body. The rate of distribution is determined by a range of factors including cardiac output and regional blood flows, rate of entry into organs and cells and affinity of the chemical for different tissues. Some of these factors are summarised in Table 2.5.2.

Metabolism is a major factor in determining response to chemicals. While it occurs predominantly in the liver, other sites may also be involved, including the lung, kidney, intestinal tract, skin and gonads, as well as the placenta and fetal tissues. Metabolism is very dependant on the substrate and the metabolic pathways available. However, some general comments can be made concerning factors that influence the rate of metabolism. These are summarised in Table 2.5.3. Most xenobiotics are eliminated from the body by renal, hepatic or pulmonary routes. For some lipid-soluble, poorly-metabolised compounds, the major route of elimination may be via breast milk (Yonkers *et al.*, 1992, 1993; Yonkers & Hamilton,1995). Some of the factors that may influence elimination are listed in Table 2.5.4.

The data suggest that men and women do differ significantly in exposures and in their responses to those exposures and that this should be considered explicitly in regulation procedures. In some instances the variations may be explained by differences between the sexes in body size or composition. In others, however, it may be necessary to look to other factors, such as hormonal regulation of specific genes, in order to understand them.

Table 2.5.1 Factors influencing the absorption of chemicals

Parameter	Physiological difference	Toxicokinetic impact
Gastric juice pH	M < F < pregnant F	Absorption of acids/bases modified by change in pH
Gastric juice flow	M > F > pregnant F	Absorption modified by decreasing flow
Intestinal motility	M > F > pregnant F	Absorption increases with decreasing motility
Gastric emptying	M > F > pregnant F	Absorption and gastric metabolism increase with decreasing gastric emptying
Dermal hydration	Pregnant F > M, F	Altered absorption in pregnant F
Dermal thickness	M > F	Absorption decreases with increasing dermal thickness
Body surface area	M > pregnant F > F	Absorption increases with increasing body surface area
Skin blood flow	Pregnant F > M, F	Absorption increases with increasing skin blood flow
Pulmonary function	M > pregnant F > F	Pulmonary exposure increases with increasing minute volume
Cardiac output	M > pregnant F >F	Absorption increases with increasing cardiac output

F, female; M, male

Table 2.5.2 Factors influencing the distribution of chemicals in the body

Parameter	Physiological difference	Toxicokinetic impact
Plasma volume	Pregnant F > M > F	Concentration decreases with increasing volume
Total body water	M > pregnant F > F	Concentration decreases with increasing body water
Plasma proteins	M, F > pregnant F	Concentration fluctuates with changes in plasma proteins and protein binding
Body fat	Pregnant F > F > M	Body burden of lipid-soluble chemicals increases with increasing body fat
Cardiac output	M > pregnant F >F	Distribution rate increases with increasing cardiac output

F, female; M, male

Table 2.5.3 Factors influencing the rate of metabolism of chemicals

Parameter	Physiological difference	Toxicokinetic impact
Hepatic metabolism	Higher BMR in M, fluctuating hepatic metabolism in pregnant F	Metabolism generally increases with BMR
Extra-hepatic metabolism	Metabolism by fetus/placenta	Metabolism fluctuates
Plasma proteins	Decreased in pregnant F	Elimination fluctuates with changes in plasma proteins and protein binding

BMR, basal metabolic rate; F, female; M, male

Table 2.5.4 Factors influencing the elimination of chemicals from the body

Parameter	Physiological difference	Toxicokinetic impact
Renal blood flow, GFR	Pregnant F > M > F	Renal elimination increases with increasing GFR
Pulmonary function	M > pregnant F > F	Pulmonary elimination increases with increasing minute volume
Plasma proteins	Decreased in pregnant F	Elimination fluctuates with changes in plasma proteins and protein binding

GFR, glomerular filtration rate; F, female; M, male

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* available from National Technical Information Service, US Department of Commerce, 5285 Port Royal Road, Springfield VA 22161, USA and http://www.epa.gov/ncea.exposfac.htm

3 Susceptible groups

3.1 The young child

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In numerous reports of toxicity, children are the most affected group, which suggests that they are particularly vulnerable.

The harmful effect of a given dose of toxin depends on a variety of factors, among them, the size of the host, the maturity of the tissues and, hence, homeostatic capacity, and the rate of cell hyperplasia, hypertrophy and maturation. Newborn infants, especially preterm infants, are small hosts, their organs of absorption and excretion are immature and they have an inherent need to gain tissue and maturity more rapidly than at any other time in their lives. This is likely to make them particularly vulnerable to their 'new' environment. At this time, even essential nutrients become toxic when they are present in excessive quantities.

Infants and young children are also vulnerable because they have little or no control over what they consume or inhale and, in any case, they commence life ignorant of danger. In contrast, many of today's older children have control and knowledge but choose to take risks, for example, as drug-users.

The risks of toxicity vary widely in different cultures and between the developed and developing world. Most of today's children live in poverty in the developing world and consequently are at much higher risk than their counterparts in the UK. However, nowadays there is much greater international movement of people, foods, and hazardous substances. Ignorance about 'new' foods from different cultures and their methods of safe preparation and use leads to increased risk of toxicity.

Congenital problems such as inherited errors of metabolism are usually diagnosed in early childhood. When untreated, they present as toxicities in which specific 'normal' nutrients and metabolites cannot be disposed of safely and, instead, act as toxins. Atopic children are another special group in which 'normal' environmental proteins become allergens, causing, at worst, anaphylaxis and death. Atopic disease has increased dramatically in the last 30 years. The cause is unknown but it seems that lack of knowledge about this major problem typifies a general ignorance about the environment and particularly, of today's 'new' hazards.

Children *are* clearly a special group and research is needed to identify current environmental hazards as well as to assess the relative risks in this group.

3.2 Immune factors and variability in toxic response

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3.2.1 Introduction

It has been estimated that the human population could be exposed to about 100 000 chemical entities. Many of those compounds have the potential to cause toxicity, although to date only a few have been documented to do so, largely because of lack of adequate surveillance procedures. However, even when there is documentation of potential toxicity in humans, the data are usually incomplete and often fragmented.

A substantial proportion of chemical-induced toxicities in the human population may be mediated through the immune system although the exact frequency is unknown. In general, a chemical can have three types of immunological effect (Vandebriel *et al.*, 1996):

- immunosuppression leading to decreased resistance to infections or to the development of tumours;
- autoimmunity where an immune reaction to 'self' components is induced by the chemical; and
- hypersensitivity, where the chemical acts as a sensitiser and induces an immune response, thereby causing tissue injury.

Immunotoxicity assessments in various animal species (rat, guinea-pig or mouse) may be able to detect the immunosuppressive properties of a chemical, but rarely give an indication as to whether the chemical is a potential allergen or will induce autoimmunity. An inherent problem is the difficulty in extrapolating data from experimental animals to the human population in general, and more specifically, to take into account the variability in the population. As mentioned in Sections 1 and 2.3, the current procedure involves the determination of the NOAEL and the subsequent derivation of an ADI by dividing the NOAEL by an uncertainty factor of 100. The uncertainty factor takes into account both the extrapolation from animals to humans and human variability (Woods, 1996). The crucial question is whether the current procedure adequately provides for immune response variability in the population. If it does not, can current assessment procedures be refined to take into account any genetic susceptibility factors and/or sensitive patient groups? The examples cited in answer to these questions refer to therapeutic drug-related problems, since there are very few data on chemical-induced immunotoxicity in humans. However, there is no reason to believe that the fundamental mechanisms are going to be different.

3.2.2 Is there a dose–response relationship for immunotoxicity?

The first point which needs to be addressed is whether a dose–response relationship exists in immunotoxic responses. For immunosuppression, it may be possible to discern such a relationship. However, with the other forms of immunotoxicity, studies with drugs in humans have shown that there is no consistent relationship between the occurrence of toxicity and external dose (Park *et al.*, 1995). A much more important factor is the internal dose and therefore the amount of antigen formed, which in most cases cannot be easily measured. In addition, sensitised individuals need only very small concentrations of antigen to evoke an immune response. Such individuals, may therefore develop toxicity at levels well below the recommended ADI.

3.2.3 What determines human variability in immune responsiveness?

The mechanism by which drugs and chemicals lead to immunologically mediated toxicity is explained by the hapten hypothesis (Pirmohamed *et al.*, 1998). This states that most chemicals (or their metabolites) are of low molecular weight (<1000 daltons) and therefore cannot act as immunogens *per se*. They act as immunogens only when they (or more usually their toxic metabolites) become covalently bound to autologous 'carrier' macromolecules, such as proteins. The term 'hapten' has been coined to describe substances which become immunogenic in this way. Because of their intrinsic chemical reactivity certain drugs, such as the penicillins, can form drug–protein conjugates directly. The majority of chemicals, however, do not react directly with proteins, but require bioactivation to chemically reactive intermediates by the cytochrome P450 enzymes. The immune response to the hapten–protein conjugate may be characterised by specifically committed T-lymphocytes and/or by antibodies directed against the drug (haptenic epitopes), the carrier protein (autoantigenic determinant) or the neoantigen created by the combination of the drug and the protein (new

antigenic determinant). In addition, the T-helper (Th) response is of two types, Th_1 and Th_2, depending on the pattern of cytokine secretion. This is important since certain forms of toxicity, for example drug-induced autoimmunity, seem to be predominantly Th_2-mediated.

T-lymphocyte activation, which is crucial in the whole process of generating an immune response against a hapten–protein conjugate, requires the antigen to be taken up and undergo intracellular catabolism in so-called antigen-presenting cells, prior to presentation (in association with major histocompatibility (MHC) molecules) of recognisable epitopes on the surface of these cells. The antigen may contain many possible epitopes, although only a few are recognised by the immune system. The predominance of one epitope (immunodominance) may be dictated by the expression of a particular MHC allele. This phenomenon is known as MHC restriction, and in essence means that the high level of polymorphism of the MHC genes results in a subset of individuals in the population who can respond vigorously to chemical-related antigens, and thus are more likely to develop hypersensitivity. Polymorphisms in the MHC genes have been associated with susceptibilities to various drug toxicities including hydralazine-induced lupus and gold-induced nephropathy (Park *et al.*, 1992).

Once an immune response against a hapten–protein conjugate has been elicited, the interaction between the antigen and the immune system causes tissue damage through four general mechanisms of hypersensitivity (according to the Gell and Coombes classification; Coombes & Gell, 1968). Cytokines play a crucial role in the immune response and, in some cases, in mediating the tissue injury resulting from it. There is variability in the human population in the degree of secretion of cytokines in response to a stimulus. Polymorphisms have been described in genes responsible for the expression of various cytokines, including tumour necrosis factor-α, interleukin-1α, interleukin-1β and interleukin-1 receptor antagonist. These polymorphisms have been linked to susceptibility to various autoimmune diseases and mortality from infectious diseases such as cerebral malaria (Wilson & Duff, 1995). Few studies have addressed the role of cytokines in chemical/drug toxicity. However, preliminary data suggest that they may also influence susceptibility to drug-induced toxicities, such as clozapine-induced agranulocytosis.

It is likely that polymorphisms in the MHC and cytokine genes are the key determinants of immunologically mediated toxicity to chemicals and drugs. However, it can also be surmised that susceptibility is multifactorial, and will involve factors other than the immune response, for example the balance between bioactivation and bioinactivation (Pirmohamed *et al.*, 1996). Thus, tissue injury from a chemical or drug will only occur when all the defence mechanisms in the body have been overcome. The situation is further confounded by heterogeneity, in that different numbers and combinations of factors may be responsible in different individuals. For almost all forms of chemical and drug toxicity, the different susceptibility factors have not been characterised and thus, at present, cannot routinely be taken into account in risk assessment procedures.

3.2.4 Are there certain patient groups who may be at increased risk?

An alternative strategy may be to target patients with certain diseases that increase the risk of immunologically-mediated toxicity. However, even here the data are fragmented and incomplete, and there are often contradictory results from different studies. Furthermore, the proportion of susceptible patients within each disease group is often unclear, and the predisposing factors are unknown. There have been reports of increased susceptibility to drug and chemical toxicity in three patient groups.

- Patients with atopic disease (up to 20% of the population) may be at increased risk of immune reactions mediated by immunoglobulin E (IgE), for example, penicillin anaphylaxis and latex allergy.

- Patients with connective tissue (autoimmune) diseases may also be at increased risk, although the data are scant. An example is sulfasalazine allergy in patients with rheumatoid arthritis.

- Immunodeficient patients, paradoxically, are also at increased risk of immunologically-mediated reactions. These include patients on immunosuppressive drug therapy and patients infected with human immunodeficiency virus (HIV). Hypersensitivity to cotrimoxazole represents the clearest example.

It interesting to note that in all three of these disease groups, there is evidence for the predominance of Th_2 subtypes.

3.2.5 Conclusions

There is no doubt that the considerable variability present in the human population is a determinant of immunologically-mediated toxicity which can occur on exposure to environmental chemicals and drugs. However, although some of the factors mediating the variability have been characterised, their specific role in predisposing to toxicity from the different chemicals has not. Certain patient groups may also be more susceptible to immunologically-mediated toxicity, but again, the data are fragmented and incomplete. Given the mechanisms of immune-mediated toxicity, it is reasonable to assume that current procedures for risk assessment, although providing a relative degree of protection, cannot provide absolute protection. It is difficult to quantify estimates of the proportion of the population that may still be susceptible because of the lack of data and ignorance of the fundamental mechanisms involved. Provision for these susceptible groups in risk assessment procedures is only likely to become a reality when more fundamental research has been carried out into the genetic and immunological factors that determine individual susceptibility to different forms of chemical toxicity. Additionally, better evidence is required as to how diseases, particularly those characterised by immune dysregulation, modify the risk of immunotoxicity.

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3.3 The elderly

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3.3.1 Background

An 82-year-old woman was admitted to hospital as an emergency case following a fall. She had been lying on the bathroom floor for about 18 hours. She lived alone and was receiving no help from outside agencies. She suffered from arthritis and depression and had experienced one or two falls in the past. Her house was rather dilapidated. When admitted to hospital she was noted to be a little confused and hypothermic and there were some signs suggesting a stroke. In hospital she recovered over the next week, her confusion improved, she became more mobile and her signs of cerebrovascular disease resolved. Prior to discharge, a home visit was carried out. There was an old-fashioned gas fire in her living room and many bottles of tablets, some full and some empty were found in the bedroom. A junior doctor raised the question of poisoning as a possible underlying cause of her illness.

This case history illustrates many of the issues pertinent to the lives of older people and how the impact of toxic substances may be influenced by the physical, mental, social, psychological and economic changes associated with ageing.

3.3.2 Key features of ageing

The key features that differentiate older people from younger ones are summarised below.

- Age is the major predictor for most of the common fatal and disabling diseases.
- The older population is very heterogeneous — from those who remain in good health to those who are disabled and ill.
- The causative factors that underlie health changes are both environmentally and genetically determined and the overall effect will be different in subsequent cohorts of older people e.g. coal miners' pneumoconiosis will decline once there are fewer former coal miners.
- Disease often presents in an untypical way — heart attacks without chest pain, infection with confusion.
- Cognitive impairment is common in the very old — perhaps 50% of those in their 90s. This affects the ability to recognise, interpret and react to both acute and chronic environmental challenges.
- Co-morbidity, both mental and physical, is common.
- Older people are the major consumers of pharmaceuticals, hence the potential for interaction is greatest.
- Recovery from illness may be prolonged.
- It becomes impossible to differentiate the effects of age from those of disease.
- The state retirement pension is below the poverty line and many older people live in relative poverty. They may use/be exposed to more hazardous but cheaper xenobiotics.
- Many older people experience social isolation, bereavement and lack transport.
- Older people may be rigid and inflexible; there is some evidence that you 'can't teach an old dog new tricks', but this is a complex issue.
- Ageism — there is widespread discrimination against older people both direct (age limits to certain treatments) and indirect ('it's your age you know').

The overall situation may be regarded as a lack of functional reserve in physiological and psychological systems in older people so that relatively minor environmental changes may result in a great deterioration.

3.3.3 The older population and toxicity

The published literature on toxicity and human ageing is very limited and confined largely to toxicity related to pharmaceuticals (Wynne *et al.*, 1987; Crome & Patterson, 1989; Aronheim & Howland, 1994; Crome, 1994).

Based on current knowledge of drugs, it is possible to make some generalisations. Absorption is unaffected by age. Distribution is altered in line with the known changes in body composition – body fat increases and body water decreases with age. Glomerular filtration decreases so that the clearance of renally eliminated compounds is reduced, and many agents that are cleared by hepatic biotransformation show reduced clearance and prolonged half-lives in line with the changes in

liver size and blood flow (Denham & George, 1990). There is also some evidence that frailty (Powell, 1997) exerts an additional detrimental effect on drug metabolism (Woodhouse, 1996).

Pharmacodynamic changes are more variable but increased sensitivity to many drugs acting in the central nervous system has been reported. Population studies have shown that age alone is a poor predictor of drug metabolism. In acute overdosage, older people take a different range of drugs owing to differences in availability, perception of anticipated outcome and underlying mental state. Inquiries about agents ingested by older people again show a difference compared with younger people, for example, many older people are likely to ingest false teeth preservatives.

The consequences of adverse effects are likely to be greater in older people. Thus postural hypotension in a younger person may cause dizziness which results in the patient lying down. Postural hypotension in an older person may result in a fall because of the impaired balance sense. The fall may result in a fracture because of osteoporosis and the fracture may result in a disability because of further fear of falling.

It has not proved possible to find a simple method of identifying subgroups within the older population that may be at special risk. There are, however, good grounds to suggest that they include people who are isolated, bereaved, poor, disabled, cognitively impaired, or with sensory deprivation, people from ethnic minorities, people who are institutionalised, who have recently moved, and people who are ill, are malnourished or frail, or take multiple medications. It is possible to quantify these groups using various epidemiological surveys. A study in North Staffordshire revealed that 27.7% of those aged 70 years or more lived alone without a personal alarm and 38.7% had no smoke alarm. Moreover, 5.4% of those in their 70s and 15.1% of those over 80 suffered from cognitive impairment (Crome *et al.*, 1997). Unfortunately, undertaking research in these groups poses great practical difficulties.

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4 Conclusions and recommendations

The undertaking of a risk assessment for human health within the regulatory setting can result in an expression of the level of concern about a particular health effect under specified condition(s) of exposure and/or feed into the development of a risk management position (e.g. the establishment of an ADI or occupational exposure limit; OEL). The latter is aimed at controlling the risks to a specified population likely to be exposed to the chemical of concern. In both cases the populations at risk of exposure can vary considerably — from the general population, in the case of a consumer product, to well-defined groups, for example in the occupational setting. In many cases a chemical may be used in a number of ways, and the same information may be used to assess risk and develop risk management positions for a number of different potentially exposed populations.

This risk assessment process is acknowledged as being subject to many uncertainties. One of the major factors contributing to uncertainty is variability within the human populations of concern. It was recognised at the workshop that one area where there is likely to be significant variability is that of exposure within a population, and considerable uncertainties exist with respect to estimating this variability. However, this aspect is the subject of a separate report within this Initiative (Risk Assessment and Toxicology Steering Committee, 1999) and is not considered further here. Variability also exists in the way individuals within the population are likely to handle a chemical once the body is exposed (i.e. variability in toxicokinetics) and in how organs and tissues respond once the chemical is delivered to the critical target site within an individual (i.e. variability in toxicodynamics). Such variability is likely to be determined in part by genetic factors, resulting in heterogeneity in both toxicokinetics and toxicodynamics, but is also likely to be influenced by many other factors such as (but not exclusively) age, sex, nutritional and pregnancy status and combinations of these.

There are often few data available on a chemical-specific basis to address factors that influence the variability in response to chemical exposure in the human population, and this gives rise to uncertainties in the risk assessment process. Historically, in the face of little or no information, the convention in many cases (e.g. for consumer and environmental risk assessment) has been to employ a default 'uncertainty factor' of 10 in the risk assessment or management process to allow for human population variability. This factor is intended to allow for variability in the sensitive portion of a population that is normally distributed for response. A second default uncertainty factor of 10 is also often used to allow for extrapolation between species in the face of little or no information, but this aspect was not the subject of this workshop and is not considered further. Thus, a NOAEL from an appropriate long-term animal study may be divided by a default uncertainty factor of 100 (10×10 as indicated above) in the development of an ADI or TDI. Equally, where a 'margin of safety' approach is used to compare a measured or estimated exposure with an experimentally determined NOAEL, in order to make a judgement on the level of concern, the values considered to provide an acceptable 'margin of safety' may be numerically equivalent to the values used in uncertainty factors. In some cases if there is concern with respect to a specific subpopulation, which is considered likely to be more responsive than the average individual within a population, then an additional uncertainty factor may be employed. Alternatively, if it is known that exposure is limited to a specific population, or it can be monitored and controlled or other action can be taken (e.g. removal from exposure), then the default uncertainty factor may be modified to a lower value, as is often the case for the occupational setting.

As indicated, it is generally assumed that the default uncertainty factor of 10 allows for the variation in the human population that arises as a consequence of the broad range of factors, mentioned above, that lead to increased responsiveness of individuals to toxic insult. However, this factor is historic, having been developed originally in the 1950s, and has little scientific foundation. Recent analyses have provided some support for its use, but it is unlikely that all of a sensitive population would be covered by such an approach, although there is little information available to judge its effectiveness. Although factors such as age (e.g. children and the elderly may respond differently to younger adults simply because of their biological age), sex and pregnancy status may influence individual response, there are relatively few data available by which to judge whether such factors would be covered by the current default position or whether additional uncertainty factors may be required to allow for such population subgroups.

Further research is needed to increase knowledge on the response of specific subpopulations to toxicological insult, in order to determine whether, on the basis of scientific evidence, additional uncertainty factors may be needed to allow for the presence of such subgroups in a population.

Such data may be difficult to obtain; any change to an uncertainty factor to account for wider human variability would need to be supported by evidence from human studies. Appropriate data may be available from research on human medicines, but are less likely to be available for other chemical exposures.

Genetic variation within the population is likely to be a major influencing factor in determining an individual's response to a chemical. Genetic variation will directly influence the way an individual handles and responds to a chemical insult and will also interact with other non-genetic factors such as those mentioned above (e.g. age, nutritional and pregnancy status). Much more information is required on the toxicokinetic and toxicodynamic processes involved before these different elements can be fully taken into account in risk assessment. Research should take into account the impact of genetic variability on the metabolism of toxic chemicals. Many chemicals have multiple detoxification pathways and the technology is now available to identify the enzyme systems involved. Genetic polymorphisms for the metabolism of pharmaceuticals are known and documented and those relating to cytochrome P450 (CYP) 2D6, CYP2C19, N-acetyltransferases and thiopurine methyltransferase may be significant determinants of response.

Further work should be undertaken on interindividual variations in toxicokinetic and toxicodynamic parameters, in particular on the inherent variability within the human population due to genetic factors affecting the metabolism of chemicals. In particular, *in vitro* screens should be developed further to determine the metabolic pathways for chemicals and their regulation in humans, in order to estimate the size of population subgroups that have a genetic deficiency in metabolism.

The nutritional status of individuals within an exposed population may be of importance in determining the response to chemical insult, particularly in the young. Sub-optimal nutrition may make an individual less able to respond to a toxic insult or inhibit recovery afterwards. Equally, in some cases where nutritional status is known to be poor (e.g. in substance abuse) it is difficult to determine what role this may play in the toxic effects observed. However, information on these aspects is relatively limited.

Further information is needed on the interaction of nutritional status, nutrition and response to chemicals.

Risk assessment and related risk management activities in general do not account for altered immunological status. It is unclear whether the current default uncertainty factor that is employed to allow for interindividual variation is sufficient to cover immunologically susceptible groups, which may include those previously sensitised to a particular chemical or who may be immunologically compromised. Whilst immunological susceptibility is recognised, the relevant population subgroups have not been identified and there is generally no surveillance of potentially susceptible individuals.

Research is needed on variations in immune response and on the importance of immunotoxicological end-points, in order to increase understanding of immunologically mediated susceptibility and how this might be addressed in risk assessment.

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Risk Assessment and Toxicology Steering Committee (1999) *Exposure Assessment in the Evaluation of Risk to Human Health*, Leicester, UK, Institute for Environment and Health

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