Derivation of Assessment Factors for Human Health Risk Assessment

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SUMMARY

The human health risk of chemical substances is generally assessed by extrapolation from heterogeneous animal data to man. In this report the extrapolation elements used in the process are reviewed in the context of the most recent, relevant data. Where appropriate substance-specific information is lacking, guidance is provided on the derivation of plausible numerical values to account for the uncertainties and variabilities in defining a 'safe dose' for man.

In cases where no default assessment factors are proposed, guidance is given on the type of additional information needed for the particular element of extrapolation. The approach proposed in this report is particularly useful for general industrial chemicals, where detailed toxicological studies are not always available or easily conducted. Professional expert judgement should be applied when using the recommended approach and the related guidance.

The elements of extrapolation considered are the establishment of the appropriate 'no observed adverse effect level' (NOAEL) for the critical effect, the difference in exposure duration between the experimental data and the assumed lifetime exposure for humans, the route to route extrapolation when the route of exposure is different for humans and the consideration of differences in sensitivity of response both between species (interspecies) and within a species (intraspecies).

The observed NOAEL is a typical starting point for risk assessment. If a NOAEL is not available or cannot be determined, then a 'lowest observed adverse effect level' (LOAEL) can be used with an appropriate assessment factor to take into account the dose interval, the shape of the dose-response curve and the severity of the effect observed at the LOAEL. This review indicated that a default value of 3 was appropriate for such an assessment factor. In the absence of a NOAEL, the Benchmark Dose, which takes into account data from the whole dose-response curve, can be used. Indeed the Benchmark Dose has been promoted more recently as an alternative to the NOAEL for the purposes of risk assessment.

Several factors contribute to the complexity of extrapolation for study duration. These include study design, half-life in the body and toxicological endpoints examined. Furthermore, exposure patterns are typically highly variable for humans as compared with the fixed parameters in animal studies. Nevertheless, a study of six-months' duration has been identified as sufficiently conservative for predicting long-term non-tumourigenic effects. Where linear bioaccumulation of a substance or linear accumulation of tissue damage is assumed during the six months' exposure, a default assessment factor of 6 is recommended for extrapolation from a robust sub-acute (28-day) study to lifetime or chronic exposure. A default of 2 is recommended for extrapolation from a sub-chronic (i.e. 90-day) to chronic exposure. Substances that have a relatively short half-life, have no toxic metabolites, are not reactive to tissue components and do not deplete essential elements can have NOAELs in a 28-day study close to those established for chronic studies.

No adjustment for exposure duration is recommended (i.e. default assessment factor of 1) where local effects via inhalation occur below the threshold of toxicity. Further work on this extrapolation element, although beyond the scope of the present report, might include the use of the point estimate of the Benchmark Dose instead of the NOAEL for investigating the ratios of short and long-term studies. Such an evaluation might help to override the obvious shortcomings of the use of NOAEL ratios. To understand better the impact of exposure duration in risk assessment, the relationship between substance half-lives and the ratio between short- and long-term NOAELs could be explored.

Route to route extrapolation is inadvisable for substances with local effects, since such effects are related more to concentration in the target tissue than to the administered dose. For substances with systemic effects, the relevance of the effects observed for the route of interest should be considered. Additional information such as dermal permeation, dose rate and uptake by other routes, is also helpful. If the route to route comparison implies a lower dose rate, this can be considered as a built-in safety margin. However, no default assessment factors are proposed for this extrapolation element and a case-by-case review is recommended.

The application of allometric scaling (based on metabolic rate and associated factors) is recommended for the interspecies extrapolation from animals to humans of systemic effects, with a default assessment factor of 5 to account for any residual interspecies variability remaining after scaling, and for any differences in intraspecies variability. For the more homogeneous worker population, where normal hygiene practices and risk management are in place, a default assessment factor of 3 is recommended. Based on the rather limited database for local effects in humans, the same factors (5 and 3) are recommended for intraspecies extrapolation for local effects. A default assessment factor of 1 (i.e. no adjustment) is considered sufficiently conservative for interspecies extrapolation of local effects by inhalation at equivalent doses.

For human health risk assessment, the default assessment factors recommended in this report are considered to be justifiable based on current science and transparent assumptions. The default values should be seen as useful ‘interim guides’ in the risk assessment process, particularly for general industrial chemicals; they are intended to be used with the guidance provided and only in the absence of appropriate substance-specific information. These default assessment factors replace those proposed previously by ECETOC in 1995. Where sufficient specific data exist on metabolic pathways, new approaches such as physiologically-based pharmacokinetic modelling are valuable tools in human health risk assessment and allow an appropriate adjustment of the values for the assessment factors.

1. INTRODUCTION

1.1 Background

Risk assessment is a conceptual framework that provides the mechanism for a structured and expert review of hazard, dose-response and exposure information relevant for predicting health or environmental outcomes (WHO, 1999). Ultimately, the goal of a risk assessment for humans is to describe with as little uncertainty as possible, the risk or lack of risk of unwanted health effects due to exposure to potentially hazardous chemicals. Alternatively, risk assessment information can also be used to establish acceptable exposure limits for humans.

During the past decade, the European Union (EU) has adopted far-reaching legislation, which requires formally that comprehensive risk assessments are conducted to assess the impact on humans and the environment of both new, and existing chemical substances. The general principles of risk assessment are defined in the relevant European Commission (EC) Directive and Regulation for new and existing substances, respectively (EC, 1993; EC, 1994). Both legislative texts are supported by the Technical Guidance Document (TGD) (EC, 1996), which, while not legally binding, is intended to ensure that a harmonised approach to risk assessment is followed by all EU Member States. Recently, the EC initiated a revision of the TGD to take into account developments in science since the mid-1990s and the experience gained by rapporteurs in Member States in implementing the risk assessment regulation; it is anticipated that the revised TGD will be published in 2003. Furthermore, in February 2001, the EC published a White Paper setting out the strategy for a future EU chemicals policy, the main objective being to ensure a high level of protection for human health and the environment (EC, 2002). To address these concerns the resulting legislation is likely to continue to focus on risk assessment.

The relatively recent promulgation of European risk assessment legislation should not imply that the process is new; scientists in industry and government have for decades been assessing the risks for human health and the environment resulting from exposure to chemical substances (see Appendix A). Several regulatory, academic and industrial organisations have published their approaches to human health risk assessment. These approaches have much in common, such as a need for an iterative framework, expert judgement and transparency in assumptions and decisions, a description of the uncertainty inherent in extrapolation of data, and a need to account for deficiencies or data gaps. Numerical values often provide a quantitative estimate of the variability and uncertainty in using experimental data to derive a 'safe dose' for humans. In addition, some agencies apply an additional 'factor' to the outcome to describe the overall uncertainty in the database and the assessment. These are referred to as assessment, adjustment or uncertainty factors by various authors and agencies. It is generally understood that 'adjustment factors' are numerical values that adjust dose to ensure normalisation for species or duration while 'uncertainty factors' are numerical values that are used to account for the lack or poor quality of information. In this report the term 'assessment' factor is used for a numerical value, which covers both dose adjustment and data uncertainty. Depending on the available data, each assessment factor may be substance-specific or assigned a generic value; the latter is termed a default assessment factor. These default factors can be derived by analysing well described datasets for

related substances; however, their use may be limited to certain classes of substances. For some substances, the available data will not include relevant information for all toxicological endpoints. In such cases, expert judgement should be used to decide whether additional testing is needed or whether the data are sufficient to allow a risk assessment using the approach described (see Annex, Section 1.1).

1.2 Terms of Reference

For the human health risk assessment of a chemical substance, the overall toxicity database includes typically both observational and experimental data of different duration and exposure routes in one or more experimental species, and when available, human exposure information. It is thus reasonable to assume that several extrapolation elements will be needed if such heterogeneous data are to be used to characterise the risk for humans. A review of the entire risk assessment process is beyond the scope of this report. Instead, the report focuses on the hazard identification, dose-response extrapolation and on the characterisation of the risk of adverse effects for humans. The report develops further many of the principles established in an earlier ECETOC report (ECETOC, 1995) and replaces the guidance provided therein on the use of assessment factors in human health risk assessment.

In establishing this Task Force, the ECETOC Scientific Committee assigned the following Terms of Reference:

- Identify and review current and emerging approaches for developing assessment factors used in deriving human occupational and non-occupational exposure levels;
- review the scientific basis for the above approaches taking into account criteria formulated in ECETOC Technical Report No. 68;
- revise Technical Report No. 68 to provide improved guidance for risk assessment with particular reference to European legislation.

Using the most recent and relevant published data, the Task Force reviewed the individual elements that are important in the extrapolation of hazard and dose-response data from animals to assess the risk for humans. The evaluations allow plausible numerical estimates to be proposed as default values for assessment factors for some extrapolation elements. In those areas where no appropriate values could be defined, guidance is given on the type of additional information that should be sought, in particular for risk assessments conducted within the European regulatory framework. The Task Force considered non-threshold effects (genotoxic agents) to be outside the scope of its remit.

The outcome of the Task Force work is presented in the form of a concise ‘core’ document that presents the key recommendations on the use and selection of the proposed default assessment factors. The core document is supplemented by a second document, the Annex, which provides the detailed arguments and summaries of the literature sources upon which the recommendations and conclusions of the Task Force are based. Thus, where further detail is needed, the Annex should be reviewed together with the relevant sections in the core document. Additionally, Appendices (A, B and C) attached in this report provide an overview of current uses of numerical factors in human health risk assessment and a review of some related emerging concepts and issues.

2. ELEMENTS OF EXTRAPOLATION

2.1 Introduction

In human health risk assessment, experimental animals are used typically as models for studying the toxic effects of chemicals in humans. The result of an animal toxicology study is mostly expressed numerically as a 'no observed adverse effect level' (NOAEL) which is related to the experimental species, study design (including dose selection and exposure, duration and route) and to the toxicological endpoints that are considered of relevance for humans. However, in some cases (e.g. absence of a NOAEL) it is more appropriate to use a study 'effect' level, usually the 'lowest observed adverse effect level' (LOAEL).

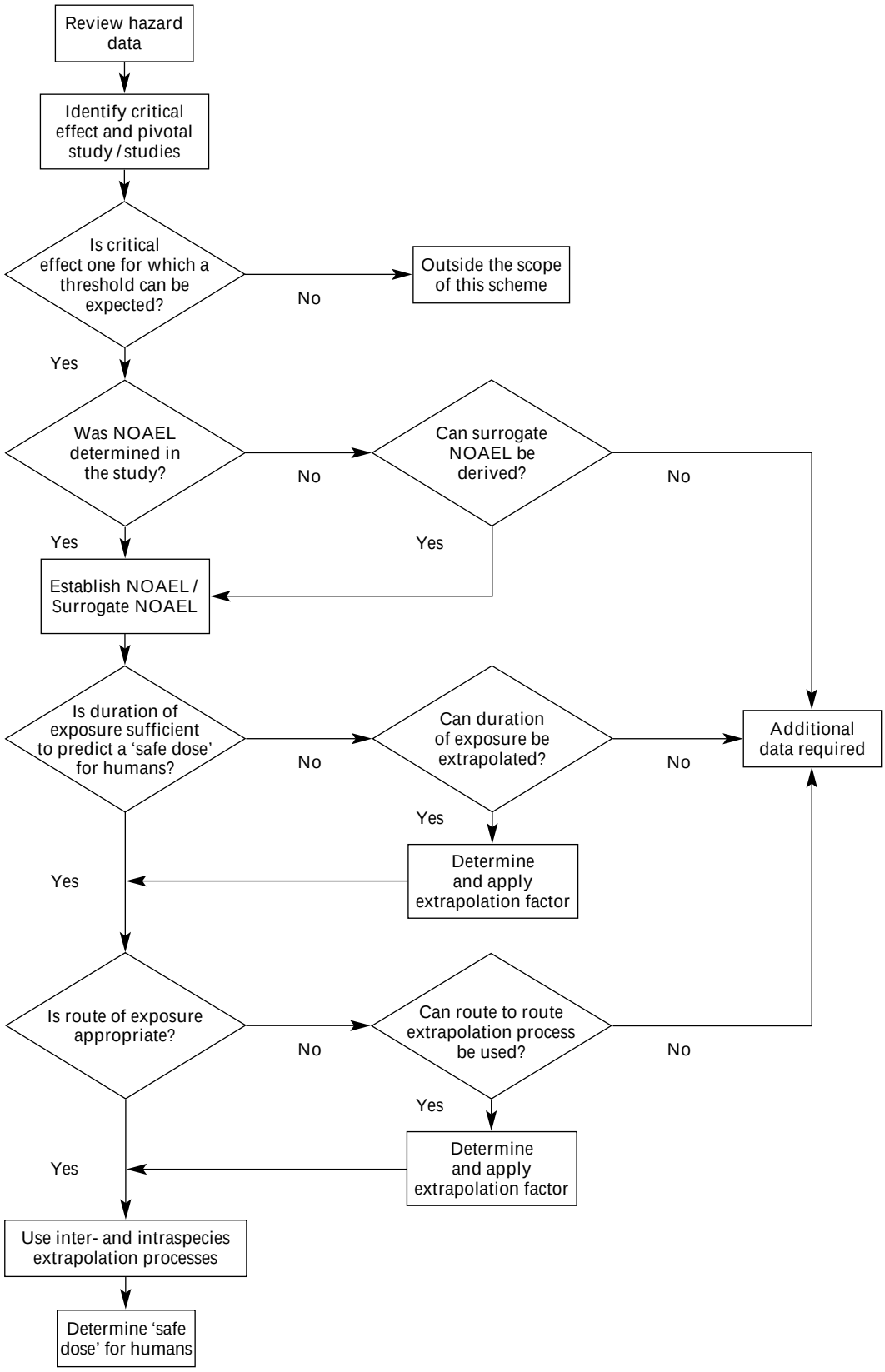
This report provides guidance for establishing an intake of a chemical substance for humans that would be without significant adverse health effects. A scheme was developed (Figure 1) which provides step-by-step guidance for deriving an approximation of a safe exposure level i.e. a 'safe dose' for humans from the appropriate NOAEL (or LOAEL) observed in animal studies. The scheme requires a review of the available hazard dataset for the substance of interest (see Annex, Section 1) followed by a series of extrapolation elements, which should be justified to allow a 'safe dose' for humans to be derived.

The following extrapolation elements are addressed in this scheme:

- Establishment of a NOAEL for the critical effect– i.e. dose-response assessment;
- duration of exposure – i.e. duration extrapolation;
- route of exposure – i.e. route to route extrapolation;
- interspecies difference in sensitivity between experimental animal and humans;
- intraspecies difference in sensitivity which is greater in humans than in the homogeneous experimental animal population.

The background to the scheme for deriving a 'safe dose' for humans, including guidance on the type of toxicological studies that should be considered and how to evaluate them, is presented in the the Annex (Section 1). Reference is also made to the use of data from sources other than standard toxicology studies, including qualitative and quantitative structure activity relationships ((Q)SARs), *in vitro* data and available human effects data.

Figure 1: Scheme for deriving a 'safe dose' for humans



2.2 Establishment of the NOAEL

Following a review of the hazard data for a substance, one or more critical effects are determined; such effects are defined as the most relevant adverse effects for humans under the appropriate exposure conditions (see Annex, Section 2). The most relevant NOAEL observed for this critical effect is then established. The NOAEL is dependent on individual study design, including dose selection and distance between doses, animal group sizes, duration of exposure, sensitivity of method used to measure an effect, and species, sex and strain of animals. The NOAEL may be close to or distant from the threshold at which no effect is likely to occur.

In a risk assessment for humans, the NOAEL from an animal study is the typical starting point and assessment factors are then applied to the NOAEL to account for both uncertainty and variability in the subsequent extrapolation elements. There are cases where the critical effect NOAEL cannot be determined and also cases where the LOAEL is considered a more appropriate starting point. Where only the LOAEL is available, an additional assessment factor is used typically (EPA, 1993; IPCS, 1994,1999; Lewis *et al*, 1990; Calabrese and Gilbert, 1993; Pohl and Abadin, 1995). The maximum value of the assessment factor recommended for extrapolation of a LOAEL to a NOAEL is generally 10.

A default value of 10 is considered by the Task Force to be overly conservative. Published studies in which the ratios of LOAELs to NOAELs were compared for a range of different chemicals and different study duration (subacute, subchronic and chronic) indicate that the LOAEL rarely exceeds the NOAEL by more than about 5-6 fold and is typically closer to a value of 3 (see Table 1 and also Annex, Section 3). The LOAEL / NOAEL ratio is highly dependent on the spacing between the doses, and since recent study design generally uses a dose spacing of 2-4, it is logical to conclude that the ratio data support a value of 3 as default. However, inclusion of a study with higher dose spacing, for instance 10 or 20 in the data analyses, will give extreme ratios that may adversely influence the overall result. ECETOC (1995) recommended a factor of 3 for LOAEL to NOAEL extrapolation in the majority of cases based on the approximate mean of the available experimental data in the literature.

Table 1: Ratio of LOAEL / NOAEL

Study Type	Mean of LOAEL / NOAEL	Reference and comments
Subchronic (n =27) Chronic (n = 25)	3.02 range (2-3, one at 5) 3.8 (range 2-4, two at 10)	Dourson and Stara, 1983, based on data published by Weil and McCollister, 1963.
Chronic (n = 175)	4.5 +/- 1.7 (95th% = 11)	Kramer et al, 1996 - oral
Chronic (n = 7)	5.7 (95th% = 11)	Kramer et al, 1996 - inhalation
Subacute (n = 95)	3.5 +/- 1.8 (95th% = 9)	Pieters et al, 1998 - subacute
Subchronic (n = 226)	4.3 +/- 2.2 (95th% = 16)	Pieters et al, 1998 - oral
Subchronic (n = 23) Chronic (n = 23)	91% ≤ 6 87% ≤ 5	Kadry et al, 1995 based on 6 chlorinated compounds
Subchronic (n = 18) Chronic (n = 18)	< 3 ≅ 3.5	Beck et al, 1993*
Developmental (n = 246)	2, 3 or 4 with equal frequencies	Faustman et al, 1994

* Beck *et al* (1993) considered that the results obtained in their analyses for subchronic and chronic ratios were an over-estimation

The size of the assessment factor for LOAEL / NOAEL extrapolation should therefore take into account not only the interval of the doses in the experiment but also the shape of the dose-response curve, including its slope, and the extent and severity of the effect seen at the LOAEL. Thus, consideration of the actual scientific information available may allow a meaningful adjustment of the LOAEL / NOAEL assessment factor. Where the interval between doses is large (e.g. 10-fold) and the effects seen at the LOAEL are minimal (indicating that the NOAEL is probably close to the LOAEL), it may be more appropriate to base extrapolation on the LOAEL (and apply an assessment factor of 3) rather than on the observed NOAEL. A lower factor, such as 2, could be used where the effect is minimal e.g. minor fatty infiltration of the liver, and the slope of the dose-response curve reasonably justifies the assumption that a halving of the LOAEL would be likely to arrive at the NOAEL. Where there is less confidence in the selected studies and the effects seen at the LOAEL are not considered to be minimal (e.g. pronounced liver cell necrosis), then the appropriate factor would be closer to 6.

In the absence of a NOAEL, the Benchmark Dose (BMD) has gained some acceptance for non-cancer endpoints, particularly developmental toxicity; more recently its use has been extended to cancer risk assessment (see Annex, Section 3.1). Even when a NOAEL is available, the BMD has been suggested as an alternative to allow more use of all the available study data (Woutersen *et al*, 2001). The BMD has been defined as the statistical lower confidence limit (usually 95%) of an extrapolated dose that corresponds to a defined incidence of an effect in the species under consideration. The BMD can be used to define or confirm an absolute effect level or, in the absence of a NOAEL, it might be an acceptable alternative index on which to base the risk assessment.

The BMD has a number of advantages since it makes full use of the dose response of the substance (including the slope of the response curve) and it reflects sample size. This is not reflected in the NOAEL, where a small sample size is likely to give rise to a higher NOAEL. The BMD however has certain limitations (e.g. the use of the lower confidence limit of the point estimate), since the 95% confidence level may give a value that is much lower than the experimental NOAEL. The confidence limits are dependent on the size of the dataset and small datasets give large margins. Thus, the outcome of the procedure is strongly determined by the size of the dataset. Furthermore the dose levels and group sizes used in current guideline studies may not be ideal for the derivation of a BMD (Woutersen *et al*, 2001).

2.2.1 Recommendations: Establishment of the NOAEL

- If an appropriate NOAEL is available, then no extrapolation and hence, no assessment factor is necessary.
- Where it is considered more appropriate to use the LOAEL, a default assessment factor of 3 is recommended. However, the factor may need to be adjusted depending on the effects observed at the LOAEL and the slope of the dose response curve.
- The BMD could be an alternative approach for defining or confirming a NOAEL depending on the data quality and dose spacing.

2.3 Duration of exposure

In the field of industrial toxicology, a study in rodents with an exposure duration of 28 days is often used for extrapolation to a lifetime NOAEL. In this report, short-term studies of 28 days or less are considered as subacute and those of 90 days (13 weeks) or longer, but less than lifetime, as subchronic.

2.3.1 Duration extrapolation (systemic effects)

Recent proposals for a default assessment factor have been based on evaluation of the ratio of NOAELs for studies of different duration, conducted in a variety of species and for several chemical classes (see Annex, Section 4). Some experts judge the highest observed ratio between short- and long-term NOAELs to be the appropriate value for a default assessment factor (McNamara, 1976), while more recent publications suggest that the geometric mean (GM) value of the ratios is more appropriate (Kalberlah and Schneider, 1998). Application of the ratio approach ignores several sources of error, the main contributor being the imprecision of the NOAEL (Brand *et al*, 1999).

The ratio approach could be potentially improved by replacing the NOAEL by the point estimate of the BMD. Although the precision of the BMD is also influenced by sample size, dose centering and other contextual factors, it is considered to be more appropriate than the NOAEL for estimating differences in sensitivity e.g. in duration and in interspecies comparisons (Brand *et al*, 2001). Therefore, it would be a worthwhile exercise to undertake a review, estimating the BMD (using data published by the US National Toxicology Program on short- and long-term studies for non-carcinogenic substances) and subsequently, deriving the BMD-subacute/BMD-chronic and the BMD-subchronic/BMD-chronic ratios. However, such an extensive study is beyond the scope of this report.

A further concept relevant to extrapolation for study duration is emerging from investigations which aim to identify the optimum duration of a study. In this, duration extrapolation would not lead to a different NOAEL. Betton *et al* (1994) carried out a critical review of the optimum duration of chronic rodent testing for the determination of non-tumourigenic toxic potential. This review indicated, that for the detection of non-neoplastic effects:

- For pharmaceuticals, a six-month study appeared adequate for predicting results following chronic administration.
- According to data published by the US National Toxicology Program, three-month studies predicted the 2-year outcome for 70% of the compounds. Despite the limitations of this review, this finding is considered encouraging as it is close to that generated previously on more detailed confidential pharmaceutical data (Lumley and Walker, 1986; Lumley *et al*, 1992).

In the more recent study, Lumley *et al* (1992) conducted a retrospective analysis on data from a range of species (e.g. rat, dog, primate) obtained with 96 pharmaceutical compounds or 154 case studies (a case study was one compound tested in one species for one or more time periods). For 124 / 154 case studies (80%), the respective toxicologist had indicated that all toxicologically significant effects were identified within one, three or six months. Where only studies with a pathological examination at six months or earlier were included, all significant findings were identified within six months for 124 / 133 studies (93%). Where new findings were observed after six months (7 compounds), their overall clinical significance in humans was questionable. The authors state that, overall, these data suggest that a six months' exposure is all that is routinely required for evaluating chronic toxic potential (excluding carcinogenicity) of a pharmaceutical compound for human use.

The data generated in 172 pesticides (including fungicides, herbicides and insecticides) for subacute, subchronic and chronic studies in dogs were reviewed by Spielmann and Gebracht (2001). Serious side effects were observed in 15 of 141 chronic toxicity studies, that were not observed in subchronic (13 weeks) studies. Furthermore, for 9 of 172 pesticides, significant new effects were seen in 52 / 104 week studies, when compared with 4- or 13-week studies; if the comparison was made with 13-week studies, then only 7 of 141 showed significant effects. However, the authors state that all significant toxicological effects were identified within an exposure period of 26 weeks. Thus, analysis of the severity of organ-specific toxic effects of pesticides revealed that chronic studies (52 / 104 weeks) in dogs did not provide specific additional information as compared with 26-week studies in the same species. If these observations occur at lower doses following chronic exposure, then the NOAEL value should be adjusted.

The problem of extrapolating the change in effect concentrations over time, is that the available data comparing NOAELs after different durations of exposure indicate that although the GM value for the subacute to chronic oral NOAEL ratios may be a factor of 4, there is wide variability with the 95th percentile being up to 46 (see Annex, Section 4.1). Similarly the GM value for the subchronic to chronic NOAEL ratios is almost 2 (1.7), while the 95th percentile value may be up to 29. As discussed later (Annex, Section 4.1), there are limitations with the use of other statistical parameters from the distribution

such as the GSD and the 95th percentile. Using these 95-percentile ratios as assessment factors for exposure duration would be in conflict with the results of the studies for an optimum study duration (Betton *et al*, 1994; Lumley *et al*, 1992). In consequence, some pragmatic selection has to be made from within this available distribution of ratios. As discussed earlier, it is clear from the available data that a study duration of six months provides essentially the same value for the NOAEL as would be found after chronic exposure. Using the conservative assumption of linear accumulation of effects with time, extrapolation from one to six months would require a factor of 6 and since the NOAEL would not change between six months and two years, this should theoretically be the maximum factor necessary. Thus, an extrapolation of study duration from 1 to 6 months would suggest a default assessment factor of 6, assuming linear bioaccumulation of the substance or assuming linear accumulation of tissue damage during the six-months' exposure. This default factor should be the same for extrapolation from one month to chronic exposure based on the studies cited above. Consequently, a default factor of 2 would be assumed to be appropriate when extrapolating from studies of three to six months. However, compounds, such as most industrial chemicals, that have relatively short half-lives, are not reactive to tissue components and do not deplete essential elements, might have NOAELs in 28-day studies close to those for chronic studies.

Where repeat dose studies of shorter duration (i.e. 1, 3 or 6 months) are used to assess effects of potential chronic exposure in humans, it is important that careful attention be given to experimental design. With more appropriate choice of dose levels and number of animals per dose group, more effects may be identified earlier (Lumley and Walker, 1986). Typically, more organs are analysed for substance-specific effects in chronic studies than in shorter subchronic studies; hence, appropriate histopathological examination should be considered for the subacute and subchronic studies.

Bachmann *et al* (1996) reported the half-life for around 100 xenobiotics, mainly pharmaceuticals but including some environmental contaminants. The GM of the half-life in rats was about one hour and the 95th percentile was less than 15 hours. Thus, with the exception of cytostatics (e.g. nitrogen mustard and fluoracil), it is unlikely that extending the exposure duration period to more than 28 days would have a significant effect on the NOAEL value. A study to examine the relationship between the half-life of pharmaceuticals and other chemicals on the one hand, and the ratio between the NOAEL subacute / NOAEL subchronic and the NOAEL subacute / NOAEL chronic on the other, could provide useful information on these aspects. However, such a study is beyond the scope of this report.

2.3.2 Recommendations: Duration extrapolation (system effects)

- A default assessment factor of 6 is recommended for extrapolation from subacute (28-day) to chronic exposure.
- A default assessment factor of 2 is recommended for extrapolation from subchronic to chronic exposure.

2.3.3 Duration extrapolation (local effects)

In duration of exposure extrapolation, it is important to distinguish between local and systemic effects. Local effects (e.g. on the respiratory tract, skin or internal organs) are related to the deposited dose per unit of surface area. Below a certain concentration, the capacity of the epithelial cells to neutralise a substance is not overwhelmed and epithelial cells retain the ability to neutralise the deposited irritant substance. A crucial point in this reasoning is to define the threshold of cytotoxicity. Evidence of histopathology (e.g. metaplasia of epithelial cells) and/or tests for epithelial cell proliferation may be needed for identifying the true threshold of cytotoxicity, which, for epithelial cells, is assumed to be similar between the species (Lewis *et al*, 1994; Johnson *et al*, 1990; Bogdanffy and Keller, 1999).

2.3.4 Recommendation: Duration extrapolation (local effects)

- No additional assessment factor is needed for duration of exposure extrapolation for substances with a local effect below the threshold of cytotoxicity.

2.4 Route to route extrapolation

Route to route extrapolation is not appropriate for substances with a local mode of action (e.g. for corrosive substances) where tissue damage is more dependent on concentration and local tissue deposition, than on dose. Moreover, skin injury may modify the uptake of irritant and corrosive substances.

Route to route extrapolation is only feasible for substances with a systemic mode of action. Thus the remainder of this section is confined to such substances.

The toxic effect of a substance is influenced by route of exposure and concomitant rate of absorption, distribution, metabolism and excretion. These parameters control the resulting internal concentration. A low rate of dosing generally causes less harmful effects than a high dose rate. Route to route extrapolations should take into account dose rate and toxicokinetic information.

Absorption

Where route to route extrapolation implies a lower rate of dosing, there is a built-in safety margin, and no further adjustment is needed.

The dose rate resulting from ingestion is dependent on the mode of administration of a substance i.e. via gavage or via the diet or drinking water. Intake and absorption from diet or drinking water takes place over several hours during feeding and drinking, while absorption after bolus administration by gavage is usually complete within 30 minutes. Absorption rate is dependent on various factors including vehicle, water solubility, molecular weight, fasting status and time of day. More precise information might be estimated from toxicokinetic studies via the oral route.

Absorption via dermal uptake can be rapid or slow, depending on the physical and chemical properties of the substance. In general, the rate and extent of absorption from dermal exposures is lower than, or equal to, absorption from oral exposure or from inhalation. This observation is supported by the well-known barrier properties of the skin. The dermal absorption rate can be estimated (ECETOC, 1993). An estimate of the amount of substance, which has permeated the skin per unit of time and unit of surface area, can be made from the maximum dermal absorption rate at saturated aqueous solubility. In the absence of information on dermal permeation, (Q)SARs may provide an estimate of the percuateous absorption rate within one order of magnitude. With appropriate information on dermal permeation, route to route extrapolation from oral data to dermal may be considered on a case-by-case basis.

With regard to inhalation, aerosols with particles of a mass median aerodynamic diameter (MMAD) greater than 10 microns are retained (100%) in the upper respiratory tract (CIIT, 1999). Those particles are transported to the throat via the mucocilliary escalator of the respiratory tract and are subsequently swallowed. This 'secondary ingestion' is comparable to oral administration. The rate and extent of deposition and absorption of respirable particles (MMAD less than 10 microns) via the alveoli could be higher than from secondary ingestion. For aerosols with low solubility (e.g. dusts of metal oxides such as manganese and cadmium), the long residence time in the lung makes the conditions for absorption more favourable than during the relatively rapid passage through the gastrointestinal tract following secondary ingestion. The opposite might also occur for substances whose solubility is pH-dependent e.g. barium salts (Tarasenko *et al*, 1977).

Distribution and metabolism

There are differences between the oral, dermal and inhalation routes in relation to the extent of metabolism of absorbed substances. Ingested substances are absorbed into the blood and transported to the liver where they may be activated or inactivated before reaching the target site; this is the so-called 'first pass effect'. The lung is the 'first pass' organ for inhaled particles (as is the respiratory tract for inhaled vapours), and the skin for dermal absorption. The liver, lung and skin have different metabolic capacity for biochemical transformation of substances and in this way, the substance or its metabolites may achieve different blood levels dependent on the route of exposure. For substances that are absorbed rapidly via all routes and where the first pass effect is not significant, the effect and response may be comparable between the exposure routes at equal absorption rates. Two chronic drinking water studies and a chronic inhalation study on vinylidene chloride were considered to provide a good example of extrapolation from the inhalation to the oral route (Pepelko and Withey, 1985).

The following points need to be taken into consideration when conducting a route to route extrapolation with systemic toxicity data (Pepelko and Withey, 1985; Pepelko, 1987):

- Absorption efficiency is known for both routes, or can be quantified;
- elimination half-life of the chemical is relatively long compared to the absorption half-life;
- first pass metabolism is minimal;
- critical target organ is not the port of entry;
- chemical undergoes no significant metabolism by intestinal microflora or pulmonary macrophages;
- chemical is relatively soluble in body fluids;
- adequate systemic toxicity data are available for the route used as a basis for extrapolation.

An example of where these conditions are fulfilled is the extrapolation from a chronic inhalation study to the drinking water route for methyl tert-butyl ether (MTBE) (Dourson and Felter, 1997). Absorption via inhalation and ingestion was observed to be 50 and 100%, respectively. Differences in distribution, metabolism and excretion were not considered to play a role. This approach was confirmed since the ratio (0.5) between the toxic potency of MTBE (mg / kg bw / day) via the inhalation and the oral routes was comparable to the predicted value on the basis of the absorbed amount.

2.4.1 Recommendations: Route to route extrapolation

- Route to route extrapolation is only feasible for substances with a systemic mode of action, and should take dose rate and toxicokinetic data into account.
- If route to route extrapolation implies a lower rate of dosing this can be considered to provide a built-in safety margin. In such cases, no assessment factor is needed i.e. an assessment factor of 1 is considered to be appropriate.
- Extrapolation from oral to dermal data may be considered on a case-by-case basis, provided appropriate information is available on dermal permeation. It is not appropriate to define a default assessment factor.

2.5 Interspecies and intraspecies extrapolation

For risk assessment purposes, experimental animals are used as surrogates for humans in exploring the toxic effects of chemical substances. In the interpretation of the findings in experimental animals, two particular aspects need to be addressed:

- Difference in sensitivity between experimental animals and humans, the so-called interspecies difference in sensitivity;
- distribution of variability in sensitivity of the experimental animal and that of humans (intraspecies difference) considered in relation to the interspecies difference in sensitivity.

2.5.1 Interspecies extrapolation using allometric scaling (systemic effects)

For interspecies differences, the default assumption is that humans are more sensitive than the experimental animal (Figure 2). However it should be recognised that humans may be more, equally, or less sensitive to the effects of a given substance relative to the experimental animal. A classic example of humans being less sensitive than the experimental animal is the susceptibility of rats to compounds, such as phenobarbitone, that induce metabolic enzymes in the liver and consequently produce an imbalance of thyroid hormone levels (McClain, 1989). Available knowledge of the mechanism of toxicity in humans and animals should therefore also be taken into consideration in the process of extrapolation.

In the absence of any substance- or species-specific mechanism or Physiologically-Based Pharmacokinetic (PBPK) modelling data, allometric scaling based on metabolic rate ($BW^{0.75}$) is considered to provide an appropriate default for an assessment factor for interspecies differences (Feron *et al*, 1990; EPA, 1992; Kalberlah and Schneider, 1998; Vermeire *et al*, 1999). Allometric scaling is based on anatomical, physiological and biochemical similarities between animal species relating quantitatively a number of morphological and biological functions. It is a tool for estimating interspecies differences of internal exposure or body burden and it provides indirectly information on differences in sensitivity between species. Typical scaling factors for interspecies adjustment are 7 for mouse, 4 for rat, and 2 for dog (Feron *et al*, 1990). However, adjustments of these scaling factors may be necessary especially for directly acting and metabolically activated / inactivated compounds. Background information as well as an overview of published evaluations of allometric scaling is provided in the Annex (Section 5). It is important to note that extrapolation using allometric scaling based on metabolic rate assumes that the parent compound is the toxic agent and that the detoxification is related to the metabolic rate and thus controls the tissue level. This is relevant for oral exposure. With regard to inhalation of substances which act systemically, the lower detoxification (metabolic) rate in larger animals is balanced by a lower intake (lower respiratory rate); thus no scaling factor is needed.

The scaling approach might not account completely for interspecies variation in biological sensitivity and might not address special cases of higher sensitivity in humans due to toxicokinetic or toxicodynamic differences between animal and humans. The database for determination of this (additional) assessment factor for interspecies sensitivity is small and most likely confounded by intraspecies variability. Freireich *et al* (1966) compared the maximum tolerated dose (MTD) of five consecutive doses of chemotherapeutic drugs in the mouse, rat, dog, monkey and human, and found that for the 18 substances examined, the largest discrepancy in the ratio of predicted to observed MTD dose for human was 3. Analysis of the Freireich data, augmented with additional data by Watanabe *et al* (1992), likewise revealed a maximal difference of 3. Depending on the species, the authors defined the MTD differently (see Annex, Section 5.2). The Task Force analysed the data from Freireich *et al* (1966) and Schein *et al* (1979), (who compared the MTD of chemotherapy drugs in the mouse, rat, dog, monkey, and human), and found that the GM of the MTD ratios between animal and man approximated the allometric scaling factors for each species, while the geometric standard deviation (GSD) of each series of dose ratios was less than 3 (Table 2).

Table 2: ECETOC evaluation of data of Freireich et al (1966) and Schein et al (1979) based on MTD ratios calculated for each substance by Travis and White (1988)

Species	BW kg	Ratio BW humans / species	$(BW_{human} / BW_{animal})^{0.25}$ (scaling factor)	GMs of MTD ratios	GSDs of MTD ratios
Mouse	0.02	3000	7.4	6.8	2.54
Rat	0.1	600	4.9	3.8	2.59
Monkey	2.5	24	2.2	2.2	2.60
Dog	7.50	8	1.7	1.3	2.51
Man	60.0	1	nr	nr	nr

BW = body weight nr = not relevant

Equations for calculating the scaling factors, the GM and the GSD are provided in the Annex (Sections 5.2 and 5.3).

Despite differences in both administration routes and basis for definition of the MTD between species, the above analysis supports the concept that adjustment of the animal dose by allometric scaling will predict reasonably the appropriate dose in humans. However, consistent with the opinions of others cited above, the GSD of 2.5 - 2.6 in this analysis suggests the likelihood of some variability or additional uncertainty around the extrapolated dose or predicted NOAEL in humans. As the Task Force analysis is based on a comparison of animal to actual human data, this 'additional' variability is probably due, not only to possible differences in biological sensitivity between species, but also intraspecies differences. Therefore, although 'residual' interspecies variability may remain following allometric scaling, this is largely accounted for in the default assessment factor proposed for intraspecies variability reflecting the inherent interdependency of the inter- and intra-species factors (see Figure 2).

The interspecies assessment factor, as derived above, is applicable where the parent substance is considered to have caused the toxic effect. In this case, the interspecies factor reflects the rate of detoxification of the toxic agent, which is related to the basal metabolic rate. In the data (Freireich *et al*, 1966) shown in Table 2, the parent substance caused the toxic effect. Extrapolation to larger animals requires dose levels to be divided by the relevant scaling factor.

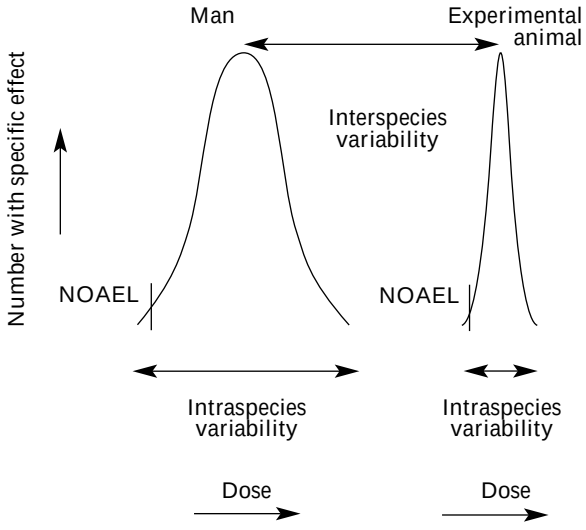
On the basis of their experience with PBPK models and allometric scaling, and where detailed knowledge was available of the substance responsible for the toxicity and its metabolism (parent substance, reactive metabolite or stable metabolite), Clewell *et al* (2002) developed a consistent approach for estimating interspecies assessment factors for systemically acting substances.

Unsaturated organic substances, such as vinyl chloride, methylene chloride and trichloroethylene, have to be activated in order to exert a toxic effect. In larger mammals, activation is slower and detoxification of the reactive metabolites usually faster, than in rats and mice. If the toxic effects are caused by a reactive metabolite, the formation is assumed to proceed more slowly and the concentration in the tissues will be lower in humans than in rodents. According to Clewell *et al* (2002) allometric scaling may sometimes underestimate the tissue dose for direct acting substances both via oral and inhalation intake, and overestimate the tissue dose in the case of reactive metabolites. Thus the availability of further information on the parent compound and its metabolism may allow modification of the default assessment factor.

2.5.2 Intraspecies extrapolation (systemic effects)

As shown in Figure 2, it is anticipated that a greater variability in response from the most to least sensitive human would be seen, relative to an experimental animal population. This is due in part to a greater variety of genetic polymorphisms in the human population, but also to 'acquired' susceptibility factors such as disease status, diet, age, sex, stress and previous or simultaneous exposure to multiple compounds (drugs, food additives, pesticides, industrial chemicals) all of which may have an impact on the NOAEL for the different individuals of a population. Hereditary differences in genetic constitution can influence variation in response in a human population e.g. by impacting the levels of metabolically activating or detoxifying enzymes or DNA repair enzymes. Research has suggested that there is a complex interaction between 'acquired' and 'inherited' susceptibility for each individual (Garte *et al*, 1997). In the absence of specific data on the influence of genetic polymorphism, it is assumed that the intraspecies default assessment factor is adequate to account for such individual differences in a population.

Figure 2: Interdependence of inter- and intra-species variability (adapted from Calabrese and Gilbert , 1993)



In an attempt to evaluate the intraspecies variability within the human population, the distributions of human data for various toxicokinetic and toxicodynamic parameters were examined (Hattis *et al* 1987, 1999; Hattis and Silver 1994; Renwick and Lazarus, 1998). These evaluations included data from 'healthy adults' of both sexes, as well as limited data from the young and elderly, mixed races and patients with various medical conditions such as cancer and hypertension.

Most of the human datasets examined by Hattis *et al* (1987, 1999) were characterised by lognormal distributions, while the data of Renwick and Lazarus (1998) were transformed to lognormal distributions by the Task Force to allow a comparison. For a lognormal distribution, the variability within an individual dataset for both toxicokinetics and toxicodynamics is represented by the GSD. The GSDs of all the datasets taken together form a lognormal distribution, which itself has a GM and a GSD. The intraspecies variability may be represented by the product of the overall GSD toxicokinetics and the overall GSD toxicodynamics. The 95th percentile of the combined distribution of toxicokinetic and toxicodynamics variability can then be obtained by multiplying the GM toxicokinetic and GM toxicodynamic by the overall GSD toxicokinetic and GSD toxicodynamic, respectively, with both GSDs raised to the power of 1.645 (i.e. GM_{TK} x $GSD_{TK}^{1.645}$) (GM_{TD} x $GSD_{TD}^{1.645}$). This provides a numerical value to represent an estimate of the total intraspecies variability for toxicokinetic and toxicodynamic parameters. The approach described is a statistical one based on published toxicological datasets.

To estimate the upper extreme of the variability in these data, the 90, 95 and 99th percentiles of the distribution of the variability for the datasets examined within each of these publications was calculated. The calculated percentiles based on both toxicokinetic and toxicodynamic parameters are presented in Table 3. Details on the calculation of these percentiles and a brief discussion of the datasets used are provided in the Annex (Section 5.4).

Table 3: Analyses of intraspecies (toxicokinetic and toxicodynamic) differences base on geometric distribution of variability

Percentile	Renwick and Lazarus (1998)	Hattis et al (1999)
90	3.7	3.2
95	4.3	3.8
99	5.6	5.0

The data of Renwick and Lazarus (1998) and Hattis *et al* (1999) were based exclusively on human data and similar values were obtained within each percentile. Considering that the data analysed by these authors included both sexes, a variety of disease states and ages, the use of the 95th percentile is considered sufficiently conservative to account for intraspecies variability in the general population. Thus, a default assessment factor of 5 is recommended for the general population with a lower factor of 3 (i.e. closer to the 90th percentile) for the more homogeneous worker population. In the worker population, the more susceptible groups are typically excluded and / or may be protected from specific exposures. Thus, the normal hygiene practices that are required in the workplace can serve to compensate in the management of risk and lower values of the assessment factor for intraspecies variability are considered appropriate.

There is currently much public interest in the possibility that infants and children represent a group that is particularly at risk from exposure to chemicals. A comprehensive evaluation of the current knowledge concerning children's health is beyond the scope of this report; however, some key references are cited here to support the conclusions. Compared to adults, neonates show higher stomach acid, slower gastric emptying, lower fat and muscle content, higher percentage of total body water, lower concentration of plasma proteins, lower activities of many metabolic enzymes, and reduced renal excretion (Warner, 1986). Many of these factors, such as metabolic enzymes and plasma protein binding, reach adult levels within the first few years, while renal tubular secretion and gastric emptying time achieve adult levels within 6 months after birth. A review by Renwick (1998) indicated that by age 6-12 months, kinetics of xenobiotics in infants were equivalent to those in adults and that clearance of many compounds was actually greater in infants than adults. As metabolic enzymes and kidney function are major determinants in the elimination of xenobiotics, children should be adequately protected by the assessment factors selected for adults. However, consideration should be given to potential sensitivity of developing organ systems or exposure patterns unique to infants and very young children.

2.5.3 Recommendations: Inter- and intra-species extrapolation (systemic effects)

- Analysis of MTD ratios for animals and humans supports the concept that allometric scaling, based on metabolic rate, provides a sound default approach for interspecies extrapolation of systemic effects.
- For intraspecies variability, a default assessment factor of 5 is recommended for the general population, with a default value of 3 for the more homogeneous worker population.
- There is little scientific basis to support the need for an additional assessment factor for children in risk characterisation, other than for substances which directly affect the developing foetus and which need to be considered on a case-by-case basis. In addition, attention should be given to substances affecting developing organ systems, such as reproductive development in pre-puberty.

2.5.4 Interspecies extrapolation for inhalation (local effects)

The local effects of inhaled substances on the respiratory tract are influenced by the physical state and chemical properties of the substance and also by the geometry and metabolic capacity of the species under consideration. These need to be taken into account when extrapolating between the animal species and humans. The available data and information from computer-derived models of the respiratory tract in humans and rodents indicate that local effects of gases and vapours observed in the rat nasal cavity when extrapolated to the human situation are likely to over-estimate effects in humans by a factor of 2 to 4 approximately (see Annex, Section 5.5). For many compounds, mice are likely to be more sensitive than rats. Thus, based on the data available at present, a default assessment factor of 1 for interspecies extrapolation for local effects is considered to be sufficiently conservative. With substance-specific data or if (Q)SAR considerations are available, the factor could even be reduced below 1. PBPK modelling can contribute to the estimation of more specific assessment factors (see Annex, Section 5.5.1).

In the case of inhaled aerosols, the final site of deposition in the respiratory tract is dependent on the size of the aerosol particles and their physico-chemical properties. Particles <100um aerodynamic diameter are considered inhalable and those <10um are considered respirable (ACGIH, 2001). The deposition of respirable aerosol particles in the respiratory tract is mainly concentrated in the upper respiratory tract (nose, pharynx) for rodents and in the lower respiratory tract (tracheobronchial and alveolar part) for primates including humans. For direct acting water-soluble particles, the local effect in each species will be observed mainly at the site of deposition i.e. the anterior and lateral part of nasal mucosa of rodents and the posterior part of the nasal mucosa and pharynx of humans and other primates. Quantification of these differences is increasingly done by mathematical modelling, but no simple assessment factor can be derived (see Annex, Section 5.6).

For aerosols it may be concluded that based on the respiratory rate of rodents leading to a greater respiratory tract burden as compared to humans, the effects observed in the rat are exaggerated and that no additional assessment factor is needed for extrapolation from rodent to human or for extrapolation from primate to human, as the effects will be similar in location and intensity.

2.5.5 Intraspecies extrapolation (local effects)

Hattis *et al* (1999) also studied the variability in toxicodynamics of local effects. The analysis combined skin effects, eye irritation and a number of respiratory effects such as pulmary function and pulmonary discomfort. The reporting of subjective symptoms was also included with an intrinsic high variability due to the methodology employed. When combining all these effects, the GM of the GSD of the distribution was 2.7 with a GSD of 1.8 i.e. slightly greater than for systemic effects (see Annex, Section 5.4 Table 9). The maximum GSD was 10 for the effect of 'pulmonary discomfort' from triallylamine exposure.

An alternative way to address intraspecies variability of local effects by inhalation is to include dose-response studies of respiratory irritants in volunteers. From the dose-response in volunteers the GSD of the irritant concentration at 50% response is a measure of the variability of human sensitivity, which may be used as a starting point for defining the intraspecies assessment factor. Some results for formaldehyde, ammonia and chlorine are summarised in Table 4.

Table 4: Intrahuman variability of local effects

Substance	Effect	GSD	Reference
Formaldehyde	eye irritation just perceptible	1.69	Kulle, 1993
Formaldehyde	eye irritation clearly perceptible	2.52	Kulle, 1993
Ammonia	unbearable irritation	1.47	Verberk, 1977
Chlorine	throat irritation just perceptible	2.15	Anglen, 1981
Chlorine	throat irritation clearly perceptible	2.05	Anglen, 1981

2.5.6 Recommendations: Inter- and intra-species extrapolation (local effects)

- A default assessment factor of 1 for interspecies extrapolation for local effects of water-soluble gases and vapours is considered to be sufficiently conservative. The factor can be reduced below 1 if substance-specific data or (Q)SAR considerations are available.
- No additional assessment factor (i.e. default assessment factor of 1) is needed for interspecies extrapolation from rodent to human for aerosols, since the respiratory rate of rodents leads to a greater respiratory tract burden as compared to humans; thus the effects observed in the rat are exaggerated and provide a 'built in' safety margin. For interspecies extrapolation from primates to humans, the effects will be similar in location and intensity.
- Based on the dose response relationships for respiratory irritants in human volunteers, an intraspecies default assessment factor for local effects in humans of 2.7, 3.0 and 4.3 can be derived (using the equations in the Annex, Section 5.3) to protect 90, 95 and 99% of the human population. These values are not greater than those for intraspecies extrapolation for systemic effects (Section 2.5.2). However, as the database used to derive the default values for such intraspecies variability in local effects is not large, it is recommended that the same values are used for the default assessment factors as for intraspecies variability for systemic effects. Therefore, for the general population based on the 95th percentile, a default assessment factor of 5 is proposed for the intraspecies factor for both local and systemic effects.

3. RECOMMENDED DEFAULT ASSESSMENT FACTORS

For the human health risk assessment of a chemical substance, the hazard or toxicity database includes typically both observational and experimental data of different duration and exposure routes in one or more species including, if available, such data in humans. Several extrapolation steps are needed if such heterogeneous data are to be used to characterise the risk for humans. The elements of extrapolation important in the hazard identification and dose-response steps of risk assessment have been reviewed in this report. The report develops further many of the principles established in an earlier ECETOC report (1995) and, by reviewing current and emerging approaches, updates the criteria cited in the earlier report.

The Task Force has focused on proposing, where possible, plausible numerical values as appropriate default assessment factors to account for the uncertainty and the variability in the available databases. The approach is particularly useful for general industrial chemicals where detailed toxicity studies are not always available or easily conducted and where professional expert judgement is required. Where more appropriate substance-specific information is lacking or cannot be obtained readily, the default assessment factors recommended in this report should be used for risk assessment following the guidance provided. The values for the defaults are considered to be justifiable, since their choice is based on current science and transparent assumptions; they should be seen as useful 'interim guides' in the risk assessment process.

The physico-chemical properties of the substance being assessed should be taken into account; these are often available or can be estimated. Any additional data on biological properties (e.g. reactivity, bioaccumulation, toxicokinetics and toxicodynamics) should also be considered to allow more specific modification of the proposed default values. In practice, it is unlikely that the available data on many substances will include relevant information for all toxicological endpoints. In such cases, expert judgement is required to decide whether additional testing may be needed or whether the data are sufficient to allow a risk assessment.

Where it has not been possible to define default assessment factors, the conclusions reached by the Task Force have been explained and guidance given on the type of additional information which should be considered for the extrapolation process.

The recommended assessment factors proposed in the preceding sections are summarised in Table 5. The single numerical value shown is considered an appropriate default assessment factor for the relevant extrapolation element. To avoid additional complexity, ranges for the default values have not been provided; however, the individual sections in Section 2 provide some guidance on when it is appropriate to use somewhat lower or higher values (e.g. extrapolation of LOAEL to NOAEL when the effects observed are minimal). Where no proposed default has been recommended in Section 2 (e.g. for route to route extrapolation), the table indicates "ND" ("no default proposed") and the guidance in the relevant parts of the Annex should be followed.

Table 5: Default assessment factors recommended for substances evaluated according to the guidance provided and in the absence of substance-specific information

Element of extrapolation	Default AF
Establishment of NOAEL	
- LOAEL to NOAEL	3
Duration of exposure	
- subacute/chronic NOAEL	6
- subchronic/chronic NOAEL	2
- local effects by inhalation	1
Route to route	
- oral to inhalation	ND
- oral to dermal	ND
Interspecies and intraspecies	
- interspecies (systemic effects)	
• mouse (scaling)	7
• rat (scaling)	4
• monkey (scaling)	2
• dog (scaling)	2
- intraspecies (systemic effects)	5
	3 (workers)
- interspecies (local effects by inhalation)	1
- intraspecies (local effects)	5
	3 (workers)

ND = no default proposed

3.1 Conclusions

In recent years a number of systematic investigations to establish scientifically based default assessment factors have been published using statistical or mechanistic approaches. The Task Force has reviewed critically these publications and derived the most scientifically supportable values for default assessment factors. Before using the default values, it is strongly recommended that all the data on a specific substance are reviewed thoroughly, and that as far as possible, substance-specific information is used to decide on the appropriate value of the assessment factor for each extrapolation step. An assessment factor for a specific substance and extrapolation element may or may not be similar to the recommended defaults where these are provided. In any case, transparency in the choice and justification of each factor is needed. Professional expert judgement should be applied when using the recommended approach, the proposed default values and the related guidance.

While this report has addressed several elements of extrapolation in the hazard identification and dose response aspects or components of risk assessment, it is recognised that the debate on this topic continues and that in certain areas, additional work, although outside the scope of the present report, would be useful. In the duration of exposure extrapolation element, several references were made to the use of NOAEL ratios for studies of different duration and in different species. As the use of the BMD increases, it would be useful to re-evaluate such ratios using the point estimate of the BMDs instead of the NOAELs for the referenced studies. Another area of further study is the possible correlation of substance half-lives with reversible effects and the magnitude of the assessment factor for duration extrapolation. Once the steady state concentration is reached at the target tissue, increasing the duration of exposure would be expected to be irrelevant for substances with reversible effects. Thus, to understand better the importance of the duration of exposure in risk assessment, another possibility might be to explore the relationship between the half-lives of substances and the ratio between short and long-term NOAELs.

In future, more information in particular with regard to the use of models, such as the BMD or toxicokinetic modelling, may become available that could substitute for the use of default assessment factors in certain areas. PBPK modelling is clearly the best approach currently available on which to base informed predictions of human dosimetry towards derivation or replacement of assessment factors. PBPK models aim to describe dose to the target tissue, which is a more relevant means of expressing dose than external exposure concentration or administered dose. If sufficient data exist, these models may be useful for deriving human dose estimates that are equivalent to the NOAEL of the animal studies, for extrapolating these dose estimates to lower realistic human exposures, and for extrapolating animal test dosing regimens to realistic human exposure scenarios. These models also have the potential for describing dosimetry in genetically susceptible human populations. Furthermore, basic model structure availability and sensitivity analyses are demonstrating that within a class of chemical substances, (Q)SAR-based estimates of model parameters may be sufficient for implementing PBPK-based approaches, thereby rendering the method less data intensive. The approach is mature and sufficiently well-developed case examples are now available that have been used in risk assessments to modify the assessment factors and illustrate its potential. Nevertheless, PBPK modelling has yet to be embraced broadly by regulatory authorities and the major effort needed by chemical companies to develop such models has restricted their application in industrial toxicology to a limited set of substances.

ANNEX: ELEMENTS OF EXTRAPOLATION

Section 1. Review of database

In the scheme (Figure 1) proposed in this report, science based assessment factors are applied to the 'no observed adverse effect level' (NOAEL) or the 'lowest observed adverse effect level' (LOAEL) as necessary, based on a consideration of the applicability of the toxicology data to the human exposure situation. The step-by-step guidance provides an approach for deriving a 'safe dose' for humans, which is defined as the most likely estimate of the exposure, or range of exposures, that will have no adverse effects on humans.

Prior to an evaluation of the hazard data, the scenarios in which the population groups of concern will be exposed to a chemical substance are reviewed. A number of factors must be considered:

- Source of exposure e.g. workplace, deliberate or accidental exposure from consumer products, food, household goods, pharmaceuticals, indirect exposure through environmental contamination (including background exposure).
- Populations exposed e.g. workers, consumers, general population, young children.
- Route of exposure e.g. skin contact, inhalation (occupational, consumer products and household goods), oral (food, drinking water, pharmaceuticals).
- Level and extent of exposure e.g. concentration, pattern, frequency of exposure (single event to long-term continuous exposure).

In estimating exposure, tonnage data and physical properties may well be relevant. It is also important to consider multiple exposure sources (e.g. workers are also consumers).

1.1 Review of hazard data

In evaluating the hazard information, all (short- and long-term) toxicology data available on the substance are reviewed. Where known, the absorption, distribution, metabolism and excretion (ADME) of the substance and / or data from a PBPK model should also be taken into account.

In practice, it is unlikely that data for all toxicological endpoints and / or ADME data will be available. In these cases, expert judgement will be required to decide whether additional testing should be conducted or whether sufficient data are available to allow a risk assessment. This judgement needs to take into account the nature of use patterns and the resulting exposure in humans and the physical / chemical properties of the substance; these factors will help predict the fate of the substance in the body.

Data from acute and repeat-dose toxicity studies should be related to the duration and route of exposure in humans. Where this is not the case, it may still be possible to extrapolate from the results of other exposure durations and routes (Sections 2.3 and 2.4, respectively).

A review of the data also needs to include assessment of the quality of the studies and of the data presented. It is important to evaluate the data package as a whole. While some studies may be considered inadequate in isolation to determine a NOAEL, when viewed in the context of other data, an overall weight of evidence may provide a greater degree of confidence. Where data packages are considered to contain inadequacies, this will add to the overall uncertainty.

1.2 Use of other data

Data from sources other than standard toxicology studies, such as qualitative and quantitative structure activity relationships (i.e. (Q)SARs), *in vitro* data and data from investigations in humans, may also prove valuable for risk assessment.

Human data from carefully controlled volunteer trials, epidemiology studies as well as reports of the effects of accidental exposures are used increasingly in hazard assessment or for setting exposure limits. Currently, the most extensive human data are available for the endpoints of skin irritation and sensitisation (ECETOC, 2002a), respiratory irritation and sensitisation, and to a lesser extent, eye and sensory irritation. There are examples where human data have reduced or even eliminated the need for assessment factors e.g. US EPA assessment on fluoride (http://www.epa.gov/iris/subst/0053.htm) and nitrate (http://www.epa.gov/iris/subst/0076.htm).

Section 2. Critical effect

Following review of all the hazard data, one or more critical effects are identified. The first step in identifying the critical effect is to consider the type of human exposure expected. This is necessary as the toxicity and hence critical effect may vary depending on the extent, duration and route of exposure. For example the primary concern may be for acute toxicity of a substance if sporadic exposures to a high dose are likely, whereas if the concern derives from daily extended exposures to a lower dose, information on repeated dose toxicity may be appropriate. The same substance may be present in the environment (food, water, air, soil) at very low levels and the concern may be from chronic low level exposure to the general population, in which case it may be more appropriate to use the critical effect seen in studies of longer duration. Furthermore, there may also be concerns for chronic toxicity even from acute or short-term exposures if the chemical is known to persist (e.g. long-term health concerns after acute exposures to dioxin).

The relevant routes of exposure may vary with the use pattern of the substance under consideration. In the workplace, inhalation and dermal exposure are the main routes of exposure to be considered while for consumers and general public (indirect exposures through the environment), the oral route is typically also relevant. Thus, for the different exposure scenarios different key studies may be chosen to identify the critical effect and the appropriate NOAEL to be used.

A substance may induce several different adverse effects (ECETOC, 2002b). It is desirable to distinguish between less severe (e.g. inflammation) and severe effects (e.g. frank necrosis) and reversible (e.g. adaptive response such as organ hypertrophy) and non-reversible effects (e.g. teratogenic effects). It is also important to consider the relevance of the observed effects for humans in particular with regard to possible species-specific effects (choice of the relevant species if studies with different species are available). Good quality human data should be considered whenever available and human experience could also be used to facilitate the identification of the critical effect and the appropriate animal studies to be used. Furthermore available information on mechanism of action, toxicokinetic data and information from substances of the same chemical class should be taken into consideration. Knowledge of (Q)SARs may provide alerts of a potential, as yet unidentified, hazard.

In view of the recognition that different exposure scenarios are possible, more than one critical effect (and therefore more than one NOAEL) may need to be considered in the risk assessment. For example, local effects may be critical in certain exposure scenarios, whereas in others systemic effects may dominate. If more than one critical effect is identified, data should be evaluated with regard to the dose response and the doses at which these effects occur in order to determine if protection against one effect (e.g. liver toxicity) will also protect against the other (e.g. teratogenicity). The NOAEL chosen may not necessarily be the lowest value, but it should be the most relevant value for humans.

2.1 Local effects

All routes of exposure (oral, inhalation and dermal) should be taken into account in the assessment of local effects. In general, local effects such as irritation need to be considered separately, as the relevant dose metric will be related to the local dose (e.g. amount per unit area or $\mu g / cm^2$ skin) as opposed to the systemic dose (typically mg / kg bw).

Oral

A specific problem arises with gavage studies where effects can differ from those following a more continuous intake (diet, drinking water). In many studies it has been demonstrated that irritant substances administered by gavage produce local toxicity due to peak concentrations in the rodent forestomach. The same dose would probably not produce forestomach lesions in feeding or drinking water studies, or in the case of microencapsulation in the diet (Dieter *et al*, 1993; Hébert *et al*, 1994). Thus, when considering such a local irritant effect, it is more appropriate to consider the NOAEL in terms of a local dose (e.g. the concentration of the administered substance), rather than on a systemic dose basis (e.g. as mg / kg bw).

Inhalation

Local effects may also be important after inhalation exposure. The concentrations of a chemical in the target tissue are dependent on its physico-chemical properties, its reactivity in the upper respiratory tract and the anatomy of the upper airways (i.e. the local distribution parameters, surface area to volume ratios). These factors are all crucial to the development of local lesions. In addition, factors such as mass transfer coefficients, mucous flow rates, clearance rates and metabolism in the target tissue are also important (DeSesso, 1993, Andersen *et al*, 1999; Frederick *et al*, 1998). Modelling local dosimetry in the respiratory tract may be useful when available.

Dermal

Local effects, such as irritation from dermal exposure, are dependent on the nature of the test substance (physico-chemical properties such as pH, pKa, solubility or reactivity). The amount of the substance per unit area and the exposure conditions (e.g. duration, occlusion, semi-occlusion) are also important factors. Local effects, especially if repeated exposures occur, may also modify skin permeability and thus impact systemic doses.

Section 3. Establishment of the NOAEL

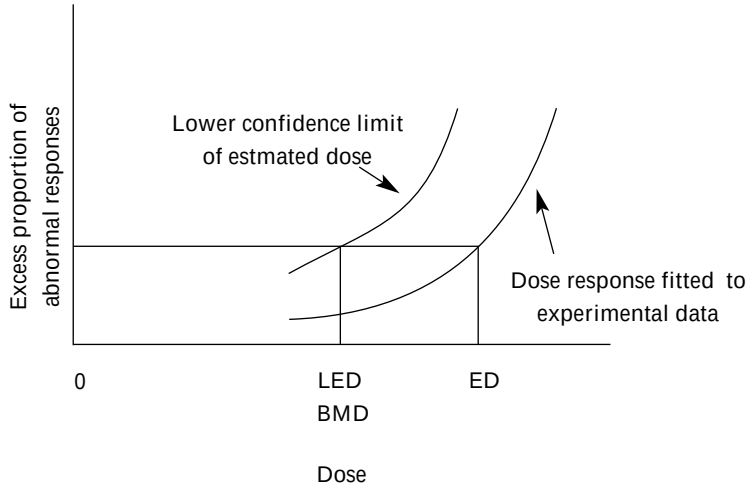
The magnitude of the NOAEL is dependent on several factors including dose selection and distance between doses, animal, species, sex, strain and group size, duration of exposure and sensitivity of method used to measure an effect. The NOAEL may be close to or distant from the actual dose or threshold, below which no effect is likely to occur. The estimated NOAEL for a study is related to the particular conditions of that study.

The maximum value of the assessment factor recommended for extrapolation of a LOAEL to a NOAEL is generally 10 (EPA, 1993). However published studies indicate that the actual magnitude of the difference between the NOAEL and the LOAEL is mainly below 10, and that it is highly dependent on the spacing between doses, as well as on the nature of the effect and the dose-response relationship. The results of the analysis of LOAEL / NOAEL ratios for a number of datasets are summarised in Table 1 (Section 2.2). In addition, ratios ranging from 2-5 were reported for a limited number of compounds considered for occupational exposure (Fairhurst, 1995). Hart *et al* (1988) reported that a ratio of 2 was often observed for a series of developmental toxicity data, although this applied only where the effects observed were minimal and indicated that the NOAEL was being approached. Naumann and Weideman (1995) recommended a factor of 3 as a best estimate, based on the available data, which approximated to a half-log value ($10^{0.5}$), although these authors preferred to use a Benchmark Dose (BMD).

3.1 Benchmark Dose

As an alternative to the NOAEL, the use of the BMD has gained popularity, particularly in developmental toxicity, although its application is being extended to other non-cancer endpoints (Crump, 1984; Kimmel and Gaylor, 1988; Barnes *et al*, 1995; Gibson *et al*, 1997; Krewski *et al*, 1999; EPA, 1991, 1995, 2000a, b). The BMD has been defined as the statistical lower-bound confidence limit (usually 95%) on an extrapolated dose that corresponds to a defined incidence of an effect in the species under consideration (Figure 3).

Figure 3: Graphical representation of the Benchmark Dose (adapted from Kimmel and Gaylor, 1988)



LED = Lowest Effect Dose; BMD = Benchmark Dose; ED = Effect Dose

The incidence level most often used is 5%, which has been found to correlate with many NOAELs (Crump, 1984, 1995; Faustman *et al*, 1994; Allen *et al*, 1994a, b; Auton, 1994; Kavlock *et al*, 1995, 1996; Allen *et al*, 1996; Gaylor and Chen, 1996; Gaylor *et al*, 1998). Although the statistical lower confidence limit is most often used, it has been suggested that, in the case of continuous data (e.g. organ weight), a better estimate of the BMD may be the point estimate, with the confidence limits being quoted to indicate the quality of the estimate (Murrell *et al*, 1998).

The BMD is estimated by applying a suitable dose-response model (e.g. Weibull, log-logistic) to the actual data and determining the statistical lower-bound confidence limit on the dose that corresponds to a specified response level that is typically 5 or 10% (i.e. $BMD_{0.05}$ and $BMD_{0.10}$, respectively). A number of software packages are available to estimate the BMD (e.g. http//www.epa.gov/ncea/bmds.htm). Both quantal data, where an animal has been classified as normal or diseased (e.g. a birth defect) or continuous data, where measurements are made on a continuous scale (e.g. organ weight or haematology) are used to estimate the BMD. In developmental toxicity studies, where most use of the BMD has been made to date, quantal data for any specific endpoints are the number of litters with one or more affected foetuses, while continuous data are the measure of responses or the proportion of foetuses affected in each litter.

The advantages of using the BMD are that it:

- Makes full use of the dose response of the substance including the slope of the response curve as all the data are fitted to the model;
- reflects the sample size (unlike the NOAEL, where a small sample size is likely to give rise to a larger NOAEL);
- can be applied consistently from one study to another;
- is not an experimental dose (unlike the NOAEL), and can thus be estimated in the absence of a NOAEL.

The use of the BMD has, however, certain limitations that require further consideration. These include the sensitivity of the BMD to the choice of model, the size of the confidence limits used, the difficulty in agreeing the measure of altered response, and the choice and ability to quantify the specific critical effect(s). The method also requires the study to have at least two dose levels, which give a graded response and provide a better starting point for risk assessment than the traditional NOAEL.

The BMD has been and still is subject to much investigation and further development (Barnes *et al*, 1995; IPCS, 1994, 1999; Gibson *et al*, 1997; EPA, 1991,1995,1996, 2000a, b). Nevertheless, it is currently recommended and used by the US EPA for developing reference dose calculations (oral RfD or inhalation RfC) for regulatory purposes. Examples include carbon disulphide, 1,3-dichloropropene, tributyltin oxide, and boric acid. In most instances, the BMD has been used for developmental toxicity (Faustman *et al*, 1994; Allen *et al*, 1994a, b; Auton, 1994; Krewski *et al*, 1999), while it is being extended for use in cancer risk assessment (Gaylor and Gold, 1998; Szymczak, 1998; Gaylor *et al*, 1999; Gaylor, 2000) and acute lethality studies (Fowles *et al*, 1999). Other examples of the use of the BMD include developmental effects of carbendazim (Mantovani *et al*, 1998) and the reproductive effects of 1,2-dibromo-3-chloropropane (Pease *et al*, 1991) and isopropanol (Allen *et al*, 1998).

Section 4. Duration of exposure

One of the possibilities for extrapolation for duration of exposure previously reported (Dutch Health Council, 1985), involved a linear correction for exposure duration. Assuming a rat lifespan of 1000 days, an assessment factor of 30 (~1000 / 28) for a 28-day study and of 10 (~1000 / 90) for a 90-day study was proposed as a conservative extrapolation to lifetime. This approach is simplistic and does not take into consideration results of any toxicological studies. Other proposals for an appropriate assessment factor have been based on evaluations of the ratio of NOAELs for studies of different duration.

For example:

- McNamara (1976) considered the highest observed ratio to be an appropriate assessment factor;
- Kramer et al (1996) proposed the 95% upper confidence limit of the 95th percentile of the observed ratios as the basis for an assessment factor;
- Kalberlah and Schneider (1998) considered the GM to be a good estimate of the assessment factor.

These proposals along with other relevant publications are discussed below.

4.1 Relevant studies

Weil and McCollister (1963), using NOAEL data from rat and dog studies for 33 different substances (e.g. agricultural chemicals, stabilisers, additives, antimycotics, water-treatment chemicals and food-packaging materials), found that 97% of the ratios comparing NOAEL (short-term) with NOAEL (long-term) were less than 10. The short-term studies were of between 29 and 210 days in duration; the long-term studies were all 2 years. The ratios were 2 or less for about 50% of the cases, with a mean ratio of 2.9 and greater than 3 in 21% (6/28) of the cases where the duration of the short-term study was 130 days or less. For the other five cases the duration of the 'short-term' study was between 130 and 210 days. Surprisingly, in four of these cases the ratio was 5 or greater. It is suggested that this apparent anomaly may have resulted from differences in study design (i.e. dose ranges) between those of shorter and longer duration.

McNamara (1976) examined the NOAEL (short-term) to NOAEL (long-term) ratio for 41 chemical substances (including pesticides, food additives, pharmaceuticals) that were reported in various literature sources. The data were mostly derived from rat and dog studies, but collected by numerous investigators using diverse study durations and techniques. The body weights of the animals were not known for all the studies and consequently estimates of daily food and substance intake were crude. Ratios of less than 3 were reported for all cases, with a mean ratio of about one. Woutersen *et al* (1984) compared the NOAELs of 82 substances, tested in subacute 14-28 day and subchronic studies under similar conditions. The ratios were equal to or less than 10 in almost all cases, but identical (factor 1) for 56% of the compounds. A factor of 4 covered 80% of the cases.

Nessel *et al* (1995) examined data to determine a scientifically based uncertainty factor for subchronic to chronic extrapolation. The median of the ratios of the subchronic to chronic NOAELs was approximately 2 for 23 oral studies and 4 for nine inhalation studies in rodents. The inhalation studies contained electrophilic and reactive compounds, such as methylbromide and formaldehyde.

Kramer *et al* (1996) performed a statistical analysis of the $NOAEL_{subacute}$ / $NOAEL_{chronic}$ ratio for 71 substances and evaluated the distribution of the ratios. A 'conversion factor' of 87 proposed by the authors for extrapolation from a subacute to a chronic NOAEL, was based on the upper 95% confidence limit of the 95th percentile of the $NOAEL_{subacute}$ / $NOAEL_{chronic}$ ratio. Use of the upper 95% confidence limit on a 95th percentile is overly conservative. Using only statistical information for extrapolation from short- to long-term NOAELs might suggest some scientific rationale, but does not consider important toxicological parameters. In fact, the derived factor (87) is higher than that expected on the basis of cumulative dose over time (1000 days / 28 days = 36) comparing chronic and subacute exposure duration.

Using the approach of Kramer *et al* (1996), Pieters *et al* (1998) analysed statistically the oral $NOAEL_{subchronic}$ / $NOAEL_{chronic}$ ratio for 149 substances and found a 'conversion factor' as defined above of 46. The GM of the ratios and the 95th percentile were 1.7 and 29, respectively. The authors recognised the conservative nature of the approach by Kramer *et al* (1996) and did not support their method for establishing an assessment factor. In comparison with the data of Weil and McCollister (1963) and of McNamara (1976) the variation in the dataset of Pieters *et al* (1998) was considerably larger (GSD, 5.6) and consequently, the 95th percentile and the upper confidence limit were higher.

Kalberlah and Schneider (1998) screened the scientific literature for papers providing a basis for 'extrapolation factors'. They also spent considerable effort on the extrapolation of the NOAEL from a short-term to a lifetime study. They concluded that the factors contributing to the spread of the distribution of the ratios between the short- and long-term NOAELs included the differences in the accuracy of the NOAEL due to variability in numbers of animals per dose group, toxicological endpoint, selection of dose levels and strain. The GM of the ratios between short- and long-term studies was proposed as a default assessment factor to take exposure duration into account. This factor was 6 in the case of extrapolation from subacute to chronic and 2 for subchronic to chronic.

Vermeire *et al* (1999) reviewed assessment factors for human health risk assessment. In the context of exposure duration, ratios of NOAELs were provided for short- and long-term studies from all known published papers and the parameters of distribution of the studies, referred to in each paper, were estimated (Tables 6 and 7).

Table 6: Subacute to chronic oral NOAEL ratios (adapted from Vermeire et al, 1999)

Number of studies	GM	GSD	P95	Subacute exposure	Chronic exposure	Species	Reference
71	4.1	4.4	46	3-6 week	1-2 year	rat	Kramer et al, 1996
20	3.1	1.9	8.9	14 day	2 year	mouse	Kalberlah and Schneider, 1998
26	3.9	2.2	14.3	14 day	2 year	rat	Kalberlah and Schneider, 1998
Weighted average	3.9	3.5	29.8				All three studies

GM = geometric mean GSD = geometric standard deviation
P95 = 95th percentile

Table 7: 'Semi-chronic' to chronic oral NOAEL ratios (adapted from Vermeire et al, 1999)

Number of studies	GM	GSD	P95	Semi-chronic exposure	Chronic exposure	Species	Reference
33	2.2	2.3	8.7	29-210 day	2 year	rat	Weil and McCollister, 1963
41	1.0	1.7	2.5	ns	ns	rat, dog	McNamara, 1976
20	1.9	3.0	12	<200 day	>200 day	various	Rulis and Hattan,1985
149	1.7	5.6	29	10-26 week	1-2 year	various	Pieters et al, 1998
23	2.0	1.8	5.1	90 day	2 year	rodent	Nessel et al, 1995
9	4.0					rodent	Nessel et al, 1995
9	2.4	1.3	3.7	90 day	1-2 year	mouse	Kalberlah and Schneider, 1998
11	1.7	1.8	4.5	90 day	1-2 year	rat	Kalberlah and Schneider, 1998
20	2.0	2.4	8.4	90 day	1-2 year	mouse + rat	Kalberlah and Schneider, 1998
21	1.7	1.7	4.1	90 day	2 year	mouse	Kalberlah and Schneider, 1998
22	2.5	1.9	7.2	90 day	2 year	rat	Kalberlah and Schneider, 1998
Weighted average	1.7	3.5	13.5				All ten studies

GM = geometric mean GSD = geometric standard deviation
P95 = 95th percentile ns = not stated

Vermeire *et al* (1999) demonstrated that within each dataset, the 95th percentiles and the GSDs were more variable than the GMs. As noted by Kalberlah and Schneider (1998), this variability in the distribution most likely resulted from the influence on the distribution of the ratios of study design factors, such as spacing of dose levels, species and strain tested, number of animals per group and toxicological endpoints examined. Thus, the GM of the distribution, which is less likely to be influenced by study design, is considered to be a more appropriate basis for establishing a default assessment factor for exposure duration.

The nature of the substances selected and their half-life and mode of action also influence the ratio between short- and long-term NOAELs. In theory, compounds that have relatively short half-lives, are not reactive to tissue components and do not deplete essential elements, should have NOAELs in 28-day studies close to those from chronic studies. Nessel *et al* (1995), using their data and that of Weil and McCollister (1963) and McNamara (1976), recommended the following for an appropriate assessment factor for extrapolation from subchronic to chronic data:

- Where there is no evidence for bioaccumulation and/or cumulative toxicity, no downward adjustment is necessary (i.e. a factor of 1 should be used);
- for extrapolation of typical subchronic toxicity data (e.g. NOAELs) a value of 2 is most plausible, and a value of 3 or less should be employed;
- when there is evidence of significant potential for bioaccumulation and/or cumulative injury (with prolonged or repeated exposure), a larger adjustment factor is required.

Section 5. Interspecies and intraspecies extrapolation

5.1 Interspecies extrapolation using allometric scaling (systemic effects)

Based on anatomical, physiological and biochemical similarities among animal species, a number of morphological and biological functions ranging from organ weights to heart rate or nitrogen excretion can be quantitatively related among species by body weight (W) according to the general allometric equation: $Y = a W^n$ where the values of 'a' and the exponent 'n' are species-independent constants for the biological function, Y (Davidson *et al*, 1986; Travis *et al*, 1990; van der Gevel and Hakkert, 1997). Extrapolation of animal data to humans based on adjustments for body size, termed 'scaling' or 'allometry', is therefore justified on the basis of the relationships described above. The body weight of an organism is the most easily and accurately obtainable measure of body size to provide a quantitative base for interspecies comparisons. Body surface area and metabolic rate or caloric requirement of the organism can also be used.

Adolph (1949) compiled a list of 34 morphological, physiological and biochemical parameters using the formula above and obtained values for the exponent 'n' ranging from 0.08 to 1.31. The GM of all values was 0.82 and a frequency distribution indicated that values from about 0.67 to 0.75 were most prominent. A number of these parameters (renal clearance, basal O_2 consumption (metabolic rate), area under the curve (AUC), maximum metabolic velocity or cardiac output) correlate to body weight to the power of 0.75. The observed mathematical relationships are fairly consistent over a wide range of species (Voisin *et al*, 1990). Further support for the power of 0.75 comes from a more theoretical approach based on fractal geometric and energy conservation rules for mammalian species (West *et al*, 1997, 1999). Several authors recommend the use of allometric scaling based on the metabolic rate (i.e. $W^{0.75}$) unless existing data preclude the use of this approach or more substance-specific data are available e.g. PBPK modelling (Feron *et al*, 1990; EPA, 1992; Kalberlah and Schneider, 1998; Vermeire *et al*, 1999). Using this relationship, extrapolation of toxicological data from rats to humans (assuming an average body weight for humans of 65kg) requires division of the rat NOAEL by a scaling factor of 4. Additional scaling factors for other animal species are shown in Table 8.

Table 8: Factors for interspecies extrapolation (oral route) based on caloric requirement as a measure of body size (adapted from Feron et al, 1990)

AnimalSpecies	Bodyweight (kg)	Scaling factor for interspecies adjustment
Mouse	0.025	7.1
Mouse	0.050	6.0
Rat	0.200	4.3
Rat	0.250	4.0
Rat	0.300	3.8
Guinea-pig	0.500	3.4
Dog	10	1.6
Dog	15	1.4

(The test species NOAEL (expressed as mg / kg / day) is divided by the corresponding factor above derived on the basis of $BW^{0.75}$)

Feron *et al* (1990) considered that the quantitative extrapolation involved two steps: a first step to adjust for differences in body size between animals and humans, and a second step requiring the application of an assessment factor for inter- and intraspecies variation in biological sensitivity. Similarly, Kalberlah and Schneider (1998) reported that scaling (based on the metabolic rate) was a method for dose adjustment in order to obtain a dose in mg toxin / kg body weight at which (without knowledge of substance and species-specific mechanisms), effects similar to those observed in animals could be expected in humans. They considered that the scaling approach did not address special cases of higher sensitivity in humans due to toxicokinetic or toxicodynamic differences between animals and humans.

5.2 Scaling factors and maximum tolerated dose comparisons

The allometric scaling of a toxicological parameter e.g. MTD, on the basis of metabolic rate (e.g. oxygen consumption) is explained below:

$$\text{Oxygen consumption} = A*BW^{0.75} \quad (= \text{mg})$$

$$\text{MTD experimental species} = Z*BW_{sp}^{0.75} \quad (= \text{mg})$$

$$\frac{\text{MTD exp. species}}{\text{Body weight species}} = \frac{Z*BW_{sp}^{0.75}}{BW_{sp}} = Z*BW_{sp}^{-0.25} \ (= \text{mg / kg})$$

$$\frac{\text{MTD human}}{\text{Body weight human}} = \frac{Z*BW_{human}^{0.75}}{BW_{human}} = Z*BW_{human}^{-0.25} (= \text{mg / kg})$$

$$\frac{MTD_{sp} \ (\text{mg / kg})}{MTD_{human} \ (\text{mg / kg})} = \frac{Z*BW_{sp}^{-0.25}}{Z*BW_{human}^{-0.25}} = \frac{BW_{human}^{0.25}}{BW_{sp}^{0.25}} = \left[\frac{BW_{human}}{BW_{sp}}\right]^{0.25}$$

A, Z = Scaling factor

An approach to developing a scientific rationale for the above mentioned interspecies sensitivity extrapolation was provided by Freireich *et al* (1966) and Schein *et al* (1979) who studied the MTD in the mouse, rat, dog, monkey and human of 5 consecutive doses of drugs used in chemotherapy. These studies were further considered by Travis and White (1988) and by Watanabe *et al* (1992) with the aim of deriving a general rule for interspecies extrapolation from animal to human. Depending on the species, the authors defined the MTD differently. In the mouse and rat, the MTD was set as equivalent to the intraperitoneal LD_{10}, while in the dog it was the highest intravenous dose that did not cause mortality. In humans, the MTD was defined as the intravenous dose causing mild to moderate sublethal toxic effects in a significant percentage of patients. Alternatively the MTD was an estimated value, calculated from a variable schedule but requiring cessation of drug application.

Using these data, the ratio between the MTD_{animal} and the MTD_{human} was calculated for each substance (Travis and White, 1988) and found to be in agreement with a lognormal distribution. The Task Force analysed further the GMs of the ratios and the variability around this estimate. The GMs of the observed ratios were then compared with the allometric scaling factors that were derived based on metabolic rate (see Table 2, Section 2.5.1).

5.3 Geometric mean and geometric standard deviation

The Task Force used the following equations for calculation of the GM, GSD and the percentiles:

$$GM = [\exp(\text{average of } \ln(x_1) \ldots\ldots \ln(x_n))]$$
$$GSD = [\exp(\text{standard normal deviation of } \ln(x_1) \ldots\ldots \ln(x_n))]$$

In some cases, only the coefficient of variation of the distribution (σ/μ) was given. The GSD was derived from the coefficient of variation according to the following equation:

$$GSD = \exp\sqrt{1n(1 + \frac{\sigma^2}{\mu^2})}$$

From the GM and the GSD, a percentile (e.g. 90th, 95th or 99th) can be estimated. The standard normal deviate of the 95th percentile of a normal distribution is equal to 1.645. In the case of a geometric distribution, the 95th percentile is derived by multiplying the GM with the GSD raised to the power of 1.645. Thus, the percentiles are obtained as follows:

$$\text{90th percentile} = GM \times GSD^{1.282}$$

$$\text{95th percentile} = GM \times GSD^{1.645}$$

$$\text{99th percentile} = GM \times GSD^{2.326}$$

5.4 Intraspecies extrapolation (systemic effects)

The datasets for the toxicokinetic components of the intraspecies variability are relatively large, as these parameters are studied routinely for drugs and chemicals. However, identifying data representing toxicodynamics only is considerably more difficult as these effects are likely to be influenced by many variables including feedback mechanisms and toxicokinetics. *In vitro* studies with human tissues would be useful in separating variability due to toxicodynamics but such studies are limited and have small sample sizes (Renwick, 1991). In spite of these limitations and considering that none of the datasets examined was generated specifically for the purpose of evaluating intraspecies variability, the similarity of the derived GM and the GSD is striking.

Table 9: Toxicokinetic and toxicodynamic datasets for examining intraspecies variability

Process	GM	GSD	Reference and type of data
Toxicokinetics	1.4	1.3	Hattis et al, 1987 (101 datasets of elimination half-lives, maximal blood concentrations, and AUC of blood concentration by time for 49 substances)
Toxicodynamics	1.3	1.5	Hattis et al, 1999 (derived by removing toxicokinetics component through division, e.g. 1.8 ÷ 1.4 = 1.3)
Toxicokinetics / toxicodynamics	1.8	2.0	Hattis et al, 1999 (21 datasets for exposure to drugs and toxicants either intravenously, orally or via the diet)
Toxicokinetics	1.4	1.2	Renwick and Lazarus, 1998 (60 datasets consisting mainly of AUC and clearance rates)
Toxicodynamics	1.5	1.3	Renwick and Lazarus, 1998 (48 datasets including effects such as heart rate, blood pressure, sedation, nausea)
Toxicokinetics / toxicodynamics	2.1	1.6	Renwick and Lazarus, 1998 (derived by multiplying toxicokinetic and toxicodynamic components, e.g. 1.4 x 1.5 = 2.1)

Hattis *et al* (1987) examined 101 datasets of individual toxicokinetic parameters (elimination half-lives, maximal blood concentrations, and the AUC of blood concentration by time) for 49 chemicals. The 95th percentile on the distribution of the GSDs for the datasets examined was calculated to be 1.81.

Hattis *et al* (1999) also studied the variability toxicodynamics for systemic effects in humans, from 21 datasets for exposure to drugs and toxicants either intravenously, orally or via the diet. The 95th percentile calculated on the GSDs of these data sets is 3.8. However, the endpoints considered by Hattis *et al* (1999) to represent toxicodynamics variability were not entirely free from toxicokinetics variability as effects for some chemicals, notably methylmercury and cadmium, were distributed based on blood levels. To remove the toxicokinetics variability, the value of 3.8 can be divided by 1.81 (i.e. the value derived from the 1987 evaluation of Hattis for toxicokinetics), to obtain a 95th percentile value of 2.1 for toxicodynamics alone.

The data of Hattis *et al* (1987, 1999) are more or less supported by those of Renwick and Lazarus (1998) who assumed a normal distribution of toxicokinetic and toxicodynamic parameters and presented the coefficient of variation as the measure of intraspecies variability. For comparison with the data of Hattis (1987, 1999), the coefficients of variation have been converted into GSDs. For the toxicokinetic data that contained 60 datasets, the 95th percentile is calculated to be 1.93. For the toxicodynamic data examined by Renwick and Lazarus (1998), which consisted of 48 datasets, the 95th percentile is calculated to be 2.23. However, in case of toxicodynamics, the majority of the effects studied (e.g. heart rate, blood pressure) were short term and thus influenced by many physiological feedback mechanisms in the body, making the estimated distribution somewhat less reliable. Combining both the toxicokinetic and toxicodynamic components of the datasets examined by Renwick and Lazarus (1998) gives a 95th percentile of 4.3.

Hattis *et al* (1987) have shown that the GM of the GSD of susceptibility (LD_{50}) in animals was similar to the GM of the GSD of the human toxicokinetic parameters studied. The GM of toxic susceptibility however includes toxicokinetic and toxicodynamic variability. In the study, systemic combined toxicokinetic and toxicodynamic variability might be described by a GM of about 1.8 with a GSD of 2.0 of the GSD of susceptibility. According to the study of Renwick and Lazarus (1998), the systemic combined toxicokinetic and toxicodynamic variability is to be described by a GM of 2.1 and a GSD of 1.6. It therefore seems that these variabilities are comparable with the interspecies variability, expressed as the GSD of 2.6 derived from the clinical studies of Freireich *et al* (1966) and of Schein *et al* (1979) and which was assumed to be caused partly by intraspecies variability.

5.5 Interspecies extrapolation for inhalation (local effects)

Local effects of inhaled substances on the respiratory tract are influenced by:

- Physical state of the substance (gas or aerosol);
- chemical properties of the substance ;
- geometry and metabolic capacity of the respiratory tract.

These factors play an important role in controlling local deposition of the substance in the airways and the area of the respiratory tract that will be affected. Interspecies differences with regard to these effects are related to the local tissue concentration in different parts of the respiratory tract and the local mode of action in the different tissues; the latter may be dependent, for example, on the metabolic capacity. As the local dosimetry for gases and vapours is different from that of aerosols, these cases will be discussed separately.

5.5.1 Inhalation of gases and vapours

Water solubility controls the rate of deposition and absorption in the respiratory tract. Gases with low water solubility are only poorly removed in the upper airways and a major part of the inhaled gas will thus reach the lower respiratory tract. The surface of the lower respiratory tract (alveoli and bronchioli) is linearly related to body mass, while the alveolar ventilation is related to body mass to the power of 0.75. This means that for irritant vapours and gases with low water solubility the dose per square cm alveolar surface is higher for smaller than for larger mammals. Thus, the exposure in the human lung, as compared to rodents, is likely to be lower.

In rodents, as obligatory nose breathers, the nasal epithelium is the most common site of toxic response with more water soluble and reactive substances. The location of the lesions in the rodent nasal passage is dependent on the nature of the substance. Reactive gases often cause more severe effects in the anterior region of the nose, while chemicals that are converted to cytotoxic metabolites cause more effects on the posterior olfactory tissue and especially the olfactory epithelium (Morgan *et al*, 1995).

The olfactory mucosa of rats has been shown to have greater xenobiotic metabolising activity than the respiratory mucosa. For some substances, especially the hydrolysis of inhaled esters, the capacity of rodent nasal mucosa may be greater than human nasal tissue (Bogdanffy and Keller, 1999). Furthermore, one of the main differences between humans and rodents is the well-developed and highly ventilated olfactory epithelium in rats. It covers 50% of the nasal cavity (Gross *et al*, 1982) exposed to the airstream inhaled, compared to a more rudimentary and poorly-ventilated hidden olfactory epithelium in humans, covering only 3% of the total nasal cavity (Negus, 1958; Sorokin, 1988).

The relevance of local effects in the rat nose for humans and other primates has been studied extensively for a number of substances. Casanova *et al* (1991) compared the covalent binding of formaldehyde to DNA in the respiratory tract of rhesus monkeys and rats and developed a toxicokinetic model taking into account the differences in anatomy of the respiratory tract of the two species. The same model was used to predict the concentration of DNA crosslinks in the nasal mucosa of humans. The rate of formation of DNA crosslinks can be regarded as a surrogate for the delivered concentration of formaldehyde. The findings indicate that rodents are more susceptible to local effects on the upper respiratory tract than primates. When using rat and monkey data to predict human crosslink rates (adjusting for differences in minute volume and bodyweight ratio), the rates predicted at concentrations below 1ppm formaldehyde, were 4-fold higher for the rat as compared with the monkey. Extrapolating from rat data alone would thus lead to an overestimation of the effect in humans.

Further support for the higher susceptibility of rodent nasal mucosa has been provided by Frederick *et al* (1998). On the basis of *in vivo* and *in vitro* experimental studies with organic acid vapours, a hybrid computational fluid dynamics (CFD) and PBPK dosimetry model was developed to estimate the regional tissue dose of organic acid in the nasal cavity of rodents and humans. The CFD-PBPK model simulations indicated that under the same exposure conditions the olfactory epithelium of the human nasal cavity was exposed to 2- or 3-fold lower tissue concentrations than that of the rat. The increased olfactory tissue dose in rats compared to humans can be attributed to the larger rodent olfactory surface area and its highly ventilated location in the rat nasal cavity. The authors suggest that, due to substantial differences in nasal anatomy and nasal air flow, the human olfactory epithelium is much better protected than that of the rat from irritant acidic vapours. In mice the local tissue dose is normally higher than in rats due to the anatomical differences (Miller *et al*, 1981).

The sensitivity of the nasal cavity of rat and human has also been studied with esters of organic acids. Frederick *et al* (1994) showed that when exposed to ethylacrylate, the carboxylesterase activity of the rat was three times higher in olfactory than in respiratory epithelium. Green (1996) showed that for methyl methacrylate (MMA), the human respiratory tissue carboxylesterase activity was 6-fold, and human olfactory carboxylesterase activity 13-fold, lower than in the rat. Andersen *et al* (1999) used these data to estimate a Dosimetric Adjustment Factor (DAF) (the factor by which the exposure level should be multiplied in order to get the same effect in man) for a range of exposure conditions for MMA. The DAF was estimated to be 3 (1.6 to 8) in the extrapolation from rat to human, suggesting that an exposure of 10 ppm MMA in the rat was equivalent to 30 ppm in humans. This is in contrast to the US EPA currently proposed DAF for MMA of 0.145, on the basis of the paper by Menache *et al* (1997) which states that 10 ppm in the rat would be equivalent to 1.45 ppm for humans. However, Menache *et al* (1997) did not take into account the difference in anatomy of the nasal cavity between human and rat. Hence, the outcome of the elaborate studies of Frederick *et al* (1998) deserve greater weight than the proposal of Menache *et al* (1997) which was not supported by experimental data.

5.5.2 Inhalation of aerosols

Water-soluble particles, trapped and dissolved in the mucous flow, exert their local effects mainly in the nose of rodents and additionally, in the trachea and lungs of monkeys and primates including humans. Water-insoluble particles are transported in humans by the mucous flow toward the posterior part of the nasal passage and are swallowed. In rodents, a greater amount of mucous flow is directed anteriorly along the lateral nasal wall and septum to the nostrils, where the secretions may be removed by licking or sneezing (Proctor and Chang, 1983).

Generally, small species, and species which are obligatory / habitual nose breathers, display lower pulmonary (alveolar) deposition rates than species which possess larger airways or those that breathe frequently through the mouth. This is due to the effective nasal filtration and increased deposition in narrow bronchi (Martonen *et al*, 1992).

The final site of deposition of aerosols in the respiratory tract is dependent on the particle size of the aerosol and its physico-chemical properties. Rats have a simple monopodial branching system, while primates have a more complex bi- or tri-podial system. Impaction is the predominant mechanism of deposition for particles greater than 2.5 m mass median aerodynamic diameter (MMAD), while particles greater than 1 m are deposited by both impaction and sedimentation. Typically, 5-10% of particles with an MMAD >4 m deposit in the tracheobronchial region. Alveolar deposition in a healthy adult human is a function of the MMAD. For particles >1 m, there is enhanced alveolar deposition when individuals breathe through the mouth as compared to the nose. Below 1 m, the two routes of breathing yield similar deposition fractions. The peak alveolar deposition occurs at an MMAD of about 3.5 m.

Alveolar deposition fractions for most MMADs are considerably lower in rodents than in humans i.e. around 10% in rats and mice and 30% in humans, dogs and monkeys.

5.6 Model addressing particle deposition in the respiratory tract

CIIT (1999), in collaboration with the National Institute of Public Health and Environment (RIVM) in the Netherlands, developed the so-called 'multiple path particle deposition model' (MPPDepM) to address particle deposition in the respiratory tract. The model describes the deposition of monodisperse and polydisperse aerosols in the respiratory tract of rats and humans for particles ranging in size from ultrafine (0.01μ) to coarse (20μ) and is based on single-path and multiple-path methods for tracking airflow and calculating aerosol deposition in the lung. The single-path method calculates deposition for a typical path, while the multiple-path method incorporates the asymmetry in lung structure, thus providing lobar specific and airway specific information. Within each airway, deposition is calculated using theoretically derived efficiencies for deposition by diffusion, sedimentation and impaction within the airway or airway bifurcation. Filtration of aerosols by the head is determined using empirical efficiency functions. Results using this software show good agreement with experimental data for regional deposition in the rat and human lung. This model is useful for estimating the deposition in the upper and lower respiratory tract in rat and human of those aerosols for which the particle size remains constant during its passage through the respiratory tract.

With stable aerosols (solids and non-evaporating liquids) this model is helpful for estimating the fraction deposited in the upper and lower part of the respiratory tract. The fraction in the upper part is transferred via the mucociliary escalator to the mouth and finally swallowed. This uptake is comparable to ingestion at a low dose-rate. The fate of the fraction in the lower part of the respiratory tract (in bronchioli and alveoli) is dependent on the stability and solubility of the solid. Stable solids may be partly removed via macrophages from the lower to the upper respiratory tract over weeks and months, and partly absorbed in the interstitial lung tissue, where they may remain for life. Dependent on the nature and the contact surface of the substance, macrophages in the lower respiratory tract will try to destroy the particles and produce active oxidant agents for this purpose. At so-called particle overload of macrophages these active oxidants are cytotoxic for macrophages, which lose their mobility and clearance ability.

The oxidants are leaking from the macrophages and cause lung tissue inflammation, which may finally result in lung tissue fibrosis and loss of diffusive capacity for oxygen. Lung cancer may finally develop in the rat, but not in other species. Since the apparent responsiveness of the rat model at overload is dependent on coexistent chronic active inflammation and cell proliferation, at lower doses where these phenomena do not occur, no lung cancer hazard is anticipated (ILSI, 2000).

The MPPDepM is useful for estimating the level of particle overload associated with cytotoxic effects for rat and human dependent on aerosol characteristics in experimental studies and occupational exposure. The ratio between the extent of deposition in the lower respiratory tract between experimental exposure of rat and occupational exposure in humans might be used as assessment factor.

Particles deposited in the lower part of the lungs may be dissolved slowly over weeks to months. Deposition in the lower respiratory tract may enhance absorption for low soluble substances as fraction of the deposited particles, due to the long contact time with the lung tissue. In contrast, particles in the upper respiratory tract are finally swallowed and removed via the faeces in a few days. The contact time in the body for the latter is thus shorter and leaching occurs to a lesser extent than the former (e.g. cadmium, manganese).

If the aerodynamic properties of the aerosol change during the inhalation process, the MPPDepM cannot be used to estimate the deposited fraction in the upper and lower respiratory tract. Fine droplets of liquid may evaporate in the respiratory tract and behave finally like gases and vapours. Hygroscopic liquid aerosols (e.g. sulphuric acid) attract water and the size of the droplets grows rapidly leading to deposition, mainly in the upper respiratory tract. Thus the aerodynamic properties of the aerosol may change during passage into the respiratory tract and deposition cannot be predicted on the basis of the composition of the original aerosol (Cocks and McElroy, 1984; Sarangapani and Wexler, 1996).

BIBLIOGRAPHY

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. TLVs and BEIs, threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH, Cincinnati, USA.

Adolph EF. 1949. Quantitative relations in the physiological constitutions of mammals. *Sci* 109: 579-585

Allen BC, Gentry R, Shipp A, Van Ladingham C. 1998. Calculation of benchmark doses for reproductive and developmental toxicity observed after exposure to isopropanol. *Reg Toxicol Pharmacol* 28: 38-44.

Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994a. Dose-response assessment for developmental toxicity. ll. Comparison of generic benchmark dose estimates with no observed adverse effect levels. *Fund Appl Toxicol* 23: 487-495.

Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994b. Dose-response assessment for developmental toxicity. lll. Statistical models. *Fund Appl Toxicol* 23: 496-509.

Allen BC, Strong PL, Price CJ, Hubbard SA, Daston GP. 1996. Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. *Fund Appl Toxicol* 32: 194-204.

Andersen ME, Sarangapani R, Frederick CB, Kimbell JS. 1999. Dosimetry adjustment factors for methylmethacrylate derived from a steady-state analysis of a physiologically based clearance-extraction model. *Inhal Toxicol* 11: 899-926.

Anglen DM. 1981. Sensory response of human subjects to chlorine in air. Dissertation, University of Michigan.

Auton TR. 1994. Calculation of benchmark doses from teratology data. *Reg Toxicol Pharmacol* 19: 152-167.

Bachmann K, Pardoe D, White D. 1996. Scaling basic toxicokinetic parameters from rat to man. *Env Hlth Persp* 104: 400-407.

Barnes DG, Daston GP, Evans JS, Jarabek AM, Kavlock RJ, Kimmel CA, Park C, Spitzer HL. 1995. Benchmark dose workshop: criteria for use of a benchmark dose to estimate a reference dose. *Reg Toxicol Pharmaco*l 21: 296-306.

Beck BD, Conolly RB, Dourson ML, Guth D, Hattis D, Kimmel C, Lewis SC. 1993. Improvements in quantitative noncancer risk assessment. *Fund Appl Toxicol* 20: 1-14.

Betton G, Cockburn A, Harpur E, Hopkins J, Illing P, Lumley C, Connors T. 1994. A critical review of the optimum duration of chronic rodent testing for the determination of non-tumourigenic toxic potential: a report by the BTS Working Party on Duration of Toxicity Testing. *Human Exper Toxicol* 13: 221-232.

Bogdanffy MS, Keller DA. 1999. Metabolism of xenobiotics by the respiratory tract. In Hayes AW, Thomas JA, Gardner DE, eds. *Toxicology of the Lung*. Taylor and Francis, Philadelphia, pp 85-123.

Brand KP, Catalano PJ, Hammitt, JK, Rhomberg L, Evans JS. 2001. Limitations to empirical extrapolation studies: the case of BMD ratios. *Risk Anal* 21: 625-640.

Brand KP, Rhomberg L, Evans JS. 1999. Estimating noncancer uncertainty factors: are ratios NOAELs informative? *Risk Anal* 19, 295-308.

Calabrese EJ, Gilbert CE. 1993. Lack of total independence of uncertainty factors (UFs): implications for the size of the total uncertainty factor. *Regul Toxicol Pharmacol* 17: 44-51.

Casanova M, Morgan KT, Steinhagen WH, Everitt JI, Popp JA, Heck H d'A. 1991. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus moneys; pharmacokinetics, rat-to-monkey interspecies scaling and extrapolation to humans. *Fund Appl Toxicol* 17: 409-428.

CIIT (Chemical Industry Institute of Toxicology). 1999. MPPDep V1.1, developed by CIIT in collaboration with the National Institute of Public Health and the Environment (RIVM), the Netherlands and the Ministry of Housing, Spatial Planning and the Environment, the Netherlands.

Clewell, HJ, Andersen ME, Barton HA. 2002. A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. *Env HIth Persp* 110: 85 -93.

Cocks AT, McElroy WJ. 1984. Modelling studies of the concurrent growth and neutralisation of sulphuric acid aerosols under conditions in the human airways. *Env Res* 35: 79-96.

Crump KS. 1984. A new method for determining allowable daily intakes. *Fund Appl Toxicol* 4: 854-871.

Crump KS. 1995. Calculation of benchmark dose from continuous data. *Risk Anal* 15:79-89.

Davidson IW, Parker JC, Beliles RP. 1986. Biological basis for extrapolation across mammalian species. *Reg Toxicol Pharmacol* 6: 211-237.

DeSesso JM. 1993. The relevance to human of animal models for inhalation studies of cancer in the nose and upper airways. Quality assurance: good practice regulation and law 2: 213-231.

Dieter MP, Goehl TF, Jameson CW, Elwell MR, Hildebrandt PK, Yuan JH. 1993. Comparison of the toxicity of citral in F344 rats and B6C3F1 mice when administrated by microencapsulation in feed or by corn-oil gavage. *Fd Chem Toxic* 31: 463-474.

Dourson ML, Felter SP. 1997. Route-to-route extrapolation of the toxic potency of MTBE. *Risk Anal* 17: 717-725.

Dourson ML, Stara JF. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Reg Toxicol Pharmaco*l 3: 224-238.

Dutch Health Council. 1985. Advice on starting points for standard setting: The explanatory derivation of recommended values for non-mutagenic, non-carcinogenic and non-immunotoxic substances. Health Council Report No 31 (in Dutch). The Hague, The Netherlands.

EC (European Commission). 1993. Commission Directive (EEC) No. 93/67 laying down the principles for assessment of risks to humans and the environment of substances notified in accordance with Council Directive 67/548/EEC. *OJ Eur Comm* L227, 9.

EC (European Commission). 1994. Commission Regulation (EC) No. 1488/94 laying down the principles for the assessment of risks to humans and the environment of existing substances in accordance with Council Regulation (EEC) No. 793/93. *OJ Eur Comm* L161, 3-11.

EC (European Commission). 1996. Technical guidance document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances. Office for Official Publications of the EC, Luxembourg.

EC (European Commission). 2001. White Paper. Strategy for a future chemicals policy. COM(2001)88 final.

ECETOC. 1993. Percutaneous absorption. Monograph No. 20.

ECETOC. 1995. Assessment factors in human health risk assessment. Technical Report No. 68.

ECETOC. 2002a. Use of human data in hazard classification for irritation and sensitisation. Monograph No. 32.

ECETOC. 2002b. Recognition of, and differentiation between, adverse and non-adverse effects in toxicology studies. Technical Report No. 85.

EPA (Environmental Protection Agency). 1991. Guidelines for developmental toxicity risk assessment. *Fed Reg* 56:63798-63826.

EPA (Environmental Protection Agency). 1992. A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg/day. *Fed Reg* 57: 24152-24173.

EPA (Environmental Protection Agency). 1993. Reference Dose (RfD): Description and use in health risk assessments. Available online at http://www.epa.gov/iris.

EPA (Environmental Protection Agency). 1995. The use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007.

EPA (Environmental Protection Agency). 1996. Benchmark dose technical guidance document. External review draft. EPA/600/P-96/002A.

EPA (Environmental Protection Agency). 2000a. Draft benchmark dose technical guidance document. *Fed Reg* 65: 69772-69773.

EPA (Environmental Protection Agency). 2000b. Benchmark dose technical guidance document. External review draft. EPA / 630 / R-00 / 001.

Fairhurst S. 1995. The uncertainty factor in the setting of occupational exposure standards. *Ann Occup Hyg* 39: 375-385.

Faustman EM, Allen BC, Kavlock RJ, Kimmel CA. 1994. Dose-response assessment for developmental toxicity. I. Characterization of database and determination of no observed adverse effect levels. *Fund Appl Toxicol* 23: 478-486.

Feron VJ, van Bladeren PJ, Hermus RJ. 1990. A viewpoint on the extrapolation of toxicological data from animals to humans. *Food Chem Toxic* 28: 783-788.

Fowles JR, Alexeeff GV, Dodge D. 1999. The use of benchmark dose methodology with acute inhalation lethality data. *Reg Toxicol Pharmacol* 29: 262-278.

Frederick CB, Bush ML, Lomax LG, Black KA, Finch L, Kimbell JS, Morgan KT, Subramaniam RP, Morris JB, Utman JS. 1998. Application of a hybrid computational flud dynamics and physiologically based inhalation mode for interspecies dosimetry extrapolation of acidic vapors in the upper airways. *Toxicol Appl Pharmacol* 152: 211-231.

Frederick CB, Udinsky JR, Finch L. 1994. The regional hydrolysis of ethylacrylate to acrylic acid in the rat nasal cavity. *Toxicol Letters* 70: 49-56.

Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE. 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and human. *Cancer Chemo Reports* 50: 219-245.

Garte S, Zocchetti C, Taioli E. 1997. Gene-environment interactions in the application of biomarkers of cancer susceptibility in epidemiology. In Applications of biomarkers in cancer epidemiology. IARC Scientific Publications 142, 251-264. International Agency for Research on Cancer, Lyon, France.

Gaylor DW. 2000. New issues in cancer risk assessment. *Drug Metab Revs* 32: 187-192.

Gaylor DW, Chen JJ. 1996. Precision of benchmark dose estimates for continuous (nonquantal) measurements of toxic effects. Reg Toxicol Pharmacol 24: 19-23.

Gaylor DW, Gold LS. 1998. Regulatory cancer risk assessment based on a quick estimate of a benchmark dose derived from the maximum tolerated dose. *Reg Toxicol Pharmacol* 28: 222-225.

Gaylor DW, Kodell RL, Chen JJ, Krewski D. 1999. A unified approach to risk assessment for cancer and noncancer endpoints based on benchmark doses and uncertainty / safety factors. *Reg Toxicol Pharmacol* 29: 151-157.

Gaylor DW, Ryan L, Krewski D, Zhu Y. 1998. Procedures for calculating benchmark doses for health risk assessment. *Reg Toxicol Pharmacol* 28: 150-164.

Gibson MC, deMonsabert SM, Orme-Zavaleta J. 1997. Comparison of noncancer risk assessment approaches for use in deriving drinking water criteria. *Reg Toxicol Pharmacol* 26: 243-256.

Green T. 1996. The metabolism of methyl methacrylate in the nasal tissues of rat and human. Central Toxicology Laboratory, Cheshire, UK.

Gross EA, Swenberg JA, Fields S, Popp JA. 1982. Comparative morphometry of the nasal cavity in rats and mice. *J Anat* 135: 83-88.

Hart WL, Reynolds RC, Krassavage WJ, Ely TS, Bell RH, Raleigh RS. 1988. Evaluation of developmental toxicity data: a discussion of some pertinent factors and a proposal. *Risk Anal* 8: 59-69.

Hattis D, Banati P, Goble R, Burmaster DE. 1999. Human interindividual variability in parameters related to health risks. *Risk Anal* 19: 711-726.

Hattis D, Erdreich L, Ballew M. 1987. Human variability in susceptibility to toxic chemicals – a preliminary analysis of pharmacokinetic data from normal volunteers. *Risk Anal* 7: 415-426.

Hattis D, Silver K. 1994. Human interindividual variability – a major source of uncertainty in assessing risks for noncancer health effects. *Risk Anal* 14: 421-431.

Hébert CD, Yuan J, Dieter MP. 1994. Comparison of the toxicity of cinnamaldehyde when administered by microencapsulation in feed or by corn oil gavage. *Fd Chem Toxic* 32: 1107-1115.

ILSI (International Life Sciences Institute). 2000. The relevance of the rat lung response to particle overload for human risk assessment. A workshop consensus report. *Inhal Toxicol* 12: 1-17.

IPCS (International Programme on Chemical Safety). 1994. Environmental Health Criteria 170. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. WHO / UNEP / ILO.

IPCS (International Programme on Chemical Safety). 1999. Environmental Health Criteria 210. Principles for the assessment of risks to human health from exposure to chemicals. WHO, Geneva.

Johnson NF, Hotchkiss JA, Harkema JR, Henderson RF. 1990. Proliferative responses of rat nasal epithelia to ozone. *Tox Appl Pharmacol* 103: 143-155.

Kadry AM, Skowronski GA, Abdel-Rahman MS. 1995. Evaluation of the use of uncertainty factors in deriving RfDs for some chlorinated compounds. *J Toxicol Env Hlth* 45: 83-95.

Kalberlah F, Schneider K. 1998. Quantification of extrapolation factors. Research project No. 116 06 113. Federal Environmental Agency. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Berlin.

Kavlock RJ, Allen BC, Faustman EM, Kimmel CA. 1995. Dose-response assessments for developmental toxicity. IV. Benchmark doses for fetal weight changes. *Fund Appl Toxicol* 26: 211-222.

Kavlock RJ, Schmid JE, Setzer RW. 1996. A simulation study of the influence of study design on the estimation of benchmark doses for developmental toxicity. *Risk Anal* 16: 399-410.
Kimmel CA, Gaylor DW. 1988. Issues in qualitative and quantitative Risk Anal for developmental toxicology. *Risk Anal* 8: 15-20.

Kramer HJ, van den Ham WA, Slob W, Pieters MN. 1996. Conversion factors estimating indicative chronic no-observed-adverse-effect levels from short-term toxicity data. *Reg Toxicol Pharmacol* 23: 249-255.

Krewski D, Zhu Y, Fung KY. 1999. Benchmark doses for developmental toxicants. *Inhal Toxicol* 11: 579-591.

Kulle TJ. 1993. Acute odor and irritation response in healthy nonsmokers with formaldehyde exposure. *Inhal Toxicol* 5: 323-332.

Lewis SC, Lynch JR Nikiforov AI. 1990. A new approach to deriving community exposure guidelines from "no-observed-adverse-effect levels". *Regul Toxicol Pharmacol* 11: 314-330.

Lewis JL, Nikula KJ, Novak R, Dahl AR. 1994. Comparative localization of carboxylesterase in F344 rat, beagle dog and human nasal tissue. *Anatom Rec* 239: 55-64.

Lumley CE, Walker SR. 1986. A critical appraisal of chronic animal toxicity studies. *Reg Tox Pharmacol* 6, 66-72.

Lumley CE, Parkinson C, Walker SR. 1992. An international appraisal of the minimum duration of chronic animal toxicity studies. *Human Exptl Toxicol* 11: 155-162.

McClain RM. 1989. The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: Implicatins for thyroid gland neoplasia. *Toxicol Pathol* 17: 294-306.

McNamara BP. 1976. Concepts in health evaluation of commercial and industrial chemicals. In Mehlman MA, Shapiro RE, Blumenthal H, eds. *Advances in Modern Technology Vol 1. New Concepts in Safety Evaluation*. Washington ,DC, pp 61-140.

Mantovani A, Maranghi F, Ricciardi C, Macri C, Stazi AV, Attias L, Zapponi GA. 1998. Developmental toxicity of carbendazim: comparison of no-observed-adverse-effect level and benchmark dose approach. *Fd Cosmet Toxic* 36: 37-45.

Martonen TB, Zhang Z, Yang Y. 1992. Interspecies modeling of inhaled particle deposition patterns. *J. Aerosol Sci* 23: 389-406.

Menache MG, Hanna LM, Gross EA, Lou SR, Zinreich J, Leopold DA, Jarabek AM, Miller FJ. 1997. Upper respiratory tract surface areas and volumes of laboratory animals and humans: consideration for dosimetry models. *J Toxicol Environ HIth* 50: 475-506.

Miller RR, Ayres JA, Jersey GC, McKenna MJ. 1981. Inhalation toxicity of acrylic acid. *Fund Appl Toxicol* 1: 271-277.

Morgan KR, Gross EA, Joyner D, Mery S. 1995. Mapping of lesions in the nose provides insight into mechanism of action of nasal toxicants. *CIIT Activities* 15: 1-2.

Murrell JA, Portier CJ, Morris RW. 1998. Characterizing dose-response 1:critical assessment of the benchmark dose concept. *Risk Anal* 18: 13-26.

Naumann BD, Weideman PA. 1995. Scientific basis for uncertainty factors used to establish occupational exposure limits for pharmaceutical active ingredients. *Hum Ecol Risk Assess* 1: 590-613.

Negus, V. 1958. *The comparative anatomy and physiology of the nose and paranasal sinuses*. E & S Livingstone, London.

Nessel CS, Lewis SC, Stauber KL, Adgate JL. 1995. Subchronic to chronic exposure extrapolation: toxicologic evidence for a reduced uncertainty factor. *Hum Ecol Risk Assess* 1: 516-526.

Pease W, Vandenberg, J, Hooper K. 1991. Comparing alternative approaches to establishing regulatory levels for reproductive toxicants: DBCP as a case study. *Environ HIth Perspec* 91: 141-155.

Pepelko WE. 1987. Feasibility of route extrapolation in risk assessment. *B J Ind Med* 44: 649-651.

Pepelko WE, Withey JR. 1985. Methods for route-to-route extrapolation of dose. *Toxicol Ind HIth* 1: 153-170.

Pieters MN, Kramer HJ, Slob W. 1998. Evaluation of the uncertainty factor for subchronic-to-chronic extrapolation: statistical analysis of toxicity data. *Reg Toxicol Pharmacol* 27: 108-111.

Pohl HR, Abadin HG. 1995. Utilizing uncertainty factors in minimal risk levels derivation. *Reg Toxicol Pharmacol* 22: 180-188.

Proctor DF, Chang JCF. 1983. Comparative anatomy and physiology of the nasal cavity. In Feron VJ, Bosland MC, eds, *Nasal tumours in animals and humans, vol 1*. CRC Press, Florida.

Renwick AG. 1991. Safety factors and establishment of acceptable daily intakes. *Food Add Contam* 8: 135-150.

Renwick AG. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Add Contam* 15: 17-35.

Renwick AG, Lazarus NR. 1998. Human variability and noncancer risk assessment. An analysis of the default uncertainty factor. *Reg Toxicol Pharmacol* 27: 3-20.

Rulis AM, Hattan DG. 1985. FDA.s priority based assessment of food additives. II: General toxicity parameters. *Reg Toxicol Pharmacol* 5: 152-174.

Sarangapani R, Wexler AS. 1996. Growth and neutralisation of sulfate aerosols in human airways. *J Appl Physio* 81: 480-490.

Schein PS, Davis RD, Carter S, Newman J, Schein DR, Rall DP. 1979. The evaluation of anticancer drugs in dogs and monkeys for the prediction of qualitative toxicities in humans. *Clin Pharmacol Therap* 11: 3-40.

Sorokin SP. 1988. The respiratory system. In Weiss L, ed, Cell and Tissue Biology, 6th ed. Urban and Schwarzenberg, Baltimore.

Spielmann H, Gerbracht U. 2001. The use of dogs as second species in regulatory testing of pesticides. Part ll: subacute, subchronic and chronic studies in the dog. *Arch Toxicol* 75: 1-21.

Szymczak W. 1998. Zastosowanie modeli BMD w ilościowej ocenie ryzyka kancerogennego. *Medycyna Pracy* XLIX: 579-587.

Tarasenko NY, Pronin OA, Silayev AA. 1977. Barium compounds as industrial poisons (an experimental study). *J Hyg Epidem Microbiol Immuno* 21: 361-373.

Travis CC, White RK. 1988. Interspecies scaling of toxicity data. *Risk Anal* 8: 119-125.

Travis CC, White RK, Ward RC. 1990. Interspecies extrapolation of pharmacokinetics. *J Theor Biol* 142: 285-304.

Van der Gevel IA, Hakkert BC. 1997. Methods of interspecies extrapolation, an evaluation. *TNO Nutrition and Food Research Institute report* V97.529. The Netherlands.

Verberk MM. 1977. Effects of ammonia in volunteers. *Int Arch Occup Environ Hlth* 39: 73-81.

Vermeire TG, Stevenson H, Pieters MN, Rennen M, Slob W, Hakkert BC. 1999. Assessment factors for human health risk assessment: a discussion paper. *Crit Rev Toxicol* 29:439-490.

Voisin EM, Ruthsatz M, Collins JM, Hoyle PC. 1990. Extrapolation of animal toxicity to human; interspecies comparisons in drug development. *Reg Toxicol Pharmacol* 12: 107-116.

Warner A. 1986. Drug use in the neonate: interrelationships of pharmacokinetics, toxicity and biochemical maturity. *Clin Chem* 32: 721-727.

Watanabe K, Bois FY, Zeise L. 1992. Interspecies extrapolation: a re- examination of acute toxicity data. *Risk Anal* 12: 301-310.

Weil CS, McCollister DD. 1963. Relationship between short- and long-term feeding studies in designing an effective toxicity test. *J Ag Fd Chem* 11: 486-491.

West GB, Brown JH, Enquist BJ. 1997. A general model for the origin of allometric scaling laws in biology. *Sci* 276: 122-126.

West GB, Brown JH, Enquist BJ. 1999. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Sci* 284: 1677-1679.

WHO (World Health Organization). 1999. Environmental Health Criteria 210. Principles for the assessment of risks to human health from exposure to chemicals. WHO, Geneva.

Woutersen RA, Til HP, Feron VJ. 1984. Sub-acute versus sub-chronic oral toxicity study in rats: comparative study of 82 compounds. *J Appl Toxicol* 4: 277-280.

Woutersen RA, Jonker D, Stevenson H, te Biesebeek JD, -3q3Slob W. 2001. The benchmark approach applied to a 28-day toxicity study with Rhodorsil Silane in rats: the impact of increasing the number of dose groups. *Fd Chem Toxic* 39: 697-707.

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ADME	Absorption, distribution, metabolism, excretion
AUC	Area under the curve
BATNEEC	Best available technology not entailing excessive cost
BMD	Benchmark dose
CFD	Computational fluid dynamics
DAF	Dose adjustment factor
DNA	Deoxyribonucleic acid
GM	Geometric mean
GSD	Geometric standard deviation
HBORV	Health based occupational reference value
HBROEL	Health based recommended occupational exposure limit
LD_{10}	Dose calculated to be lethal to 10% of organisms
LOAEL	Lowest observed adverse effect level
MCS	Multiple chemical sensitivity
MMA	Methyl methacrylate
MMAD	Mass median aerodynamic diameter
MTBE	Methyl tert-butyl ether
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
OEL	Occupational exposure limit
P95	95th percentile

PBPK	Physiologically-based pharmacokinetic
pKa	Acid disscociation constant, expressing ratio of ionised and unionised forms of a substance in water at equilibrium
(Q)SARs	(Quantitative) structure activity relationships
RD_{50}	Decrease of 50% in respiratory rate
RfC	Reference dose calculation, inhalation
RfD	Reference dose calculation, oral
STEL	Short-term exposure limit
TDI	Tolerable daily intake
TLV	Threshold limit value
TRC	Threshold of regulatory concern
TTC	Threshold of toxicological concern
TWA	Time weighted average

APPENDIX A: GENERAL PRACTICE OF RISK ASSESSMENT

As defined by the US National Academy of Sciences paradigm (NAS, 1983) and used generally by several regulatory and international bodies, the four distinct and essential components of risk assessment are:

- Hazard identification;
- dose-response assessment;
- exposure assessment;
- risk characterisation.

The final step of risk characterisation involves the integration of information on the hazard, dose response and exposure. For the majority of chemicals to which humans may be exposed, a wide range of data on possible effects on humans is often available. The data include human experience from the workplace, data from epidemiological studies, and information from physicians' reports or human volunteer studies. Such data are typically of varying quality and completeness and are more often seen as complementary to data from animal studies (ECETOC, 2002a). Therefore, the question of how to extrapolate the results of laboratory studies to humans in a meaningful manner has become an important aspect of risk characterisation.

A.1 The 'safety factor' approach

The starting point for extrapolation involves compiling hazard identification and dose-response data obtained from toxicology studies conducted in laboratory animals. Of necessity, these are performed at high doses, typically ranging from a dose that produces adverse effects, which may be a maximum tolerated dose (MTD), to a dose below that which is the 'no observed adverse effect level' (NOAEL). The results from these animal studies are then extrapolated on the basis of judgements made on the effects expected to occur in humans.

Historically, the so-called 'safety factor' approach was introduced in the USA in the mid-1950s in response to legislative needs in the area of the safety of chemical food additives (Lehman and Fitzhugh, 1954). This approach proposed that the chemical additive should not occur in the total human diet in a quantity greater than 1/100 of the amount that is a maximum safe dose in long-term animal experiments. The authors considered that this approach was a good target but not an absolute yardstick and believed it would provide a reasonable safeguard to minimise the danger of adverse effects arising in humans. Based on this 'safety margin' approach of Lehman and Fitzhugh, the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) developed the concept of the Acceptable Daily Intake (ADI). The ADI is defined as "an estimate of the amount of food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk". Thus, a long-term animal NOAEL expressed (in mg/kg diet) divided by 100, provided the ADI for humans. The 100-fold safety factor as proposed by Lehman and Fitzhugh was based on a limited analysis of subchronic/chronic data on fluorine and arsenic in

rats, dogs and humans, and also on the assumption that "the human population as a whole is heterogeneous". The fraction of the population expected to be protected by the 100-fold factor also remains unclear. Several authors have considered this factor as arbitrary (Vermeire *et al*, 1999). Nevertheless, since its introduction, there have been a number of studies that undertook a retrospective assessment of its validity (Dourson and Stara, 1983; Renwick 1991, 1993; Renwick and Lazarus, 1998).

The 100-fold safety factor was later understood to comprise a factor of 10 for the hypothesised increased sensitivity of humans relative to laboratory test animals (interspecies variability) and an additional factor of 10 for the presumed range in biological sensitivity found in the human population (intraspecies variability). Although slightly different rationales for the 100-fold factor were given by various authors (Lehman and Fitzhugh, 1954; Bigwood, 1973; Lu, 1979; Vettorazzi, 1976, 1980), the safety factor is considered to account for both inter- and intra-species variabilities (Dourson and Stara, 1983).

The 100-fold safety factor has been adopted into guidelines and recommendations by several international agencies and governmental bodies. There are numerous publications providing additional perspectives on the 100-fold factor and on other 'factors' which may be used in place of or in addition to the original 'safety factor' for the extrapolation of animal data to humans. Depending on the authors or agencies, these factors are referred to variously as safety, assessment, adjustment or uncertainty factors. In this ECETOC report, the term 'assessment factor' is used. Essentially, these factors are used in numerical approaches to account for uncertainty and variability. In practice, they are applied normally to a NOAEL or its substitute to derive a safe dose for humans. The selection and justification of the applied factors have been reviewed for food additives and environmental exposures to industrial and agricultural chemicals (Dourson and Stara, 1983; Lu, 1979).

A.2 Occupational versus non-occupational approaches

Two distinct approaches for the risk assessment of chemical exposures in the occupational and non-occupational settings have evolved over several decades, and each has become well established in its own field. While the classical 'safety factor' approach (Section 1.2) has often been adopted in the non-occupational setting, the establishment of Occupational Exposure Limits (OELs) has not involved consistently the application of such factors to NOAELs. The use of 'safety factors' in determining OELs has been reviewed by Illing (1991), Galer *et al* (1992), Fairhurst (1995) and, specifically for developmental toxicity endpoints, by Hart *et al* (1988). The approaches currently used by various national and international agencies for developing exposure limits for occupational and non-occupational settings are described in Appendix B.

The same general process should be used to assess risk in the occupational and non-occupational settings; the approach should be consistent but sufficiently flexible to allow the possibility of different outcomes, reflecting for example, different populations.

This report does not address any potential risks in either the occupational or non-occupational settings that may occur from acute exposures as a result of an accident. In such cases, the risk assessment should be conducted on a case-by-case basis, since the application of generic assessment factors may not be appropriate.

A.3 Non-threshold effects

For most toxicological endpoints, it is generally agreed that there is a threshold below which no adverse effect occurs. For some substances it is difficult to define a 'threshold level', particularly where the mechanism of action for those substances is not considered to involve a threshold step. The risk assessment of such substances presents several challenges that are beyond the scope of this report. While some may consider the use of assessment factors in such cases, the Task Force recommends that a decision to use such an approach be made on a case-by-case basis.

A.4 Risk management

The general practice of assessment of risk for human health covers the assembly and interpretation of all relevant hazard and exposure information, which enable the risk assessor in the risk characterisation step to define the risks for humans. Subsequently, the risk assessor together with the risk manager can evaluate whether the predicted risks are of concern or not and whether measures for risk reduction need to be considered. Alternatively, the information can be used to establish acceptable exposure limits for humans including OELs and short-term exposure limits (STELs).

Risk assessment and risk management must be conducted as two related but separate processes. The former is based on scientific principles exclusively, while the other takes into account additional factors including socio-economics, technical feasibility (e.g. Best Available Technology Not Entailing Excessive Cost; BATNEEC), societal perceptions and expectations, governmental policy and government and industry standards.

BIBLIOGRAPHY: APPENDIX A

Bigwood EJ. 1973. The acceptable daily intake of food additives. *CRC Crit Rev Toxicol*: 41-93.

Dourson ML, Stara JF. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Reg Toxicol Pharmacol* 3: 224-238.

ECETOC. 2002a. Use of human data in hazard classification for irritation and sensitisation. Monograph No. 32.

Fairhurst S. 1995. The uncertainty factor in the setting of occupational exposure standards. *Ann Occup Hyg* 39: 375-385.

Galer DM, Leung HW, Sussman RG, Trzos RJ. 1992. Scientific and practical considerations for the development of occupational exposure limits (OELs) for chemical substances. *Reg Toxicol Pharmacol* 15: 291-306.

Hart WL, Reynolds RC, Krassavage WJ, Ely TS, Bell RH, Raleigh RS. 1988. Evaluation of developmental toxicity data: a discussion of some pertinent factors and a proposal. *Risk Anal* 8: 59-69.

Illing HP. 1991. Extrapolating from toxicity data to occupational exposure limits: some considerations. *Ann Occup Hyg* 35: 596-580.

Lehman AJ, Fitzhugh OG. 1954. 100-fold margin of safety. *Assoc Food Drug Off US Bull* 18: 33-35.

Lu FC. 1979. Assessment at an international level of health hazards to humans of chemicals shown to be carcinogenic in laboratory animals. In Coulston EF, ed, *Reg Asp Carcin*. Academic Press, New York, pp 315-328.

NAS (National Academy of Science). 1983. Committee on the Institutional Means for Assessment of Risks to Public Health Risk Assessment in the Federal Government: Managing the process. National Academy Press, Washington DC, pp 1-50.

Renwick AG. 1991. Safety factors and establishment of acceptable daily intakes. *Food Add Contam* 8: 135-150.

Renwick AG. 1993. Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Add Contam* 10: 275-305.

Renwick AG, Lazarus NR. 1998. Human variability and noncancer risk assessment. An analysis of the default uncertainty factor. *Reg Toxicol Pharmacol* 27: 3-20.

Vermeire TG, Stevenson H, Pieters MN, Rennen M, Slob W, Hakkert BC. 1999. Assessment factors for human health risk assessment: a discussion paper. *Crit Rev Toxicol* 29:439-490.

Vettorazzi G. 1976. Safety factors and their application in the toxicological evaluation. In *The evaluation of toxicological data for the protection of public health*. Pergamon Press, Oxford, pp 207-223

Vettorazzi G. 1980. *Handbook of International Food Regulatory Toxicology Vol 1: Evaluations*. Spectrum, New York, pp 66-68.

APPENDIX B: EXISTING APPROACHES

The general principle of extrapolation from a hazard dataset derived from one or more test species to describe the risk for humans is well established. Several regulatory agencies and non-regulatory scientific organisations have adopted approaches that can be divided broadly into those developed for protection of the general public (non-occupational approaches) and those for protection of the worker population (occupational approaches).

B.1 Non-occupational approaches

B.1.1 General principles and current practices

In non-occupational approaches to risk assessment, a number of structured schemes have been developed, most involving the application of uncertainty factors to the lowest (appropriate) animal NOAEL to derive a human TDI (Tolerable Daily Intake).

Current approaches adopted by the WHO International Programme for Chemical Safety (IPCS), the EC Scientific Committee on Food, the respective agencies in Germany and in The Netherlands, and the approach of the US Environmental Protection Agency (EPA) are described below.

B.1.1.1 IPCS approach

IPCS has produced guidelines for the derivation of guidance values for health-based exposure limits. An approach similar to that designed for setting ADIs for food additives was proposed by Renwick (1991, 1993) and Renwick and Lazarus (1998) which attempted to provide a scientific basis for the default values of 10 used to account for each of the interspecies and interindividual (intraspecies) differences in extrapolating from animal to human.

When determining a value for interspecies and intraspecies differences, all appropriate animal and human scientific data that are available are considered towards reducing or increasing the traditional default of 10. To achieve this, each of these two elements (inter- and intra-species factor) is subdivided into toxicokinetics and toxicodynamics.

- Toxicokinetics: absorption, distribution, metabolism and elimination of the substance, to and from the site of toxicity;
- toxicodynamics: activity or potency of the substance at the site of toxicity.

Correction factors are applied to each area when data are available.

For the interspecies differences, toxicokinetic data including absorption or bioavailability, distribution, rate of metabolism and elimination, with data such as peak blood concentrations, area under the curve (AUC) is considered, while toxicodynamic data includes identification of active metabolite, nature of target tissue, repair mechanisms, and sensitivity of target tissue (*in vitro*).

Research has indicated that the potential is greater for differences between common laboratory animals and humans in toxicokinetics than in toxicodynamics and that therefore an equal split of the default of 10 between the two factors was not appropriate. Instead default values of 4 and 2.5 were assigned for kinetic and dynamic differences respectively, based on the data currently available on several compounds and also on physiological differences between test species and humans.

For intraspecies differences, toxicokinetic and toxicodynamic data in a wide representative sample of the general population are necessary. The differences in kinetics may vary widely and those individuals with values for a kinetic parameter higher than the mean must be taken into account. Renwick (1991, 1993) originally proposed that the human intraspecies factor of 10 should be divided into 4 for kinetic differences and 2.5 for dynamic differences. However, IPCS (1994) considered that the variability for both aspects of intraspecies variation (toxicokinetic and toxicodynamic) was similar and concluded that the 10-fold safety factor should be split evenly into 3.2 for kinetics and 3.2 for dynamics. Renwick and Lazarus (1998) subsequently supported this by analysing a more extensive database (mainly on pharmaceutical products) on human variability. It was concluded that the 10-fold default was appropriate in most circumstances. The numbers and groups falling outside of this were dependent on the statistics used but could include the elderly and patients with disease. However, children and infants (but not neonates) were not regarded as a special group as they would be adequately covered by the normal adult factors applied (Renwick, 1998). The slightly greater variability in dynamic data was not sufficient to warrant unequal subdivision of the 10-fold factor and therefore, the default factors should be 3.2 for both toxicokinetics and toxicodynamics. Renwick also proposed refinements to the process of determining assessment factors, although work is still underway to determine suitable defaults for more specific areas.

In the absence of suitable data, the default of 10 remains for each of the interspecies and intraspecies factors, giving a total of 100. Further, additional factors could be added into the total uncertainty factor to account for the nature of the toxicity and the adequacy of the database. Use of additional factors must be decided on a case-by-case basis. These values may be selected from a continuous scale 1 to 100 and a factor of less than 1 is possible if data exist to show that humans are less sensitive than the experimental species.

Table 10: Summary of IPCS approach

	Toxicokinetics	Toxicodynamics
Interspecies uncertainty	4	2.5
Intraspecies uncertainty	3.2	3.2

While the approach proposed by IPCS appears simple and scientifically based, there are insufficient examples and advice as to the suitability of the type of data that can be used to assign the various elements of the assessment factors. Use of this approach has been infrequent and is subjective. The approach was used by IPCS recently in the review of boron where the overall uncertainty factor applied was 25, based on interspecies similarities, such as metabolism, absorption, elimination, and slight differences in boron blood levels after dosing (IPCS, 1998). However, using the same IPCS guidelines, a WHO working group meeting on chemical substances in drinking water, subsequently used a factor of 60 based only on the intraspecies kinetics data considering renal clearance data in humans (WHO, 1998).

B.1.1.2 EC Scientific Committee on Food

The EC Scientific Committee on Food (SCF, 1995) developed principles with regard to substances migrating from food packaging into food. The SCF criteria for the evaluation of substances are provided in Annex 4 of their document. For substances migrating into food at levels below 0.05mg / kg food, only mutagenicity data are required. This level of 0.05mg / kg food corresponds to an intake of 0.8ug / kg bw / day and the current SCF document adjusts this dose to 1ug / kg bw / day (assuming an intake of 1kg food / person / day and a bodyweight of 60kg). This implies that in the absence of any evidence of mutagenicity, an exposure of 0.8ug / kg bw / day is considered to be of no concern (see Appendix B.1.2). At migration levels of 0.05-5mg / kg food (equivalent to 0.8-83ug / kg bw / day and rounded to 1-100ug / kg bw / day by the SCF), a 90-day subchronic study is additionally required, but no longer-term or reproductive toxicity studies are needed. A complete test package is required for migration levels above 5mg / kg including chronic studies and reprotoxicity studies. A TDI is defined only for substances with a complete test package. As a general principle, for the derivation of a TDI, a factor of 100 is applied to a NOAEL from a chronic study, although modifications of this approach are possible depending on the individual dataset.

B.1.1.3 Germany

A basic scheme for setting indicative values for indoor air quality was published by a joint working group of the AUH (Ausschuss für Umwelthygiene; a committee of senior officers of health) and the IRK (Innenraumlufthygiene-Kommission; indoor air hygiene commission of the Umweltbundesamt) in 1996 (Sagunski, 1996). This scheme also includes general measures to be taken if these limits are exceeded.

An indicative limit value RWII (Richtwert II) defines the need for immediate action and is derived from a proven effect (LOAEL). As the RWII is intended for legal purposes, a human LOAEL derived from occupational experience, epidemiological studies or case reports, is given preference to a NOAEL from an animal study. The limit value RWI (Richtwert I) is derived by dividing RWII by 10 and should guarantee no adverse health effects from lifetime exposure.

Different assessment factors are used depending on the data available. If the LOAEL or NOAEL is derived from a study with exposure durations resembling workplace exposure (i.e. 8-h / day, 5 days / week) the exposure is adjusted to 24-h / day and 7 days / week by multiplication by a factor of 5. Where needed, a NOAEL is derived from a LOAEL by using an assessment factor of 3. An intraspecies extrapolation factor of 10 is always used. If animal data are used, an additional interspecies factor of 10 is applied. In special cases where there is concern that sensitive sub-populations, such as young children, may not be protected by such a factor, an additional factor of 2 may be applied.

B.1.1.4 The Netherlands

In the Netherlands, the Dutch Health Council (1985) method is practised. The NOAELs are extrapolated to so-called Human Limit Values by considering the difference in body weight and in addition applying:

- Classical assessment factors of the Joint Expert Committee of Food Additives. In this case an assessment factor of 10 is used for interspecies variation and an additional assessment factor of 10 applied for intraspecies variation;
- interspecies assessment factor on the basis of caloric demand, which might be related to detoxifying processes and an adapted assessment factor for uncertainty. An assessment factor on the basis of $BW^{0.75}$ (BW=body weight) is then used for the interspecies differences with an additional assessment factor of 30, accounting for variations and errors (interspecies, intraspecies and observation errors, respectively 10, 10 and 3) log normally distributed and assembled into:

$$\log (AF) = \sqrt{\log (10)^2 + \log (10)^2 + \log (3)^2} \approx 1.4925 \approx \log (31.1)$$

Overall this is close to using an assessment factor of 100.

Recently (Vermeire *et al*, 1999) proposed a new strategy for assessment factors in deriving Human Limit Values, which has not been generally adopted by the Dutch authorities. This new strategy proposes the following default values for assessment factors to be considered in deriving so-called Human Limit Values.

Table 11: Default values for assessment factors (adapted from Vermeire et al, 1999)

Extrapolation element	Assessment factor
1. Interspecies	3
2. Intraspecies	10
3. Duration of exposure	10
4. Critical Effect	1
5. Dose Response	1
6. Confidence of the database	1

B.1.1.5 US EPA

The approach adopted by the US EPA for assessing the risk of health effects (other than cancer and gene mutation) is based on a threshold concept which assumes that exposure levels can be defined that are unlikely to produce a toxic effect. Originally, this exposure level was referred to as the ADI, but in 1988 EPA proposed the use of Reference Dose (RfD) to reflect that this level is an estimate and to avoid any inference of a strict demarcation between acceptable and unacceptable levels (Barnes and Dourson, 1988). Analogous to the oral RfD, EPA has coined the term "Inhalation Reference Concentration" (RfC) for those effects of the respiratory system or peripheral to the respiratory system when inhalation is the route of concern. Both the RfD and RfC are defined as estimates of a daily exposure (oral and inhalation, respectively) to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects over a lifetime (EPA, 1993, 1994). The RfD is expressed in mg / kg / day while the RfC is expressed in mg / m^3.

The EPA risk assessment process comprises four steps: 1) hazard identification, 2) dose response evaluation, 3) exposure assessment, and 4) risk characterisation. The RfD is derived from the lowest "NO(A)EL" for the critical effect divided by uncertainty factors. The critical effect is identified based on a review of all available data with consideration being given to the type of effect, route and length of exposure producing the effect, study quality, and a weight-of-evidence determination supporting the plausibility of the effect. Unless a specific animal model is identified as being clearly relevant to humans, the NOAEL for the critical effect is generally based on the most sensitive species. This NOAEL is divided by uncertainty factors to account for inter- and intra-species differences with a default value of 100 (i.e. 10 for interspecies and 10 for intraspecies). If the NOAEL is based on human data, then an interspecies factor of 1 may be used. If a NOAEL was not identified for the critical effect or data are not available from a study of an appropriate duration, then an additional uncertainty factor of up to 10-fold may be used to extrapolate a NOAEL from a LOAEL or to extrapolate from subchronic to chronic exposure. An additional modifying factor up to 10-fold may also be used based on scientific uncertainties not covered by the other factors, e.g. number of species tested.

EPA also uses BMD methods to estimate the RfD or RfC (see Annex, Section 3.1).

US Food Quality Protection Act

The Food Quality Protection Act (FQPA; Public Law 104-170) became law in 1996. This act amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA). Among its major provisions, this law mandates EPA to expand its risk assessment approach for food-use pesticides to combine risk from multiple sources of exposure (e.g. dietary, drinking water, residential), assess the cumulative risk of multiple chemicals with a common mechanism of toxicity, and to use an additional 10-fold 'safety' factor if needed to assure protection of infants and children.

The latter provision is of interest especially in the context of this report since the law states that "In the case of threshold effects, …..an additional 10-fold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children…..the administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for infants and children". In the four-step risk assessment process, the implementation of the FQPA safety factor should occur after the data analysis is complete, making a clear distinction between the FQPA safety factor which is in fact a risk management practice and other uncertainty factors used for the derivation of the RfD (www.epa.gov / pesticides / trac / science / determ.pdf). A reference dose, either acute or chronic, modified by an FQPA factor is then referred to as a population adjusted dose.

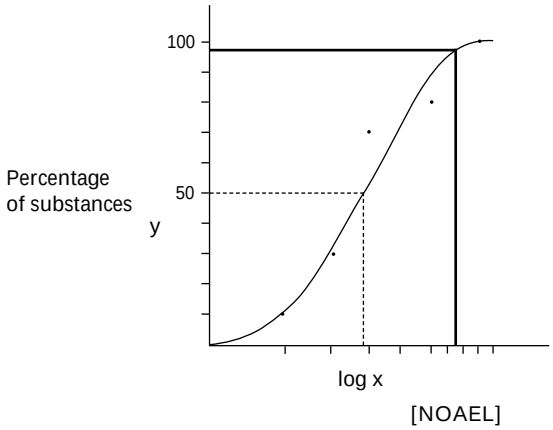
The discussion on how to implement the provisions of FQPA is ongoing and subject to public debate. The Office of Pesticide Programs within EPA is developing science policies in nine areas that are needed to implement FQPA's provisions. These areas cover application of FQPA's 10-fold safety factor, various types of exposure assessments (dietary, water, residential), aggregation of exposures from all non-occupational sources, and cumulative risk assessments for compounds with a common mechanism of toxicity (EPA, 1999). Some of these areas, in particular aggregate exposure and cumulative risk assessments, are resulting in the development of new models.

B.1.2 Threshold of concern at low doses

Going beyond the consideration of individual substance data, a multitude of substances can be pooled in a meta-analysis to derive statistically a threshold of toxicological concern (TTC) value. A TTC is a dose or concentration at which the majority of substances do not affect organisms. In such a meta-analysis, individual studies are combined to define both qualitative and quantitatively possible effects for the plethora of substances. The result obtained will be a dose below which, to a certain probability, no adverse effects will occur. Whereas the TTC conceptualises the scientific basis of the meta-analysis approach, the threshold of regulatory concern (TRC) refers to the legal implementation of the scientific facts; no regulatory concern would be raised based on the *de minimis* principle in order to allocate resources appropriately. Basically, however, TTC and TRC are the same.

Figure 4: Probabilistic approach by meta-anyalysis

For y% of all substances pooled in a meta-analysis no-adverse-effects are observed below a dose x.



Several authors (Rulis, 1986; Cheeseman *et al*, 1999; Kroes *et al*, 2000) have used the Gold carcinogen potency database (which is continuously updated) for systematic investigations. All have come to the conclusion that there is a sound basis for establishing a TTC at 0.5 ppb in the diet, corresponding to 1.5 g / person / day.

Further, meta-analyses have demonstrated that even higher thresholds of concern than 1.5 g / day can be obtained, when substances were considered in certain structurally related classes. For 600 chemicals allocated into three structural classes paralleling anticipated toxic potential, the picture could be refined and a human exposure threshold calculated for each (Munro *et al*, 1996; Munro and Kroes, 1998). For the class of substances presumed to have the highest toxicity setting, a threshold of concern at 1.5 g / person / day was by far sufficient, while for substances with a low anticipated toxicity a 20-fold higher exposure was tolerable. Cheeseman *et al* (1999) defined a threshold of 15 ppb (approximately 45 g / person / day) for substances, which met the following criteria:

- Lack of mutagenicity;
- no structural alerts;
- acute oral toxicity exceeding 1000 mg / kg bw.

The data available to date confirm that different thresholds of concern are needed for different substance classes. For clarity the term 'reduced concern level' (RCL) should be used for the higher threshold level in order to distinguish it from the TTC. This is in alignment with the FDA nomenclature (FDA, 1993). Both the TTC / TRC and the RCL approaches or modifications of these are used in several regulatory frameworks.

Regulatory implementation of 'threshold of concern' concepts

Proposed initially for application in the field of indirect food additives (Frawley, 1967), the threshold of regulatory concern concept has subsequently gained acceptance and was introduced into regulations and considerations in the USA (FDA, 1995). Thus, an indirect food additive present in the total diet at up to 0.5ppb, requires no formal safety evaluation provided that it is not suspected to be a mutagen and/or carcinogen. If exposure exceeds that level, a reduced test programme may become operative for a regulatory submission, depending on the concern level determined (FDA, 1993). Thus, only a reduced data package is required.

Within the EU the TTC/TRC concept has not yet been accepted. RCL approaches, however, are operative in some regulations. Both the EC SCF and the German Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) have set a threshold for tiered toxicity tests. The SCF has suggested a tiered testing requirement for indirect additives present in foodstuffs (SCF, 1990, 2000). Thus, for a chemical present in food at 50ppb or less, only *in vitro* mutagenicity is required. With a daily intake of 1kg of food and a body mass of 60kg, this corresponds to a daily dose of approximately 1 g/kg bw (see Appendix B.1.1.2). The dose of 1 g/kg bw is also used as a threshold for assessing the need for toxicity testing by the BgVV in their approach for assessing the safety of textile processing aids (BgVV, 1996). The BgVV also requires data on skin sensitisation, where dermal contact is anticipated.

B.2 Occupational approaches

B.2.1 General principles and current practices

In the late 1930s and early 1940s, two factors came together to provide the genesis of the concept of occupational exposure limits (OELs). These were the relatively new discipline of industrial hygiene, seeking ways of applying the principle that 'prevention is better than cure', and the developments in analytical methodology and instrumentation, which made measurement of exposure in the workplace a practical proposition. These developments led to the need for quantitative criteria against which to judge the acceptability of measured exposure levels and the concept of Threshold Limit Values (TLVs) began to be developed under the auspices of the American Conference of Governmental Industrial Hygienists (ACGIH). Over the following decades the concept of OELs developed steadily and is now enshrined in the occupational health legislation of most developed countries. Apart from the ACGIH TLV system, a number of other approaches to OEL setting have been developed in industrialised countries. These have been extensively reviewed (Alexiadis, 1990).

The aim of these various approaches for setting OELs is to attempt to identify the highest level of exposure to which workers can be occupationally exposed (typically assuming 8-hr / day, 5 day working week) without experiencing adverse health effects. In all approaches an expert group evaluates the relevant data, recommends an OEL and may or may not publish details of the evaluation. Although there is considerable variation in the quality and degree of detail published, there is a steady trend towards greater 'transparency', permitting easier identification of the logic path followed in each case. In general, the following steps are common in all approaches:

1. Assemble all available data on the hazards of the substance.
2. Determine whether the database is adequate for setting an OEL.
3. Identify the adverse effects that may arise from exposure to the substance.
4. Establish the critical adverse effect(s) for deriving the OEL.
5. Identify and review the quality of the relevant studies (human or animal) that characterise the key effect(s).
6. Establish whether the substance acts via a non-threshold mechanism or whether a threshold model can be used.
7. Assess the dose-response data for each key effect. Establish NOAELs where possible, or if necessary, establish LOAELs.
8. Decide whether a STEL is required in addition to an 8-hr time weighted average (TWA) limit.
9. Establish an 8-hr TWA OEL at or below the NOAEL (or LOAEL), incorporating the appropriate assessment factor.
10. Establish a numerical STEL value (if required).
11. Document the entire process, such that the rationale for the OEL is clear.

The procedure followed for setting exposure limits in the occupational situation generally involves moving directly from the database (NOAEL or LOAEL) to an OEL without the intermediate definition of a specific 'assessment factor'. In this respect it differs from the procedures adopted for the establishment of ADIs. It is nevertheless possible, where the documentation is sufficiently 'transparent', to infer what 'assessment factors' have been applied by comparing the values of established OELs with those of the relevant NOAEL / LOAELs.

For example, in the UK, the Health and Safety Executive (HSE) has carried out a retrospective analysis of Occupational Exposure Standards (OESs) (equivalent to OELs) established for 24 substances in the UK since 1990 (Fairhurst, 1995). This review indicated 'assessment factors' in the range of 1-10 for most substances where the database was from animal studies (higher factors applied in a few cases where the nature of the critical effect called for more caution). Factors of 1-2 were applied where the database was derived from human evidence.

In the USA the process is relatively transparent with various groups defining OELs generally based on the approach described above. The magnitude of the assessment factors used depends upon the quantity, quality and type of data available. The total assessment factor may range from 1, for chemicals with extensive hazard data in humans, up to 1000 or more, with 100 (10 for interspecies and 10 for intraspecies) being the most commonly used.

B.2.1.1 European Union (EU)

The regulatory process for developing OELs in the EU is defined in Council Directive 98/24/EC on the protection of the health and safety of workers related to chemical agents at work ('Chemical Agents Directive'). Under this Directive, the EC can develop OELs to be set at the community level in the form of either Indicative Limit Values (ILVs) or Binding Limit Values (BLVs).

The Scientific Committee on Occupational Exposure Limits (SCOEL) is the scientific advisory group responsible for evaluating available scientific information and recommending substance-specific OELs to the EC. SCOEL has defined its principles and approaches for establishing health-based OELs (SCOEL, 1998).

SCOEL recommends the use of good human data rather than animal data, but recognises that human data are often unavailable or scientifically inadequate. In such cases, the OEL is derived from well-conducted animal studies and the use of assessment factors.

SCOEL has not developed a standard approach for applying assessment factors in deriving OELs; a case-by-case approach is followed. However, several factors are noted as relevant in deriving OELs:

- Working population is less heterogeneous than the general population;
- working population is commonly exposed to chemical substances for 8-hr/day, 5 days/week, 240 days/year for a working lifetime (up to 45 years). This contrasts with daily uptake over a full lifetime, for which ADI values and similar limits for the general population are developed;
- health of workers may be controlled in EU countries by periodic health surveillance and monitoring programmes.

For these reasons SCOEL recognises that, for the development of OELs, it is generally appropriate to apply lower assessment factors than those that are used to develop limit values for the general population. However, they have not established specific assessment factors, other than noting that higher factors are needed when there is less confidence in the toxicological database. Factors are established on a case-by-case basis and documented in their OEL recommendations.

The OELS set by the EC are a reference for the European Member States and national limit values may not exceed these. The limit values must be incorporated into national legislation within 3 years. Most of the European countries have defined a similar methodology to the EC, mainly based on expert judgement. In addition many countries have a consultative Tripartite Committee (representatives from government; workers and employers) to review the OEL before adoption.

Some Member States have defined specific rules to apply assessment factors for setting OELs and these are discussed below.

B.2.1.2 Germany

BK-Tox

For substances with a limited dataset (e.g. only acute and subacute data), the "Beraterkreis Toxikologie" or BK-Tox (an advisory toxicology group of the Committee for Hazardous Working Materials) can establish workplace exposure limits (TRGS 901, 1997). The default assessment factors used by this group are summarised in Table 12.

Table 12: Default assessment factors used by BK-Tox

Extrapolation Element	Default AF
Inter- and intra-species	5*
Study duration (systemic effects):	
- subacute to subchronic	2
- subacute to chronic	6
- subchronic to chronic	2
Study duration (local effects):	
- subacute to subchronic	4
- subacute to chronic	12
- subchronic to chronic	4

* for interspecies extrapolation by oral route, allometric scaling based on metabolic rate is used

Route of exposure extrapolation is considered possible if absorption and metabolism by the oral and inhalation routes are similar. Extrapolation is not possible e.g. for local irritant substances or for substances with very low solubility. Instead, the decision could be based on the comparison of acute oral and inhalation toxicity and known (Q)SARS.

BAuA

The BAuA uses assessment factors in the risk assessment of new substances (BAuA, 1994). The aim of the BAuA approach is a realistic assessment of chronic exposure by inhalation at the workplace, by extrapolating from 'base set' data i.e. in most cases, acute data plus a subacute oral study (28-day study in rats). It comprises three steps, namely, time extrapolation (subacute to chronic), route extrapolation (oral to inhalation) and species extrapolation (rat to man).

For route to route extrapolation it is assumed that:

1 mg / kg / d oral = 5.2, 3.5 or 2.6 mg / m^3 by inhalation, 4, 6 or 8 h / d, respectively.

Route to route extrapolation is used only if the following criteria are met:

- Solubility of the substance in biological media;
- high deposition rate of the inhaled substance;
- no first pass effect dependent on the route of administration;
- similar rates of absorption from oral and inhalation exposure;
- time dependent blood levels are comparable between inhalation and oral exposure;
- critical toxic effect is of a systemic nature.

For species comparison (by inhalation) it is assumed that 1 mg/m^3 (rat) = 1 mg/m^3 (humans).

For interspecies extrapolation, their approach favours the scaling system based on metabolic rate.

For intraspecies extrapolation, the BAuA sees no rationale for a default value. It is considered that the default of 10 commonly used for the general population is too high for populations of workers.

B.2.1.3 The Netherlands

Hakkert *et al* (1996) developed an integrated method for the establishment of Health-Based Recommended Occupational Exposure Limits (HBROELs) for existing substances. Vermeire *et al* (1999) refer to the method of Hakkert *et al* (1996), but use the term Health Based Occupational Reference Value (HBORV) rather than HBROEL. A starting point is that workers may be exposed predominantly, but not exclusively, by two routes, dermal and inhalation. HBROELs are assessed if possible for both routes separately and for every effect.

A number of default assessment factors for the extrapolation of NOAELs to a safe occupational exposure level have been defined (see Table 13).

Table 13: Assessment factors applied to derive HBROELs (adapted from Hakkert et al, 1996)

Extrapolation elements	Assessment factor
Interspecies	
- mouse	7* x 3
- rat	4* x 3
- rabbit	2.4* x 3
- dog	1.4* x 3
Intraspecies	3
Duration of exposure	
- chronic to chronic exposure	1
- subacute to semichronic exposure	10
- semichronic to chronic exposure	10
- other aspects	1
Type of critical effect	1
Dose-response curve	1
Confidence in database	1

* The first value is a calculated assessment factor, based on species differences in metabolic rate according to $BW^{0.75}$

BIBLIOGRAPHY : APPENDIX B

Alexiadis A. 1990. Comparison of worldwide procedures for setting occupational exposure limits (OELs). *Occ HIth Ontario* 11:168-192.

Barnes DG, Dourson M. 1988. Reference dose (RfD) – description and use in health risk assessments. *Reg Toxicol Pharmacol* 8: 471-486.

BAuA (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin). 1994. Neue Stoffe am Arbeitsplatz: Ein Bewertungskonzept. *Amtl Mitt Bundesanst, Arbeitsschutz*, Dortmund : 1-143.

BGVV. 1996. Arbeitsgruppe 'Textilien'. Prüfung der gesundheitlichen Unbedenklichkeit von Textilhilfsmitteln und-farbmitteln. *Bundesgesundhbl* 11: 430.

TRGS 901. 1997. Begründungen und Erläuterungen zu Grenzwerten in der Luft und am Arbeitsplatz. *Bundesarbeitsbl* 4: 42-53.

Cheeseman M, Machuga E, Bailey A. 1999. A tiered approach to threshold of regulation. *Food Chem Toxic* 37: 387-412.

Dutch Health Council. 1985. Advice on starting points for standard setting: The explanatory derivation of recommended values for non-mutagenic, non-carcinogenic and non-immunotoxic substances. Health Council Report No 31 (in Dutch). The Hague, The Netherlands.

EPA (Environmental Protection Agency). 1993. Reference Dose (RfD): Description and use in health risk assessments. Available online at http://www.epa.gov/iris.

EPA (Environmental Protection Agency). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA /600/8-90/066F.

EPA (Environmental Protection Agency). 1999. Implementing the food quality protection act. Prevention, Pesticides, and Toxic Substances (7506C). EPA 735-R-99001.

Fairhurst S. 1995. The uncertainty factor in the setting of occupational exposure standards. *Ann Occup Hyg* 39: 375-385.

FDA (Food and Drug Administration). 1993. Toxicological principles for the safety assessment of direct food additives and color additives used in food ("Red Book II"), Springfield, VA, USA.

FDA (Food and Drug Administration). 1995. Food additives: threshold of regulation of substances used in food-contact articles. Final rule. *Fed Reg* 60: 36582-36596.

Frawley JP. 1967. Scientific evidence and common sense as a basis for food packaging regulations. *Food Chem Toxic* 5: 293-308.

Hakkert BC, Stevenson H, Bos PMJ, Hemmen JJ. 1996. Methods for the establishment of health-based recommended occupational exposure limits for existing substances. *TNO Nutrition and Food Research Institute report* V96.463. The Netherlands.

IPCS (International Programme on Chemical Safety). 1994. Environmental Health Criteria 170. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. WHO / UNEP / ILO.

IPCS (International Programme on Chemical Safety). 1998. Environmental Health Criteria 204. Boron. WHO / UNEP / ILO.

Kroes R, Galle M, Schilter B, Trans LA, Walker R, Würtzen G. 2000. Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. *Food Chem Toxic* 38: 255-312.

Munro I, Ford R, Kennepohl E, Sprenger JG. 1996. Correlation of structural class with no-observed-effects levels: a proposal for establishing a threshold of concern. *Food Chem Toxic* 34: 829-836.

Munro I, Kroes R. 1998. Application of a threshold of toxicological concern in the safety evaluation of certain flavouring substances. Annex 5. WHO Additive Series No. 40.

Renwick AG. 1991. Safety factors and establishment of acceptable daily intakes. *Food Add Contam* 8: 135-150.

Renwick AG. 1993. Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Add Contam* 10: 275-305.

Renwick AG. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Add Contam* 15: 17-35.

Renwick AG, Lazarus NR. 1998. Human variability and noncancer risk assessment. An analysis of the default uncertainty factor. *Reg Toxicol Pharmacol* 27: 3-20.

Rulis AM. 1986. De minimis and the threshold of regulation. In Felix CW, ed, *Food protection technology, proceedings of the 1986 conference on food protection*. Lewis, Chelsea MI.

Sagunski H. 1996. Richtwerte für die Innenraumluft – Basisschema. *Bundesgesundhbl* 11: 416-426.

SCF (Scientific Committee on Food). 1990. Guidelines for the presentation of data for toxicological evaluation of substances to be used in materials and articles intended to come into contact with foodstuffs.

SCF (Scientific Committee on Food). 1995. Compilation of supplements to practical guide No. 1.

SCF (Scientific Committee on Food). 2000.Guidelines for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation. SCF / ICS / PLEN / GEN / 90Final.

SCOEL (Scientific Committee on Occupational Exposure Limits). 1998. Methodology for the derivation of occupational exposure limits: key documentation.

Vermeire TG, Stevenson H, Pieters MN, Rennen M, Slob W, Hakkert BC. 1999. Assessment factors for human health risk assessment: a discussion paper. *Crit Rev Toxicol* 29:439-490.

WHO (World Health Organization). 1998. Guidance for drinking water quality. Health criteria and other supporting information. Boron. 2nd ed. Add to Vol 2. WHO, Geneva, pp 15-29.

APPENDIX C: ADDITIONAL CONCEPTS AND ISSUES

C.1 Discomfort

C.1.1 Sensory irritation

Sensory irritation is a common biological effect of many chemicals used in the work place. Humans exposed to a sensory irritant, experience a burning sensation in the eyes, nose, and the throat and may also cough. These responses, mediated via the trigeminal nerve ending and laryngeal receptors respectively, trigger defence mechanisms that protect the respiratory system from injury or minimise the absorption of toxicants into the body (changes in ventilation, bronchomotor tone, blood pressure and airways mucous secretion).

Most of the methods developed to quantify the trigeminally-mediated sensations in humans are based on psychophysical and electrophysiological techniques. Psychophysical approaches include assessment of thresholds, ratings of stimulus intensity at supra-threshold concentrations or the assessment of the subject's ability to localise chemosensory stimuli. However when testing thresholds, cognitive functions clearly play an important role due to the complex experimental procedures involved e.g. the single staircase paradigm where memory and stimulus discrimination against background noise play an important role.

Electrophysiology measures appear to allow the assessment of sensory functions in a more detailed fashion. The negative mucosal potential, recorded from the surface of the olfactory epithelium, is thought to reflect functional aspects of trigeminal chemosensors (nociceptors). The event-related potentials recording response to trigeminal stimulants are largely of cortical origin and reflect different stages of the cognitive processing of trigeminal function. However, these measures do not reflect all aspects of perceived sensations. When using these techniques it seems to be possible to describe in great detail how and where processing of irritation takes place, and how it may interact with olfactory mediated sensations (Hummel, 2000).

Alarie (1966) described an animal bioassay for use in detecting the sensory-irritant properties of airborne chemicals, based on the unique respiratory pattern exhibited by male Swiss-Webster mice. On exposure to sensory irritants, a decrease in their respiratory rate was observed due to a pause after inspiration that lengthened the time of expiration. Expressed as a percentage decrease from pre-exposure level, this is proportional to the concentration of the airborne chemical to which the mouse is exposed. The term RD_{50} was defined as the dose that evoked a decrease of 50% in the respiratory rate.

A correlation was made by Buckley *et al* (1984) between exposure to the RD_{50} concentrations of 10 chemicals and respiratory tract damage, located mainly in the respiratory epithelium of the anterior part of the vestibule and the olfactory epithelium in the dorsal meatus.

A validation of the mouse test was made by Alarie (1981) by comparing the reaction of human volunteers when exposed to chemicals. At the RD_{50} level, most of the volunteers experienced intolerable burning of the eyes, nose and throat, while at 0.1 RD_{50} only slight irritation was recorded, with minimal or no effects at 0.01 RD_{50}. A correlation ($R^2 = 0.90$) between the ACGIH TLVs and 0.03 RD_{50} was demonstrated.

In a group of inhaled aldehydes, Steinhagen and Barrow (1984) found good agreement, with the exception of crotonaldehyde and formaldehyde, between the RD_{50} of Swiss-Webster mice and current TLV values. The model proposed recommended that the TLVs of airborne chemicals should fall between the 0.01 RD_{50} value, where it is expected that minimal or no sensory irritation would occur in humans, and the 0.1 RD_{50} value, which might be slightly irritant but tolerable. The 0.1 RD_{50} value is also recommended as the ceiling value. Schaper (1993) confirmed the results of Alarie (1981) on 295 individual chemicals or mixtures. There was a linear relationship between the logarithm of the TLVs and the logarithm of the RD_{50} and the ratio was approximately 0.03 for the individual or combination of mouse strains. Nevertheless subjectivity and confusion with odour perception may impair the validity of this test in humans. The tendency to report symptoms in response to odours with very low irritancy properties may result from various psychological causes (Dalton *et al*, 1997). For example, smelling particular odour elicits physiological responses (Lehrer, 1997).

In a study with odour identification and a supra-threshold concentration test to assess the trigeminal and aesthetic properties and rating in response to different levels of phenyl ethyl alcohol and pyridine in groups of multiple chemical sensitivity subjects (MCS), chronic fatigue syndrome subjects, asthmatics, and healthy controls, no difference was found between the groups for odour detection and odour identification. However the MCS group was differentiated from the other groups in the symptomatic and aesthetic rating of phenyl ethyl alcohol but not pyridine (Caccappolo *et al*, 2000).

C.1.2 Odour

The human sense of smell serves as an early warning system for the detection of polluted air; it also determines the flavour and palatability of foods and beverages. The relationship between objective and subjective exposure to odorants is difficult to establish, due to the wide variety of sensitivity in humans. In the same individual, wide variations in the detection level of the olfactory function may be recorded, according to his or her physiological and psychological state. The individual's age is a factor. Doty *et al* (1984) found that peak performance occurred in the third through fifth decades and declined markedly after the seventh. More than 50% of 65-80 year-olds evidenced major olfactory impairment; this rose to 75% after 80 years of age. The latter parameter is not of importance in the normal workforce that is aged between 18-65 years.

Exposure to odorant concentrations is conceived as an ambient stressor with which individuals have to cope. When exposed to odorants, some people became annoyed and a few reported general health complaints. Odour annoyance correlates well with socio-emotional and adaptive effects. Exposure itself may not be a direct cause of general health complaints. Annoyance is the intervening variable between exposure and general health complaints. A possible explanation for the relation between annoyance by malodour and general health complaints might be found in the personality and attitudes of exposed individual. Finally, a combination of risk perception and personality also play a role in this comfort phenomenon (Calvalini, 1994).

In summary, annoyance and discomfort from exposure to sensory irritants and malodorous chemicals are subjective individual perceptions, which vary according to the sensitivity of the nasal epithelium receptors and are related to the age of the exposed persons. Health complaints following exposure to sensory irritants or malodorous substances are related to individual appraisal and 'coping' strategy and are affected by demographic characteristics. Olfactory perception tests, which attempt to quantify the level of sensory irritation or the odour perception threshold of exposure to a chemical, are good indicators of the presence of a chemical in the environment, but are generally not suitable for setting health-based OELs.

None of the existing tests currently qualify for the purpose of setting OELs. There is a general agreement that all such tests should be regarded as 'sophisticated tools' that need to undergo thorough validation before they could be used for setting OELs. Therefore the setting of OELs for sensory irritants or malodorous chemicals should generally be based on toxicological data.

In setting a reference concentration for the population around a chemical plant, a health based value should be used, to take into account the wider intraspecies variation of the sensitivity of the people, from newborn infants to elderly adults in all states of health. The 'all-day and all-life' duration of exposure should also be taken into consideration and a larger assessment factor used than for OELs. As odour perception is a critical point for the neighbourhood, the odour detection limit is mainly used as the nuisance reference concentration, to avoid permanent discomfort of the population from a chemical produced in a plant.

BIBLIOGRAPHY: APPENDIX C

Alarie Y. 1966. Irritating properties of airborne materials to the upper respiratory tract. *Archs Env Hlth* 13: 433-439.

Alarie Y. 1981. Bioassay for evaluating the potency of airborne sensory irritants and predicting acceptable levels exposure in humans. *Fd Cosmet Toxic* 19: 623-626.

Buckley LA, Jiang XZ, James RA, Morgan KT, Barrow CS. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. *Toxic Appl Pharmacol* 74: 417-429.

Caccappolo E, Kipen H, Kelly-McNeil K, Knasko S, Hamer RM, Naterlson B, Fiedler N. 2000. Odor perception: multiple chemical sensitivities chronic fatigue and asthma. *JOEM* 42: 629-638.

Calvalini PM. 1994. Industrial odorants: the relationship between modeled exposure concentrations and annoyance. *Arch Env Hlth* 49: 344.

Dalton P, Wysocki CJ, Brody MJ, Lawley HL. 1997. Perceived odor, irritation, and health symptoms following short term exposure to acetone. *Am J Ind Med* 31: 558-569.

Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. 1984. Smell identification ability: changes with age. *Science* 226: 1441-1443.

Hummel T. 2000. Assessment of intranasal trigeminal function. *Int J Psychophys* 36: 147-155.

Lehrer PM. 1997. Psychophysiological hypotheses regarding multiple sensitivity syndrome. *Env Hlth Perspect* 105: 479-483.

Schaper M. 1993. Development of a data base for sensory irritants and its use in establishing exposure limits. *Am Ind Hyg Assoc J* 54: 488-544.

Steinhagen WH, Barrow CS. 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. *Toxicol Appl Pharmacol* 72: 495-503.

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No. 63 Reproductive and General Toxicology of some Inorganic Borates and Risk Assessment for Human Beings
No. 64 The Toxicology of Glycol Ethers and its Relevance to Man
No. 65 Formaldehyde and Human Cancer Risks
No. 66 Skin Irritation and Corrosion: Reference Chemicals Data Bank
No. 67 The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and Related Food Webs
No. 68 Assessment Factors in Human Health Risk Assessment
No. 69 Toxicology of Man-Made Organic Fibres
No. 70 Chronic Neurotoxicity of Solvents
No. 71 Inventory of Critical Reviews on Chemicals (Only available to ECETOC members)
No. 72 Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation
No. 73 The Value of Aquatic Model Ecosystem Studies in Ecotoxicology
No. 74 QSARs in the Assessment of the Environmental Fate and Effects of Chemicals
No. 75 Organophosphorus Pesticides and Long-term Effects on the Nervous System
No. 76 Monitoring and Modelling of Industrial Organic Chemicals, with Particular Reference to Aquatic Risk Assessment
No. 77 Skin and Respiratory Sensitisers: Reference Chemicals Data Bank
No. 78 Skin Sensitisation Testing: Methodological Considerations
No. 79 Exposure Factors Sourcebook for European Populations (with Focus on UK Data)
No. 80 Aquatic Toxicity of Mixtures
No. 81 Human Acute Intoxication from Monochloroacetic Acid: Proposals for Therapy
No. 82 Risk Assessment in Marine Environments
No. 83 The Use of T25 Estimates and Alternative Methods in the Regulatory Risk Assessment of Non-threshold Carcinogens in the European Union
No. 84 Scientific Principles for Soil Hazard Assessment of Substances
No. 85 Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies

Joint Assessment of Commodity Chemicals (JACC) Reports

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

Special Reports

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

Documents

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