INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 170

**ASSESSING HUMAN HEALTH RISKS OF CHEMICALS: DERIVATION
OF GUIDANCE VALUES FOR HEALTH-BASED EXPOSURE LIMITS**

This report contains the collective views of an international group of
experts and does not necessarily represent the decisions or the stated
policy of the United Nations Environment Programme, the International
Labour Organisation, or the World Health Organization.

First draft prepared at the National Institute of Health Sciences,
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The International Programme on Chemical Safety (IPCS) is a joint
venture of the United Nations Environment Programme, the International
Labour Organisation, and the World Health Organization. The main
objective of the IPCS is to carry out and disseminate evaluations of
the effects of chemicals on human health and the quality of the
environment. Supporting activities include the development of
epidemiological, experimental laboratory, and risk-assessment methods
that could produce internationally comparable results, and the

development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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I   Chairman of meeting

II   Joint Rapporteur

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

     Every effort has been made to present information in the criteria
monographs as accurately as possible without unduly delaying their
publication. In the interest of all users of the Environmental Health
Criteria monographs, readers are kindly requested to communicate any
errors that may have occurred to the Director of the International

Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

                    *   *   *

        A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

                    *   *   *

ENVIRONMENTAL HEALTH CRITERIA FOR GUIDANCE VALUES FOR HUMAN EXPOSURE LIMITS

        This Environmental Health Criteria monograph was developed in the course of three meetings, i) a Discussion Group, World Health Organization, Geneva, Switzerland, 14-17 January 1992, opened by Dr E. Smith, IPCS, ii) a Consultation, Langen, Germany, 19-22 January 1993, opened by Dr D. Kello, World Health Organization, Regional Office for Europe, and iii) the final Task Group, World Health Organization, Geneva, 14-18 June 1993, opened by Dr E. Smith, IPCS.

        Dr E. Smith and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively.

        The WHO Regional Office for Europe collaborated with the International Programme on Chemical Safety in the development of the Guidance Value concept.

ABBREVIATIONS

ADI   acceptable daily intake
AUC   area under the curve
EPI   exposure/potency index
LO(A)EL   lowest-observed-(adverse)-effect level
NO(A)EL   no-observed-(adverse)-effect level
SAR   structure-activity relationship
TI   tolerable intake
UF   uncertainty factor

SUMMARY

        Guidance values for exposure to chemicals in environmental media should be developed in IPCS Environmental Health Criteria (EHC) monographs and can be modified by national and local authorities in their development of limits and standards for environmental media. For any chemical, the steps involved are:

1.   Evaluate and summarize the information on toxicity in animals and humans and exposure in humans which is most relevant to derivation of guidance values. The most appropriate format for presentation of the data relevant to derivation of guidance values is a written narrative summarizing the critical data complemented by graphical presentation.

2.   Such data can be used to derive a Tolerable Intake (TI) for various routes of exposure for effects considered to have a threshold. This will involve application of uncertainty factors, generally to the no-observed-adverse-effect level (NOAEL) for critical effects in the most relevant study. For non-threshold effects, the dose-response relationship will be characterized to the extent possible.

3.   Estimate the proportion of total intake that originates from various media (e.g., indoor and ambient air, food and water), based on exposure estimates for a consistent set of assumed volumes of intake (using the International Commission on Radiological Protection (ICRP) reference man) and representative concentrations in the general environment, for a given situation. In the absence of adequate data on concentrations in various media, mathematical models may be used to estimate the distribution through the various media.

4.   Allocate a proportion of the TI to various media of exposure (based on the exposure estimate described in step 3 above) to determine the intake or exposure in each medium.

5. Develop guidance values from intakes assigned to each medium, taking into account (if necessary) body weight, volume of intake and absorption efficiency (the *relative* absorption efficiency in situations where the guidance value is derived on the basis of a TI by another route of exposure). In EHC monographs, development of guidance values would be undertaken for a clearly defined exposure scenario, based on the data for ICRP reference man, and not necessarily representative of national or local exposure conditions. Guidance values would commonly be derived for a representative general population with representative exposure conditions. The guidance values should be adapted at national and local levels as appropriate for local circumstances.

6.   The basis for the derivation of both the TI and the guidance values should be described clearly in EHC monographs (see level of detail in examples in Appendix 1).

1.   INTRODUCTION

1.1 Scope and purpose

     The objective of IPCS Environmental Health Criteria (EHC) monographs is to provide evaluated information, including guidance for exposure limits, for the protection of human health and the maintenance of environmental integrity against the possible deleterious effects of chemical and/or physical agents. EHC monographs contain a comprehensive review and evaluation of available information on the biological effects of selected chemicals and physical agents that can influence human health and the environment. The evaluation typically contains information on the relative contribution of concentrations in various media to a total dose for human or environmental targets, data on dose-effect and dose-response relationships and numerical values, such as Tolerable Intake (TI) and

advisory Guidance Value (GV) to enable regulatory authorities to set their own exposure limits whenever necessary.

Though effects on environmental organisms are not addressed in this report, a holistic approach is implicit in the protection of human health and environmental integrity. Such approaches have been developed by some national institutions for the protection of human health (see, for example, Health and Welfare Canada, 1992 and US EPA, 1993). A more integrated approach aimed at the protection of both man and the ecosystem has been developed in the Netherlands (USES, 1994) and is incorporated in some national legislation (Canada, 1988).

Evaluation for human health protection in EHC monographs entails consideration of the general and occupationally exposed populations and susceptible subgroups. The approach described herein relates primarily to long-term exposure of the general population in the ambient environment (i.e. principally ambient air, food, water and, occasionally, other media). Some degree of human variability is taken into account in the uncertainty factors applied in the derivation of the TI (see section 4.5). Where a uniquely sensitive group forms a significant proportion of the population then the TI would be developed based on that group. In cases where the exposure profiles of this subgroup and the general population are similar, the guidance values should be based on the TI for the sensitive subgroup. If the exposure profiles differ, guidance values should be calculated separately for the subgroup and general population based on their respective TIs and exposure profiles, and the more conservative values adopted. Idiosyncratic hypersusceptibility (excessive reaction following exposure to a given dose of a substance compared with the large majority of those exposed to the same dose) in a few individuals would not be the basis for the derivation of the TI in EHC monographs.

Though the basic methodology would be similar, development of guidance values relating to intermittent, short-term (e.g., accidental) and occupational exposures are not addressed in detail

herein, since this would entail consideration of additional relevant factors. (See, for example, discussion in section 3 concerning development of TIs for occupational exposure).

1.2 Guidance value

The term guidance value is considered appropriate for the type of advice provided by the IPCS in its EHC and other documents because it does not carry connotations of formal standards and regulatory limits. In addition, its derivation is consistent with the process of health risk assessment and risk characterization for risk management. In this context guidance values are defined as:--

values, such as concentrations in air or water, which are derived after appropriate allocation of the TI among the different possible media of exposure. Combined exposures from all media at the guidance values over a lifetime would be expected to be without appreciable health risk. The aim of a guidance value is to provide quantitative information from risk assessment for risk managers to enable them to make decisions concerning the protection of human health.

1.3 Quality of data

Review and evaluation of data for inclusion in EHC monographs
necessarily involves a critical approach to the selection and quality
of data sources. Draft documents are prepared by various
institutes/authors and assessed by various expert groups each with a
different membership. Consequently, there can be a lack of
consistency in the selection of data sources and variation on the part
of different authors and assessors in the interpretation and
extrapolation of data. The formulation of criteria for determining
the quality of data is a current IPCS activity and considered to be
critical to the derivation of sound guidance values in EHCs.

Many toxicological studies are directed mainly to hazard
identification. The available data may not always contain sufficient
information on the dose-response relationship for risk assessment and
for the derivation of TIs for guidance values. Reports and
publications in which no-observed-effect level (NOEL) or NOAEL values
are presented should include sufficient information on all possible
effects investigated and those observed or not observed to allow an
assessment of the validity of the derived values.

1.4 Clarity and transparency of presentations

Data on the dose-response relationship for the critical effect
which served as the basis for the derivation of the guidance values
(GVs) should be characterized in EHC monographs to the extent possible
(including graphical presentation, similar to that illustrated in
Appendix 3 for benchmark doses). It is recognized that in many cases,

the data base will be insufficient for provision of such information
and that it may only be possible to develop single guidance values in
individual media with little additional risk characterization.
Similarly, the basis for the uncertainty factors by which the NOAEL or
lowest-observable-adverse-effect level (LOAEL) have been divided to
obtain the TI should be clearly specified. The conversion of the TI
into media-specific GVs should be presented in sufficient detail to
allow the values to be adapted to national or local circumstances (see
examples in Appendix 1 for relevant level of detail).

2.   GUIDANCE VALUES

2.1 General considerations

A consistent methodology should be used in the derivation of
quantitative guidance values for human exposures to chemical
substances present in food, drinking-water, air and other media by
 ad hoc IPCS Task Groups (of varying membership) reviewing and
evaluating data and finalizing EHC monographs on various chemicals.
This approach embodies the concept that, to the extent possible,
guidance values for the protection of human health should reflect
consideration of total exposure to the substance whether present in
air, water, soil, food or other media. Guidance values should be
derived for a clearly defined exposure scenario, based on the data for
the ICRP reference man (Appendix 4), and therefore might not represent
national or local circumstances.

2.1.1 Precision of a guidance value

The precision of the guidance values is dependent upon the
validity and reliability of the available data. Frequently, there are
sources of uncertainty in the derivation of TIs (see section 4.8) and

in their allocation as a basis for GVs, so that the resulting values represent a best estimate based on the available data at the time. A description of the derivation of guidance value should clearly indicate the nature and sources of uncertainty and the manner in which they have been taken into account in the derivation. The numerical value of GVs should reflect the precision present in their derivation; usually GVs should be given to only one significant figure.

2.2 Derivation of guidance values

Establishing TIs is central to the determination of guidance values. A TI is defined as:--

an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk. It may have different units depending upon the route of administration upon which it is based and is generally expressed on a daily or weekly basis. Though not strictly an "intake", TIs for inhalation are generally expressed as airborne concentrations (i.e. µg or mg per m^3). The TI is similar in definition and intent to terms such as reference dose (RfD) (Barnes & Dourson, 1988), reference concentration (RfC) (Jarabek et al., 1990) and acceptable daily intake (ADI).

This monograph addresses two areas that are critical in the methodology for the derivation of guidance values for human exposures to chemical substances in the environment:

*   *Development of a tolerable intake on the basis of interpretation* of the available data on toxicity. For practical purposes, toxic effects are considered to be of two types, threshold and non-threshold. For substances where the critical effect is considered to have a threshold (including non-genotoxic carcino- genesis for which there is adequate mechanistic data), a TI is developed usually on the basis of a NOAEL. Development of guidance values in EHC monographs for non-threshold effects (e.g., genotoxic carcinogenesis and germ cell mutations) is discussed in section 3.1.1.

*   *Allocation of the proportions of the tolerable intake to various media.* Depending on available information, the development of guidance values for compounds present in more than one environmental medium will require the allocation of proportions of the TI to various media (for example, air, food and water). For the derivation of guidance values, the allocation will be based on information on relative exposure via different routes.

2.3 Interpretation and use of guidance values

Media exposure allocations of TIs for the derivation of guidance values in EHC monographs are based on relative exposure by different routes for a given scenario. Though this is suggested as a practical approach, the use of allocations based on exposure in different media does not preclude the development of more stringent limits. It is also important to recognize that the proportions of total intake from various media may vary, based on circumstances. Site- or context-specific guidance values better suited to local circumstances and conditions could be developed from TIs presented in the EHC in situations where relevant data on exposure are available, and

particularly where there are other significant sources of exposure to
a chemical substance (e.g., in the vicinity of a waste site).
Regulatory authorities may also take other factors into account, such
as cost, ease and effectiveness of control, to develop risk management
strategies appropriate for local circumstances, although the ultimate
objective of control should be reduction of exposure from all sources
to less than the TIs. In addition, where data on organoleptic
thresholds are included in EHC monographs, these can also be
considered by relevant authorities in the development of limits.

     The basis for derivation of guidance values in EHC monographs
must be clearly specified in sufficient detail to enable, where
appropriate, step-by-step development of exposure limits for national
or local conditions by appropriate regulatory or other authorities
(Appendix 1).

2.4 Terminology

Adverse effect: change in morphology, physiology, growth,
development or life span of an organism which results in impairment of
functional capacity or impairment of capacity to compensate for
additional stress or increase in susceptibility to the harmful effects
of other environmental influences. Decisions on whether or not any
effect is adverse require expert judgement.

Critical effect(s): the adverse effect(s) judged to be most
appropriate for determining the TI.

No-observed-adverse-effect level (NOAEL): greatest concentration or
amount of a substance, found by experiment or observation, which
causes no detectable adverse alteration of morphology, functional
capacity, growth, development or life span of the target organism
under defined conditions of exposure. Alterations of morphology,
functional capacity, growth, development or life span of the target
may be detected which are judged not to be adverse.

No-observed-effect level (NOEL): greatest concentration or amount
of a substance, found by experiment or observation, that causes no
alterations of morphology, functional capacity, growth, development or
life span of target organisms distinguishable from those observed in
normal (control) organisms of the same species and strain under the
same defined conditions of exposure.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration
or amount of a substance, found by experiment or observation, which
causes an adverse alteration of morphology, functional capacity,
growth, development or life span of the target organism
distinguishable from normal (control) organisms of the same species
and strain under the same defined conditions of exposure.

Benchmark dose: the lower confidence limit of the dose calculated
to be associated with a given incidence (e.g., 5 or 10% incidence) of
effect estimated from all toxicity data on that effect within that
study (Crump, 1984).

Uncertainty factor (UF): a product of several single factors by
which the NOAEL or LOAEL of the critical effect is divided to derive a
TI. These factors account for adequacy of the pivotal study,
interspecies extrapolation, inter-individual variability in humans,
adequacy of the overall data base, and nature of toxicity. The term

uncertainty factor was considered to be a more appropriate expression than safety factor since it avoids the notion of absolute safety and because the size of this factor is proportional to the magnitude of uncertainty rather than safety. The choice of UF should be based on the available scientific evidence.

Toxicodynamics: the process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicokinetics: the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the substances and their metabolites from the body. Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as pharmacokinetics, but the latter term should be restricted to the study of pharmaceutical substances.

Tolerable intake (TI): an estimate of the intake of a substance which can occur over a lifetime without appreciable health risk. It may have different units depending upon the route of administration. Though not strictly an "intake", TIs for inhalation are generally expressed as airborne concentrations (i.e., µg or mg per m^3).

Default value: pragmatic, fixed or standard value used in the absence of relevant data.

Guidance values (GVs): values, such as concentrations in air or water, which are derived after appropriate allocation of the TI among the different possible media of exposure. Combined exposures from all media at the guidance values over a lifetime would be expected to be without appreciable health risk. The aim of the guidance value is to provide quantitative information from risk assessment for risk managers to enable them to make decisions concerning the protection of human health.

3.   APPLICATION OF THE TOXICITY DATA BASE TO DETERMINE TOLERABLE
     INTAKES

3.1 Approaches to risk assessment

     A review of the data base on a chemical should be undertaken to determine the critical effect(s), which can be considered to be of two types: those considered to have a threshold and those for which there is considered to be some risk at any level (non-threshold: genotoxic carcinogens and germ cell mutagens). Data available for risk assessments include studies in humans and animals, structure-activity relationships (SAR) and *in vitro* investigations. Risk assessments should be based on all available data at the time of review, but it is appreciated that recognition of additional hazards or risk may emerge which will require subsequent re-evaluation. Wherever possible, appropriate human data should be used as the basis for the risk assessment.

     For threshold effects, where data in humans are used as the basis for development of TIs, uncertainty factors should be applied to observed effect levels to allow for the magnitude of any effect seen in the exposed group and their sensitivity compared with the general population or target group. The incidence of effects detected in

humans *in vivo* will be the result of inter-individual differences in
both toxicokinetic and toxicodynamic aspects. The extent of any
possible human variability not present within the exposed population
groups should be considered in the development of uncertainty factors.

        Information on the NOAEL (or LOAEL) by different routes is
sometimes available. In cases where information exists on only one
route, e.g., inhalation, the bioequivalence for exposure from other
routes should be estimated if suitable information and models are
available. The aim of the risk assessment is to estimate an overall
tolerable intake derived from data on toxicity using appropriate
routes of administration. Guidance values can then be developed
through allocation of the TI to the various media of human exposure,
based on considerations of relevant exposure profiles.

3.1.1 Non-threshold effects

        There is no clear consensus on appropriate methodology for the
risk assessment of chemicals for which the critical effect may not
have a threshold, such as genotoxic carcinogens and germ cell
mutagens. A number of approaches based largely on characterization of
dose response have been adopted for assessment of such effects.
However, these approaches are not amenable to the development of
guidance values in EHC monographs because they require socio-political
judgements of acceptable health risk. Those preparing EHC and other
documents for the IPCS should evaluate the relevant available data and
characterize the dose-response relationship for such effects to the
extent possible, based on one or more methods as considered
appropriate (some approaches are described below). This should enable
the development of guidance values or limits by appropriate

authorities on the basis of information on such effects included in
EHC monographs.

Approaches have included:

*   quantitative extrapolation by mathematical modelling of the
        dose-response curve to estimate the risk at likely human intakes
        or exposures (low-dose risk extrapolation)

*   relative ranking of potencies in the experimental range

*   division of effect levels by an uncertainty factor.

        Low-dose risk extrapolation has been accomplished by the use of
mathematical models such as the Armitage-Doll multi-stage model. In
more recently developed biological models, the different stages in the
process of carcinogenesis have been incorporated and time to tumour
has been taken into account (Moolgavkar et al., 1988). In some cases
where data permit, the dose delivered to the target tissue has been
incorporated into the dose-response analysis (physiologically based
pharmacokinetic or PBPK modelling). It should be noted that crude
expression of risk in terms of excess incidence or numbers of cancers
per unit of the population at doses or concentrations much less than
those on which the estimates are based may be inappropriate, owing to
the uncertainties of quantitative extrapolation over several orders of
magnitude. Estimated risks are believed to represent only the
plausible upper bounds and vary depending upon the assumptions on
which they are based.

Comparison of human exposure to the carcinogenic potency in the experimental range can also be used to indicate the magnitude of risk as a basis of derivation of guidance values. One such measure which provides a practical way to prioritize substances on the basis of their carcinogenic potency in a range close to the observed dose-response is the Exposure/Potency Index (EPI) (Health and Welfare Canada, 1992). The EPI is defined as the estimated daily human intake or exposure divided by the intake or exposure associated with a 5% incidence of tumours in experimental studies in animals or epidemiological studies in human populations (Tumorigenic Dose$_5$; TD$_5$) (Fig. 1). A calculated EPI of 10^{-6} represents a one million fold difference between human exposure and the intake which is at the lower end of the dose-response curve. Wherever possible, relevant toxicokinetic and mechanistic data are taken into account in the development of the EPIs.

An alternative approach is to divide the highest dose at which there is no observed increase in tumour incidence in comparison with controls by a large composite uncertainty factor (for example 5000; Weil, 1972). The magnitude of the factor could be a function of the weight of evidence (e.g., numbers of species in which the tumours have been observed or nature of the tumours). This approach is sometimes used when data on dose-response are limited.

A risk management approach which has been adopted for compounds for which the critical effect is considered not to have a threshold involves eliminating or reducing exposure as far as is practicable or to the lowest level technologically possible. Characterization of the dose-response as indicated in the procedures described above can be used in conjunction with this approach to assess the need to improve technology to reduce exposure.

3.1.2 Threshold effects

For compounds with critical effects for which there is a
 threshold, a primary objective of a review of data is to consider the comparability of experimental species and humans, and determine the highest doses or exposures that can be administered experimentally to animals or taken up by humans without producing the critical effect (see Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food, section 5.5.1) (WHO, 1987). In studies in experimental animals, the value of the NOAEL is an observed value that is dependent on the protocol and design of the study from which it was derived. There are several "study-dependent" factors that influence the magnitude of the value observed, including:

*   the species, sex, age, strain and developmental status of the
     animals studied

*   the group size

*   the sensitivity of the methods used to measure the response

*   the duration of exposure

*   the selection of dose levels, which are frequently widely spaced,
     so that the observed value of the NOAEL can be in some cases
     considerably less than the true no-adverse-effect level.

3.1.2.1 Uncertainty factors

        There is enormous variability in the extent and nature of
different data bases for risk assessment. For example, in some cases,
the evaluation must be based on limited data in experimental animals;
in other cases detailed information on the mechanism of toxicity
and/or toxicokinetics may be available, while in some cases the risk
evaluation can be based on data on effects in exposed human
populations. Consequently, for the general population, the range of
uncertainty factors applied in the derivation of TIs has been wide
(1-10 000), although a value of 100 has been used most often. For
example, the historic use of a factor of 100 based on animal studies
in the absence of specific data to suggest a more appropriate value
was first proposed by Lehman & Fitzhugh (1954) and later used in the
derivation of ADIs for food additives by WHO (WHO, 1987; Lu, 1988).
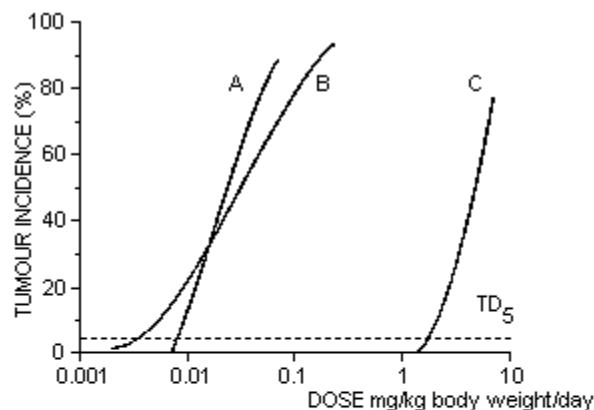
$$\text{Exposure/Potency Index (EPI)} = \frac{\text{Human daily exposure from all sources}}{TD_5}$$

**Fig. 1. Dose-response curves for three hypothetical
compounds showing different potencies and dose-
effect relationships. The Tumorigenic Dose$_5$ (TD$_5$)
provides an estimate of the dose required to
produce a 5% incidence of tumours in the
experimental animals.**

More recently, additional uncertainty factors have been incorporated
to account for, for example, deficiencies in the data base, such as
the absence of a NOAEL (US EPA, 1985a,b) or the absence of chronic
data (NAS, 1977).

        If data from well-conducted studies in human populations are the
basis for the safety evaluation, a factor of 10 has been considered
appropriate, as a default value (WHO, 1987). Thus the value of 100
has been regarded as comprising two factors of 10 each to allow for
interspecies and inter-individual (intraspecies) variations. A scheme
has been proposed which retains the two 10-fold factors as the
cornerstone for extrapolating from animals to man but which allows
subdivision of each to incorporate appropriate data on toxicodynamics
or toxicokinetics where these exist (Renwick, 1993a) (see Fig. 2).

        This approach improves the extrapolation process, and where

appropriate data can be introduced, it has the effect of replacing
"uncertainty" factors with "correction" factors. Data on differences
in dynamics and kinetics between humans and common laboratory animals,
such as rats, mice and dogs, indicated that there was greater
potential for differences in kinetics than in dynamics so that an
equal split of the 10-fold factor was inappropriate. The usual
10-fold factor (log 1) should be split into default values of 2.5
($10^{0.4}$) for dynamics and 4 ($10^{0.6}$) for kinetics (Renwick, 1993a).
A similar split was proposed for interindividual differences between
humans in toxicokinetics (pharmacokinetics) and toxicodynamics (using
pharmacokinetic-pharmacodynamic modelling). However, it was
considered that the variability for both aspects was similar and it
was concluded that the 10-fold factor should be split evenly between
both aspects, i.e. 3.2 ($10^{0.5}$) for kinetics and 3.2 ($10^{0.5}$) for
dynamics. The commonly applied 100-fold uncertainty factor should be
split as indicated in Fig. 2.

     Precise default values for kinetics and dynamics cannot be
expected on the basis of subdivision of the imprecise 10-fold
composite factor. The values above are reasonable since they provide
a positive value > 2 for both aspects and are compatible with the
species differences in physiological parameters such as renal and
hepatic blood flow. Since the data base examined was limited, it is
proposed that the values for subdivision of inter-species and
inter-individual variation presented in Fig. 2 be adopted on an
interim basis. Adoption of the approach should encourage the
development and generation of appropriate data, which could then
contribute to any future revision of the default values, and further
improve the scientific basis of the use of uncertainty factors.
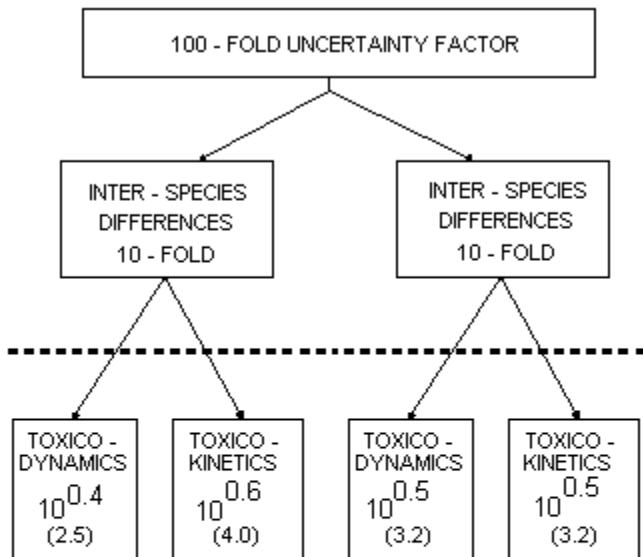

**Fig. 2. Subdivision of the 100-fold uncertainty factor showing
the relationship between the use of uncertainty factors
(above the dashed line) and proposed subdivisions based on
toxicokinetics and toxicodynamics (based on Renwick, 1993a).
Actual data should be used to replace the default values if
available.**

     It was recognised that appropriate toxicokinetic and

toxicodynamic data are rarely available for the same compound and that
to incorporate data in one area only would require the normal
composite factor of 10 to be subdivided. For example, if the
mechanism of action for the critical effects and differences in
sensitivity between the test species and man based on *in vitro*
studies were known, then these data could contribute quantitatively to
the risk assessment by replacement of the default factor for
interspecies differences in toxicodynamics, or differences in
sensitivity (the value of 2.5 in Fig. 2) by the value indicated by the
actual data. However, there could still be differences in
toxicokinetics between the test species and humans so that a portion
of the normal 10-fold factor would need to be retained (the value of 4
in Fig. 2).

3.1.2.2 Relevant toxicokinetic and toxicodynamic data

     Toxicokinetics includes data on the rate and extent of absorption
(bioavailability), pattern of distribution, rate and pathway of any
bioactivation, and rate, route and extent of elimination. Factors
such as peak plasma concentration (C_{max}), and area under the plasma
concentration-time curve (AUC) of the toxic entity are particularly
important since they are usually indicative of the extent and duration
of exposure of the target organ (Renwick, 1993a). Dosimetric
adjustments of administered animal dose to equivalent human dose are
also possible (Jarabek et al., 1990). However it is important to
define which parameter is relevant to the toxicity since some are
dependent on the C_{max} and not AUC (e.g., the teratogenicity of
valproic acid; Nau, 1986) while for long-term bioassays, the AUC may
be of greater importance. Appropriate toxicodynamic factors include
the identification of the toxic entity (i.e. parent compound or a
metabolite), the nature of the molecular target, the presence and
activity of protective and repair mechanisms and the *in vitro*
sensitivity of the target tissue (see Renwick, 1993a for details and
examples). These toxicokinetic and toxicodynamic parameters should be
compared between the test species and humans for derivation of
interspecies factors where this is possible. Modification of the
10-fold factor for inter-individual variability in humans would
require data on toxicokinetics and toxicodynamics in a wide and fully
representative sample of the general or exposed population, including
an assessment of neonates if appropriate.

     It is emphasised that in the absence of reliable information on
toxicokinetics and toxicodynamics, the default values for these
factors become the commonly used composite value of 100 (i.e., 10 for
inter-individual variability and 10 for interspecies variation).

3.1.2.3 Uncertainty factors for occupational exposure

     The consideration of uncertainty factors given above relates
primarily to exposure of the general population. However, the general
principles for derivation of TIs for occupational exposure would be

somewhat similar (see, for example, Zielhuis & van der Kreek, 1979a,b;
Hallenbeck & Cunningham, 1986) although they have not been widely
adopted for this purpose. However, although the components of the
uncertainty factor relating to the nature and severity of the toxic
effect, the adequacy of the data base and interspecies variability
would be similar for the development of guidance values for
occupational exposure, the nature of the population exposed differs.
The more vulnerable members of the human population (i.e. the very

young, the sick and the elderly) do not form part of the exposed
occupational population, whereas for the development of TIs for the
general population, these groups must be considered. Furthermore,
workplace levels and patterns of exposure can be controlled and the
exposed population protected or monitored on an individual or group
basis. For these reasons, it is often appropriate to use
significantly lower uncertainty factors when deriving health-based
limits for occupational exposure compared with those used for the
development of TIs for the general population.

4.   PROCEDURE FOR EXTRAPOLATION FROM A TOXICITY DATA BASE TO A
     TOLERABLE INTAKE

4.1 Overall procedure

     The procedure, which is presented in Fig. 3, is designed to be
applicable to widely differing data bases on toxicity. The procedure
is also suitable for the incorporation of human data, under which
circumstances some of the uncertainty factors will not be required.
The scheme is presented as a series of steps, but it is important that
the full data base continue to be reviewed to ensure that the final
decision is appropriate. A TI for a reversible toxic effect in an
animal species, for which there is complete toxicological data but
without appropriate toxicokinetic or toxicodynamic data, is based on
the commonly used and appropriate factor of 100. The scheme
incorporates those aspects which would normally be considered in the
conversion of a NOAEL (or LOAEL or equivalent) from an animal study
into a TI in such a way that appropriate mechanistic or toxicokinetic
data can contribute numerically to the uncertainty factor and hence to
the TI.

     The procedure suggested here and discussed more fully in Renwick
(1993a) is based, in part, on discussions occurring over a number of
years regarding the basis of uncertainty factors (see, for example,
Zielhuis & van der Kreek, 1979a,b; Dourson & Stara, 1983; Lewis et
al., 1990; Rubery et al., 1990). To some extent, the principles
outlined here have been adopted in approaches of various national
agencies (e.g., Jarabek et al., 1990; Health and Welfare Canada, 1992;
US EPA, 1993).

4.2 Selection of pivotal study and critical effect(s)

     Determination of the NOAEL, LOAEL or equivalent (possible use of
benchmark dose approach) is the first step in derivation of the TI.
This requires a thorough evaluation of available data on toxicity.
Sophisticated detection methods may be of such sensitivity that
effects can be detected at lower doses than by normal techniques; the
adversity of these effects requires very careful evaluation in the
determination of the NOAEL. For some chemicals, a review of the data
base may reveal that two (or possibly more) adverse effects occur at
low doses with NOAELs within one order of magnitude. Under such
circumstances and providing: a) that the data on which the NOAELs are
based are of sufficient quality to be used for risk evaluation; and b)
that the NOAELs *may* require different uncertainty factors based on,
for example, data on mechanisms or nature of toxicity (see below),
then each effect should be considered in the following scheme and the
one with the lower resulting TI used for development of guidance
values. Available LOAELs within the same order of magnitude as the
lowest reported NOAELs need also to be considered in this exercise
since they could lead to the development of more conservative TIs.
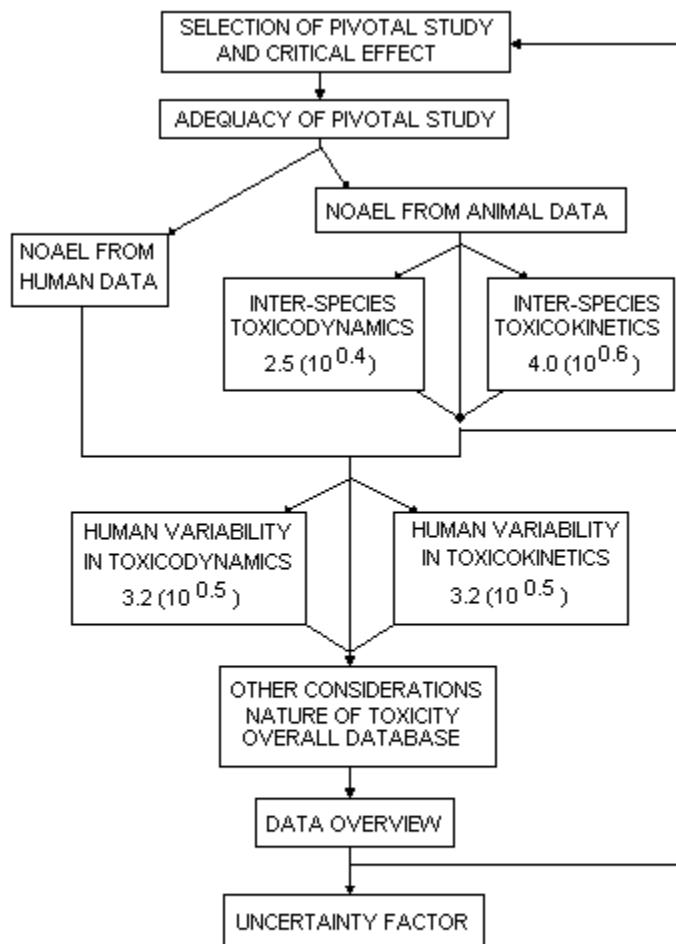
Fig. 3. Procedures for the derivation of uncertainty factors

　　Graphical presentation of available data can facilitate
identification of effect levels relevant to development of TIs.
Although the form of graphical presentation is necessarily dependent
upon the size of the data base, a dose-duration graph in which NOELs,
NOAELs and LOAELs are presented as a function of duration of exposure
is considered to be helpful and is more fully described in Appendix 2.

4.3 Adequacy of the pivotal study

　　In situations where a NOAEL has *not* been achieved but the data
on effects are of sufficient quality to be the basis of the risk
assessment, then a no-adverse-effect level should be developed by the
application of an appropriate uncertainty factor to the LOAEL.
Uncertainty factors of 3, 5 or 10 have been used previously to
extrapolate from a LOAEL to a NOAEL depending on the nature of the
effect(s) and dose-response relationship (see, for example, US EPA,
1993). Alternatively, a benchmark dose may be developed by
mathematical modelling of the dose-response data as an alternative to
the uncertainty factor in extrapolating to the NOAEL (see Appendix 3).
The pivotal study may also be considered inadequate for other reasons
(e.g., duration of study, numbers of animals per group and sensitivity
of the analyses of effect), and an additional uncertainty factor

applied.

4.4 Interspecies extrapolation

     In situations where appropriate toxicokinetic and/or
toxicodynamic data exist for a particular compound, then the relevant
uncertainty factor in Fig. 3 should be replaced by the data-derived
factor. Data on PBPK and/or data on target organ exposure should be
included when they are available. Subdivision of the 10-fold
uncertainty factor has been used in the development of a reference
concentration for 1,2-epoxybutane (US EPA, 1993). Chemicals for which
the approach described here has been applied include saccharin
(Renwick, 1993b), erythrosine (Poulsen, 1993), butylated
hydroxyanisole (BHA) (Wurtzen, 1993) and diethylhexyl phthalate (DEHP)
(Morgenroth, 1993).

     If a data-derived factor is introduced then the commonly used
10-fold factor would be replaced by the product of that data-derived
factor and the remaining default factor. For some classes of
compounds a data-derived factor for one member of the class may be
applicable to all members, thereby producing a group-based
data-derived factor (see Calabrese, 1992). The interspecies
uncertainty factor is not necessary if the NOAEL or LOAEL is based on
human data.

4.5 Inter-individual variability in humans

     A factor of 10 is normally used to allow for differences in
sensitivity *in vivo* between the population mean and highly sensitive
subjects. In cases where there are appropriate data on the
inter-individual variability in toxicokinetics or toxicodynamics for a
particular compound in humans, then the relevant uncertainty factor
should be replaced by the data-derived factor. Data on PBPK may also
be able to contribute to this assessment. If a data-derived factor is
introduced, then the commonly used 10-fold factor would be replaced by
the product of the data-derived factor and the remaining default
factor. (For additional discussion, see Calabrese, 1985; Hattis et
al., 1987).

     For some compounds, it may be known that a subset of the
population would be particularly sensitive, for example due to
deficiencies in detoxication processes. Many of the enzymes involved
in xenobiotic biotransformation are polymorphically distributed in the
human population. Such polymorphism should be taken into account
where the enzymatic differences result *either* in a marked change in
bioavailability or clearance of the parent compound *or* in a major
change in the extent of formation of the toxic entity. In cases where
the default factor will not adequately cover this additional
variability, then the default should be modified appropriately.
Alternatively, these groups may require special strategies for health
protection. In cases where the risk assessment is based on *in vivo*
data in the sensitive subgroup, then the composite factor (10) should
be reduced to a much lower value. A value of 1 could be used if there
is an extensive data base in humans and the data base adequately
addresses any identified sensitive subgroups. For example, the US EPA
estimated an oral reference dose for fluoride based on the absence of
dental mottling in children 12 to 14 years of age. Since this group
was considered to be a sensitive subpopulation, a factor of 1 for
inter-individual variation was considered to be appropriate (US EPA,
1993).

4.6 Other considerations

4.6.1 Adequacy of the overall data base

     Major deficiencies in a toxicity data base (other than those
related to the pivotal study) which increase the uncertainty of the
extrapolation process should be recognized by the use of an additional
uncertainty factor. Since the quality and/or completeness of
different data bases vary, the additional uncertainty factor will also
vary. For example, a value of 1 would be applied to a data base that
was considered complete for the evaluation of the compound under
consideration, but a factor of 1-100 might be necessary for limited
data bases. If minor deficiencies in the data exist with respect to
quality, quantity or omission, then an extra factor of 3 or 5 would be
appropriate. An extra factor of 10 would be appropriate where major

deficiencies in the data exist with respect to quality, quantity or
omission, such as a lack of chronic toxicity studies and reproductive
toxicity studies (for additional discussion see Dourson et al., 1992).

     It should be appreciated that when very large uncertainty factors
are incorporated, the derived TI should be considered as an very
imprecise temporary estimate pending the generation of a better data
base. It should be recognized that inadequacies of the pivotal study
(section 4.3) could also be considered as a subset of inadequacies of
the data base; the total factor for limitations of the pivotal study
plus adequacy of the overall data base should not exceed 100 since
such a data base is generally not acceptable for development of a TI.

4.6.2 Nature of toxicity

     The nature of toxicity, i.e. whether the effect is adverse or
not, is considered in the determination of NOAEL and LOAEL. For
example, a concentration or dose which induces a transient increase in
organ weight without accompanying biochemical or histopathological
effects might be considered to be a NOAEL. If there are accompanying
adverse histopathological effects in the target organ, the lowest
concentration or dose at which these effects occur would be considered
a LOAEL. The sensitivity of analyses of effects should also be taken
into account in establishing the NOAEL or LOAEL (see discussion in
section 4.2).

     In addition, a number of bodies, including the WHO and FAO Joint
Expert Committee on Food Additives (JECFA) and the Joint Meeting on
Pesticide Residues (JMPR) have incorporated an additional "safety
factor" of up to 10 (corresponding to an uncertainty factor in the
current discussion) in cases where the NOAEL is derived for a critical
effect which is a severe and irreversible phenomenon, such as
teratogenicity or non-genotoxic carcinogenicity, especially if
associated with a shallow dose-response relationship (Weil, 1972; WHO,
1987, 1990). Provision for the application of additional safety
factors is included in the sequence shown in Fig. 3.

4.7 Final review of the total uncertainty factor

     It is important that there is a final review of the total
uncertainty factor applied, particularly in cases where a low value
has been used, based on toxicokinetic or toxicodynamic data, to
replace one of the default values. Under such circumstances, a TI

derived on the basis of the appropriate overall uncertainty factor for
that toxic effect might be greater than that which would be produced
by an alternative, well-defined toxic end-point observed at slightly
higher intakes or exposures. For this reason, there are arrows shown
in Fig. 3 leading back to the data base.

4.8 Precision of the tolerable intake

        The TI is calculated by dividing the NOAEL for the critical
effect by the derived total uncertainty factor. The precision of the
estimate depends in large part on the magnitude of the overall
uncertainty factor used in the calculation. The precision is probably
to one significant figure at best, and more usually to one order of
magnitude, and for uncertainty factors of 1000 or more the precision
becomes even less. Because of the imprecision of the default factors
and in order to maintain credibility of the risk assessment process,
the total default uncertainty factor should not exceed 10 000. If the
risk assessment leads to a higher factor then the resulting TI would
be so imprecise as to lack meaning. Such a situation indicates an
urgent need for additional data.

4.9 Alternative approaches

        Approaches being developed to characterize quantitatively the
dose-response relationship for non-threshold effects (including the
benchmark dose and categorical regression) are described in
Appendix 3.

5. ALLOCATION OF TOLERABLE INTAKES TO DERIVE GUIDANCE VALUES

5.1 General considerations

        Allocations of the TIs to various media for the development of
guidance values are based on relative proportion of total exposure
from each of the media. This necessitates the presentation of
consistent and detailed estimates of exposure for as many media as
possible in draft EHCs prior to review and evaluation. Wherever
possible, estimation of exposure should be based on concentrations in
environmental media including (but not necessarily limited to) air,
food, drinking-water, soil and consumer products. With respect to
soil, wherever possible, estimated exposure should take into account
both ingestion and dermal contact. Since the bioavailability of
contaminants in soil from both ingestion and dermal contact may be
limited, this should be taken into account in assessing the
contribution that soil makes to total intake from all media.

        It is recommended that unless there are other age groups which
are more sensitive or have widely differing exposure profiles, intake
from each of the media (generally expressed as µg/kg body weight per
day) should be estimated for adults, based on ICRP reference values
for body weights and ingestion volumes (ICRP, 1974; Appendix 4).
Wherever possible, estimation of exposure should be based on ranges of
mean concentrations in environmen-tal media on a global basis. Where
data are more limited, ranges of individual values could be used.
Estimates of exposure as a basis for derivation of guidance values are
presented in the examples in Appendix 1.

        Where the data on concentrations of a substance in environmental
media are inconsistent or inadequate, exposure can be estimated based
on models which incorporate as much data as possible on, for example,

production, use patterns and physical and chemical properties. Models
to predict distribution in environmental media and estimation of
proportion of total exposure by various routes from consumer products
are available (Mackay, 1991; USES, 1994). For estimation of
proportions of exposure from various environmental media for
development of guidance values in EHCs, it is recommended that the
latest version of the Mackay level III model be used (Mackay et al.,
1992). It is important that all assumptions concerning releases and
physico-chemical properties and limitations of the estimated
proportions be clearly specified. In some cases, it may also be
possible to estimate the contribution of each medium to total exposure
on the basis simply of data on physical and chemical properties (e.g.,
for substances which are likely to be present primarily in one
environmental medium).

       When available, toxicokinetic data should be used to the extent
possible in extrapolating across routes in the approaches to
allocation described below. Dermal exposure and absorption should
also be taken into account in the derivation of guidance values,

although relevant data are often not available. It is also recognized
that a source in one medium (e.g., potable water) may lead to
additional intake from other routes (e.g., dermal and inhalation) and
that, where possible, such intake should be considered in the
derivation of guidance values.

       In addition, total allocations of less than 100% of the TI are
encouraged to account for, for example, those media for which exposure
has not been characterized and cross-route exposure. The magnitude of
the proportion of total intake which is not allocated should vary as a
function of the adequacy of characterization of total exposure from
all media.

       In cases where the proportion of total exposure from a specific
medium is small (less than a few percent), allocation for derivation
of guidance values is not recommended since this would result in
direction of risk management strategies to media which are
inconsequential in contributing to total exposure.

5.2 General approach

       The steps subsequent to development of a TI in deriving guidance
values for a general population are as follows:

1. If necessary, conversion of TIs for systemic effects for different
routes of exposure to a common unit for comparison based on
consideration of volumes and rates of inhalation and ingestion and
relevant toxicokinetic data, such as bioavailability, if available.

2. Allocation of TI to various routes and media based on estimated
exposure developed on the basis of available data on measured
concentrations or predicted proportions (i.e., model-derived values)
to which humans are exposed. Default values can be used in the
absence of data on measured concentrations or predicted proportions of
total exposure in various media.

3. Development of guidance values from intake assigned to each
medium, taking into account, for instance, body weight, volume of
intake and (relative) absorption efficiency (*relative* where guidance
value is derived on the basis of a TI by another route of exposure).

Guidance values for drinking-water are generally expressed in μg/litre
or mg/litre, those in food as μg/g or mg/kg, those in air as μg/m^3
or mg/m^3, and those for dermal exposure as μg/m^2 surface area.

5.3 Detailed approach

        In the following section, an approach to the allocation of
tolerable intakes for development of guidance values (general
population) is provided by way of example for most of the scenarios
which may arise based on evaluations presented in EHCs.

        The five most likely scenarios are considered to be:

5.3.1 Biomarkers of exposure

        There is a common biomarker related to the critical effect which
integrates exposure from all sources. For example, Choudhury et al.
(1992) describe a model which predicts blood lead concentrations as a
function of concentrations in various media.

*   The contributions from the various media are determined based on
        a quantitative biomarker. Following allocation to various media
        based on an exposure scenario, guidance values are developed
        through incorporation of adjustment of body weight and volume of
        intake for each medium.

5.3.2 Critical effects which are not route specific

        TIs have been derived for each route, e.g., TI for oral exposure
(TI_o) and TI for inhalation (TI_i), and are based either on the
same or on different critical effects which are not at the portal of
entry. The TIs for the two routes are similar within one order of
magnitude since such variation is consistent with that inherent in
deriving TIs, as discussed in section 4, e.g., developmental toxicity
of 2-methoxyethanol (Doe et al., 1983; Wickramaratne, 1986). This
reflects the assumption that, in the absence of data to the contrary,
exposure via each route is considered to contribute to a combined dose
at the target site(s), i.e., additivity of dose at the target site(s).

*   Allocate one TI to various media based on an exposure scenario to
        determine the intake in each medium on which guidance values
        should be based. Selection of the TI_o or the TI_i for this
        purpose should be based on either:

        a)   if there is one major route of exposure then the TI for that
             route should be used (if there is confidence in the data
             base on which the exposure estimates are based); or

        b)   the more conservative TI (if there is uncertainty about the
             relative contribution of various routes or media to total
             exposure).

5.3.3 Difference in magnitude of effect by route of exposure

        TI_o and TI_i for *similar* effects vary by 1 to 2 orders of
magnitude (exact magnitude of the difference for which this approach
is appropriate will be dependent upon availability of additional data;
e.g., manganese is more potent by inhalation than by ingestion).

* Derive the guidance values independently for each route (for example, the oral and inhalation routes, based on the TI_o and TI_i, respectively), but allocate the proportion of the TI for each route to the appropriate medium or media based on an exposure scenario.

5.3.4 Route-specific effect variation at portals of entry
       (due to local bioactivation or local effects)

       TI_o and TI_i for *route-specific* effects at the site of entry vary by 1 to 2 orders of magnitude (exact magnitude of the difference for which this approach is appropriate will be dependent upon knowledge of additional data; e.g., nasal toxicity following inhalation of acrylic acid).

* Derive the guidance values independently for each route (for example, the oral and inhalation routes, based on the TI_o and TI_i, respectively), using the full TI for each route to the appropriate medium or media based on an exposure scenario.

5.3.5 Limited data base

       In this scenario, the data base is limited such that only either a TI_o or a TI_i can be developed.

* Allocate the available TI to various media based on an exposure scenario to determine the intake in each medium on which guidance values should be based, if the effects are qualitatively similar, if toxicokinetic data are consistent with this approach and if there are no effects at the site of entry. If any one of these criteria is not met, do not derive guidance values for the alternate route. If a TI is available for a route of exposure which does not make an important contribution to total intake, do not derive guidance values for that route.

6. EXAMPLES OF THE DERIVATION OF GUIDANCE VALUES

 Example 1

       The principal route of exposure is oral. Based on estimated exposure for a scenario in the general environment, 50% of total intake comes from food, 20% from water and 30% from air.

       Data are adequate to establish both a TI_o and a TI_i. The TI_o and the TI_i are based on similar effects and are similar (within one order of magnitude).

       Allocate 50% of TI_o to food to derive a guidance value for food

* multiply TI_o by 0.5

       Allocate 20% of TI_o to water to derive a guidance value for drinking-water

* multiply TI_o by 0.2

       Allocate 30% of TI_o to air to derive a guidance value for air

       *   multiply TI_o by 0.3

Example 2

      Based on an exposure scenario, 70% of total intake comes from air, 20% from water and 10% from food. The compound is also present in some consumer products but quantification of exposure is not possible. There are no data on concentrations in soil but due to its physicochemical properties, concentrations in this medium are likely to be low.

      Data are sufficient to establish a TI_i and a TI_o. The TI_o and the TI_i are based on similar effects and are similar to within an order of magnitude.

      Convert TI_i so that the values for the TIs for different routes are expressed in the same units for comparison (generally mg/kg body weight per day). This requires incorporation of information on inhalation volumes, body weight and toxicokinetic data, if available.

      Use TI for principal route of exposure to derive guidance values:

      Allocate 63% of TI_i to air to derive a guidance value for air.

       *   multiply TI_i by 0.63

      Allocate 18% of TI_i to water to derive a guidance value for drinking-water.

       *   multiply TI_i by 0.18

      Allocate 9% of TI_i to food to derive a guidance value for food.

       *   multiply TI_i by 0.09

      Reserve 10% for exposure from consumer products and soil. (Wherever possible, there should be an attempt to quantitatively estimate the proportion of total intake from these sources).

      Develop a guidance value for each medium by (if necessary) adjustment for body weight, volume of intake and relative absorption.

Example 3

      The principal route of exposure is oral. Based on estimated exposure, 50% of total intake comes from food, 20% from water, 20% from air and 10% from soil (after taking bioavailability into account from the oral and dermal routes). The compound is believed not to be present in consumer products.

      Data are adequate to establish both a TI_o and a TI_i. The TI_o and the TI_i are based on the same effects but the compound is much more toxic by the oral route (e.g., TI_o is less than the TI_i by more than two orders of magnitude).

      Allocate 50% of TI_o to food to derive a guidance value for food

*   multiply TI_o by 0.5

Allocate 20% of TI_o to water to derive a guidance value for drinking-water

*   multiply TI_o by 0.2

Allocate 10% of TI_o to soil to derive a guidance value for soil

*   multiply TI_o by 0.1

Allocate 20% of TI_i to air to derive a guidance value for air

*   multiply TI_i by 0.2

 Example 4

        The principal route of exposure is oral. Based on estimated exposure, 50% of total intake comes from food, 20% from water and 30% from air. There are no data indicating exposure from soil and consumer products.

        Data are adequate to establish both a TI_o and a TI_i for route-specific effects. The TI_o and the TI_i are based on route-specific effects and the compound is much more toxic by the oral route (e.g., TI_o is less than the TI_i by more than two orders of magnitude).

        Because the effects are route specific and the TIs are different by two orders of magnitude, each TI can be allocated in full to appropriate media.

        Allocate 50/70 (71%) of TI_o to food to derive a guidance value for food

*   multiply TI_o by 0.71

        Allocate 20/70 (29)% of TI_o to water to derive a guidance value for drinking-water

*   multiply TI_o by 0.29

        Allocate 100% of TI_i to air to derive a guidance value for air

*   multiply TI_i by 1

 Example 5

        The principal route of exposure is inhalation.

        Data are inadequate to establish a TI_i.

        Data are sufficient to establish a TI_o.

        Available toxicokinetic data are inadequate for or inconsistent with extrapolation across routes.

        Do not establish guidance values.

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APPENDIX 1

EXAMPLES - DEVELOPMENT OF GUIDANCE VALUES

     The following practical examples are provided to illustrate the
manner in which tolerable intakes (TIs) may be developed and allocated
for the derivation of guidance values for a general population (on the
basis of calculated proportions of exposure from various media). In
the calculation of guidance values, TIs may be rounded up to 1 or 2
significant figures depending on the quality of the data base and the
extent of uncertainties involved in deriving the TI. The level of
detail shown is that which is considered necessary for EHCs and should
be sufficient for adaptation at national and local levels.

Compound A

     Chlorinated hydrocarbon

 Estimates of exposure

        Estimated daily intakes of Compound A for adults (µg/kg
body weight per day)[1] in the general population are as follows:

```
        Ambient air[2]                          < 0.03
        Drinking-water[3]                 0.00007-< 0.0004
        Food[4]                                 0.004
        Soil                                   no data
        Consumer products                     no data

        Total Intake                            0.03
```

[1]   Assumed to weigh 64 kg, breathe 22 m^3 of air per day and drink
        1.4 litres of water Per day (ICRP, 1974) and to consume 125 g per day
        of a meat composite (the compound was not detected in other dietary
        composites).

[2]   Based on a mean concentration of Compound A reported in a survey
        of ambient Air from 22 sites (< 0.10 $µg/m^3$); concentrations in
        indoor air were similar to those in ambient air.

[3]   Based on a range of mean concentrations of Compound A in
        drinking-water of 0.003 µg/litre to < 0.02 µg/litre.

[4]   Based on a concentration of 0.0018 µg/g of Compound A detected in
        a representative daily diet.

        On the basis of these estimates, it is considered that the
percentage of total exposure from various media for the general
population (midpoints of estimated intakes) is as follows:

```
        outdoor/indoor air    =    < 0.03/0.03 = 85.9% (86%)
                                   (< 0.03 considered to be 0.03 minus
                                   intake from other media)

        drinking-water        =    0.000245/0.03 = 0.82% (0.8%)

        food                  =    0.004/0.03 = 13.3% (13%)

        soil                  =    no data

        consumer products     =    no data
```

 Development of TI

        The only data identified on long-term toxicity following
inhalation are the results of a single subchronic study for which no
effects were observed at any concentration. Available data are
considered inadequate, therefore, to establish a TI on the basis of
the results of studies in which Compound A has been administered by
inhalation. Moreover although the general population appears to be
exposed to Compound A principally in air, based on limited available
data on concentrations in food, the estimated intake in food is within
the range of that estimated for air for some age groups. In addition,
the principal route of intake of the most exposed age group (i.e.
suckling infants) is ingestion (of mothers' milk). Owing to the lack
of adequate long-term toxicity studies by the inhalation route and the
possible relatively important contribution that food makes to total

exposure to Compound A, a TI is derived on the basis of a long-term
ingestion bioassay, as follows:

$$TI = \frac{60 \text{ mg/kg body weight per day} \times 5}{100 \times 7} \quad \text{approx.} \quad 0.43 \text{ mg/kg (430 µg/kg) body weight per day}$$

where:

*   60 mg/kg body weight per day is the NOAEL, determined in a
    well-conducted and documented long-term (chronic and
    carcinogenesis) bioassay, with renal tubular degeneration
    observed at higher doses

*   5/7 is the conversion of five days per week of dosing to seven
    days per week

*   100 is the uncertainty factor (×10 for inter-individual
    variation; ×10 for interspecies variation; available data on
    toxicokinetics and toxicodynamics were inadequate to modify the
    10 × 10-fold uncertainty factor)

Derivation of Guidance Values

Outdoor/indoor air

The proportion of TI allocated to outdoor air based on exposure
estimates = 86%

    86% × TI (430 µg/kg body
    weight per day)   = 370 µg/kg body weight per day

    daily inhalation volume
    for adults   = 22 m^3

    mean body weight of adults   = 64 kg

$$\text{Guidance value for outdoor/indoor air} = \frac{370 \text{ µg/kg} \times 64 \text{ kg}}{22 \text{ } m^3}$$

$$= 1100 \text{ µg/}m^3$$

Drinking-water

The proportion of TI allocated to drinking-water based on
exposure estimates = 0.8% (too small to permit development of
meaningful guidance values since it contributes negligibly to total
intake)

Food

The proportion of TI allocated to food based on exposure
estimates = 13%

    13% × TI (430 µg/kg
    body weight per day)   = 57 µg/kg body weight per day

        (tolerances in various foodstuffs can be developed on the basis
        of the amounts ingested.)

   Soil

        Owing to lack of relevant data, it is not possible to allocate a
        proportion of the TI to this source.

   Compound B

        Chlorinated hydrocarbon solvent

   Estimates of Exposure

        Estimated daily intakes of Compound B for adults (µg/kg body
   weight per day)[1] in the general population are as follows:

        Ambient air[2]   0.01-0.27
        Indoor air[3]   1.4
        Drinking-water[4]   0.002-0.02
        Food[5]   0.12
        Soil   no data
        Consumer products   no data

        Total Intake   1.5-1.8

        On the basis of these estimates, it is considered that the
   percentage of total exposure from various media for the general
   population (based on midpoints of estimated intakes) is as follows:

        outdoor air   = 0.14/1.67 = 8.3%
        indoor air   = 1.4/1.67 = 83.8% (84%)
        drinking-water   = 0.011/1.67 = 0.65%
        food   = 0.12/1.67 = 7.1%
        soil   = no data
        consumer products = no data

   [1]   Assumed to weigh 64 kg, breathe 22 m^3 air and drink 1.4 litres
          of water per day (ICRP, 1974).

   [2]   Assumed to spend 4 h/day outdoors and based on a range of mean
          concentrations of Compound B (0.2 to 5.0 µg/m^3) from a survey.

   [3]   Assumed to spend 20 h/day indoors and based on the mean
          concentration of Compound B of approximately 5.1 µg/m^3 in the
          indoor air of 757 randomly selected homes examined in a survey.

   [4]   Based on a range of mean concentrations of Compound B (0.1 to
          0.9 µg/litre) in drinking-water from a number of surveys.

   [5]   Based on the average levels of Compound B in the various
          composite food groups in a study on the daily intake of these
          food groups.

       Development of TIs

A Tolerable Intake for Compound B can be derived as follows:

$$TI = \frac{[(678\ mg/m^3) \times (0.043\ m^3/day) \times (6/24) \times (5/7)]}{(0.0305\ kg) \times 1000}$$

= 170 µg/kg body weight per day

where:

*   678 mg/m^3 is the lowest-observed-adverse-effect level (LOAEL) overall in mice determined in an adequate long-term inhalation study and based on reduced survival and hepato-toxicity in males, and lung congestion and nephrotoxicity in males and females.

*   0.043 m^3/day is the assumed volume of air inhaled by mice

*   6/24 and 5/7 is the conversion of 6 h/day, 5 days/week to continuous exposure.

*   0.0305 kg is the average body weight of the mice in the critical study.

*   1000 is the uncertainty factor (×10 for inter-individual variation, ×10 for interspecies variation since available data on toxicokinetics and toxicodynamics were inadequate for modification of these factors, ×10 for use of a LOAEL rather than a NOAEL).

In order to ensure that the TI derived on the basis of an inhalation study is sufficiently protective, another TI can be derived on the basis of studies in which Compound B was administered by ingestion. With the exception of one investigation in which reversible erythropoietic damage was reported at low concentrations (50 µg/kg body weight per day) but not confirmed in other studies, the lowest NOAEL in the longest-term (90-day) available study in which Compound B was administered orally in drinking-water to rats is 14 mg/kg body weight per day, based on effects on body weight gain, the ratio of liver or kidney weight to body weight, and serum 5'-nucleotidase activity at the next highest dose. A LOEL of 20 mg/kg body weight per day based on a slight increase in liver weight was reported in a 6-week study on mice. Values for the TI derived on the basis of the results of these two studies are within the same order of magnitude as the TI calculated from the inhalation study.

Derivation of Guidance Values

Since the TIs derived on the basis of studies by inhalation and ingestion are within the same range and inhalation is the most important route of exposure of the general population, the TI developed for the inhalation route will be used as the basis for derivation of guidance values.

 Outdoor air

The proportion of TI allocated to outdoor air based on exposure estimates = 8.3%

8.3% × TI (170 µg/kg body

```
        weight per day)              = 14 µg/kg body weight per day

        daily inhalation volume
        for adults                   = 22 m³

        proportion of the day
        spent outdoors               = 4/24

        volume of outdoor air
        inhaled daily                = 22 m³ × 4/24 = 3.7 m³

        mean body weight of adults   = 64 kg

        Guidance value for                14 µg/kg × 64 kg
        outdoor air                  =
                                             3.7 m³

                                     = 242 µg/m³
```

   Indoor air

        The proportion of TI allocated to indoor air based on exposure
        estimates = 84%

```
        84% × TI (170 µg/kg body
        weight per day)              = 140 µg/kg body weight per day

        daily inhalation volume
        for adults                   = 22 m³

        proportion of the day
        spent indoors                = 20/24

        volume of indoor air
        inhaled daily                = 22 m³ × 20/24 = 18 m³

        mean body weight of adults   = 64 kg
```

```
  Guidance value for                 140 µg/kg × 64 kg
  indoor air                     =

                                          18 m³

                                   = 498 µg/m³
```

   Drinking-water

        The proportion of TI allocated to drinking-water based on
   exposure estimates = 0.65% (too small to permit development of
   meaningful guidance values since it contributes negligibly to total
   intake)

   Food

        The proportion of TI allocated to food based on exposure
   estimates = 7.1%

        7.1% × TI (170 µg/kg body

```
weight per day)                    = 12 µg/kg body weight per day or
                                     10 µg/kg body weight per day to
                                     one significant figure
```

(tolerances in various foodstuffs could then be developed on the
basis of amounts ingested.)

  Soil

      Owing to lack of relevant data, it is not possible to allocate a
proportion of the TI to this source.

Compound C

      Naturally occurring inorganic chemical

 Estimates of Exposure

      The percentage of total exposure from various media for adults in
the general population in country 1 is as follows:

```
outdoor/indoor air      = 0.02%
drinking-water          = 6.9%
food                    = 80%
soil                    = 0.11%
consumer products       = 12.8%
```

      In contrast, the percentage of total exposure from various media
for adults in the general population in one area in country 2 is as
follows:

```
outdoor/indoor air      = 35%
drinking-water          = 11%
food                    = 55%
```

 Development of TIs

      It is concluded, on the basis of data from several studies in
human populations, that the TI is 200 µg/kg body weight per day.

Derivation of Guidance Values - Country 1

 Outdoor/indoor air

      The proportion of TI allocated to air based on exposure estimates
= 0.02% (too small to permit development of meaningful guidance
values)

 Drinking-water

      The proportion of TI allocated to drinking-water based on
exposure estimates = 6.9%

```
6.9% × TI (200 µg/kg body
weight per day)                    = 13.8 µg/kg body weight per day

daily volume of ingestion of
drinking-water for adults
in Country 1                       = 1.5 litres
```

```
     mean body weight of adults
     in Country 1                      = 70 kg

Guidance value for                     13.8 µg/kg × 70 kg
drinking-water                  =
                                              1.5

                                = 644 µg/litre
```

Food

The proportion of TI allocated to food based on exposure estimates = 80%

```
     80% × TI (200 µg/kg body      160 µg/kg body weight per day
     weight per day)            = or 200 µg/kg body weight per
                                   day to one significant figure
```

(tolerances in various foodstuffs can then be developed on the basis of amounts ingested.)

Soil

The proportion of TI allocated to air based on exposure estimates = 0.11%

(too small to permit development of meaningful guidance values)

Consumer products

The proportion of TI allocated to consumer products based on exposure estimates = 12.8%

```
     12.8% × TI (200 µg/kg body
     weight per day)               = 26 µg/kg body weight per day
```

(limits in consumer products can be developed on the basis of patterns of use.)

Derivation of Guidance Values - Country 2

Outdoor/indoor air

```
     The proportion of TI allocated to air based on exposure
     estimates = 35%

     35% × TI (200 µg/kg body
     weight per day)               = 70 µg/kg body weight per day

     daily inhalation volume for
     adults in Country 2        = 20 m³

     mean body weight of
     adults in Country 2        = 60 kg

Guidance value for                     70 µg/kg × 60 kg
outdoor/indoor air              =

                                         20 m³

                                = 210 µg/m³
```

Drinking-water

The proportion of TI allocated to drinking-water based on exposure estimates = 11%

11% × TI (200 µg/kg body
weight per day)   = 22 µg/kg body weight per day

daily volume of ingestion of
drinking-water for
adults in Country 2   = 1.5 litres

mean body weight of
adults in Country 2= 60 kg

Guidance value for   22 µg/kg × 60 kg
drinking-water   = ─────────────────────
                                             1.5

                             = 880 µg/litre

Food

The proportion of TI allocated to food based on exposure estimates = 55%

55% × TI (200 µg/kg body
weight per day)   = 110 µg/kg body weight per day

(tolerances in various foodstuffs can be developed on the basis of amounts ingested.)

Soil

No data are available.

Consumer products

No data are available.

APPENDIX 2

GRAHICAL APPROACHES

The use of graphs of dose-effect and dose-response toxicity data to complement the text discussion in the development of TIs and guidance values is considered valuable. Such graphs can display an overview of the full range of dose-response information. Graphs can range from simple "thermometer" presentations as employed by the US Agency for Toxic Substances and Disease Registry (ATSDR, 1989), to dose-effect and dose-response graphs for specific toxic effects such as genotoxicity (Waters et al., 1988) or developmental toxicity (Kavlock et al., 1991), or to dose-duration graphs described by Hartung (1986), Hartung & Durkin (1986), and Dourson et al. (1985).

Fig. 4 is an example of a dose-duration graph and presents data for methoxychlor adapted from Dourson et al. (1985). This figure summarizes the available frank-effect levels (FEL), adverse-effect levels (AEL), no-observed-adverse-effect levels (NOAEL), and

no-observed-effect levels (NOEL). Adverse-effect levels are presented
as a function of both dose in mg/day and exposure as a fraction of
lifespan.

   Each point in the graph represents one dose group from one study.
The size of the point is a rough indication of its usefulness for
determining tolerable intakes, where larger points indicate more
useful information. Other information includes target organs. These
data can also be used to estimate a best fitting line for NOAEL across
duration.
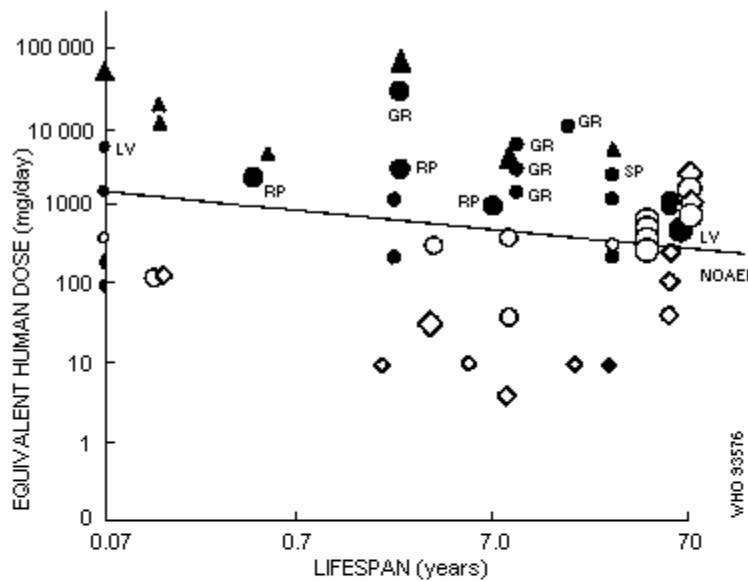
Fig. 4. Effect-dose-duration plot of all relevant human and animal oral
toxicity data for methoxychlor. Effect levels are shown for different
targets (LV = liver, RP = reproductive organ, GR = growth reduction,
SP = spleen). Animal doses have been converted by a body surface
area factor to approximate the equivalent human dose. Dose durations
are divided by the appropriate species lifespan to yield a fraction
which, when multiplied by 70 years (the assumed average human
lifespan), gives the corresponding position on the x axis, ie. a lifetime
exposure study in any species would be shown as 70 years. Study
usefulness is denoted by symbol size. Effect levels, listed in order of
decreasing severity, are:

   ▲ Frank-effect level (FEL)
   ● Adverse-effect level (AEL)
   ◯ No-observed-adverse-effect level (NOAEL)
   ◇ No-observed-effect level (NOEL)
   (based on Dourson et al., 1985)

APPENDIX 3

ALTERNATIVE APPROACHES

   Alternative approaches being considered in the derivation of TIs
for threshold effects include the benchmark dose and
categorical regression.

Benchmark dose

   The benchmark dose (BD) is the lower confidence limit (LCL) of
the dose that produces a small increase in the level of adverse

effects (e.g., 5 or 10%; Crump, 1984) to which uncertainty factors
(UF) can be applied to develop a tolerable intake (see Fig. 5, adapted
from Kimmel & Gaylor, 1988).
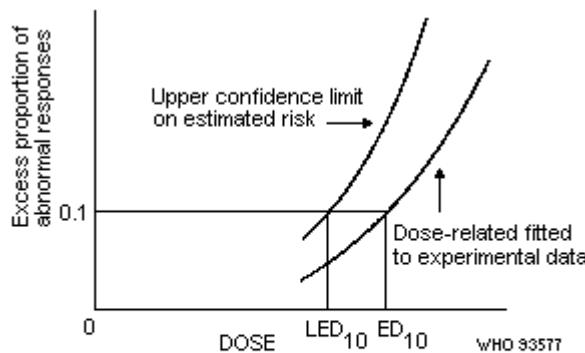
Fig. 5. Graphical illustration of benchmark dose (BD).
In this example LED_{10} = BD. BD could also be calculated
as LED_{05}, LED_{01} or other values. ED stands for
effective dose. (Adapted from Kimmel & Gaylor, 1988)

     The BD has a number of advantages over the NOAEL. Firstly, it is
derived on the basis of data from the entire dose-response curve for
the critical effect rather than that from the single dose group at the
NOAEL (i.e. one of the few (usually three) preselected dose levels).
Use of the BD also facilitates comparison of studies on the same agent
or the potencies of different agents. The BD can also be calculated
from data sets in which a NOAEL was not determined, eliminating the
need for an additional uncertainty factor to be applied to the LOAEL.
Lastly, definition of the BD as a lower confidence limit accounts for
the statistical power and quality of the data. That is, the
confidence intervals around the dose-response curve for studies with
small numbers of animals and, therefore, lower statistical power would
be wide; similarly, confidence intervals in studies of poor quality
with highly variable responses would also be wide. In either case,
the wider confidence interval would lead to a lower BD, reflecting the
greater uncertainty of the data base. On the other hand, narrow
confidence limits (reflecting better studies) would result in higher
BDs.

     One of the chief disadvantages of this approach is that it is not
possible to determine a BD for many types of data on toxicity (e.g.,
histopathological data).

     Several methods have been published for determining both the
dose-response curve from which the BD is derived and appropriate
uncertainty factors to estimate the TI (e.g., Crump, 1984; Dourson et
al., 1985; Kimmel & Gaylor, 1988; Gaylor, 1989; Allen et al., 1992).
However, there is as yet, no consensus on the incidence of effect to
be used as a basis for the BD, although it should be comparable to the
level of effect typically associated with the NOAEL. For data bases
on developmental toxicity, it has been estimated that this level of
effect is in the range of 1-10% (Crump, 1984; Gaylor, 1989, 1992);
this range is similar for other toxic end-points (Farland & Dourson,
1992; Shoaf, 1994). Allen et al. (1992, 1993) have estimated that a
BD calculated from the LCL at 5% is, on average, comparable to the
NOAEL, whereas choosing a BD from the LCL at 10% is more
representative of a LOAEL (Farland & Dourson, 1992). Choosing a BD

that is comparable to the NOAEL has two advantages: (i) it is within the experimental dose-range, eliminating the need to interpolate the dose-response curve to low levels; and (ii) justification of the application of similar UFs as are currently applied to the NOAEL for interspecies and inter-individual variation.

Categorical Regression

The theory and application of categorical regression has been addressed by Hertzberg & Miller (1985), Hertzberg, (1989), Guth et al. (1991) (inhalation exposure to methylisocyanate), and Farland & Dourson (1992) (oral exposure to arsenic). Data on toxicity are classified into one of several categories, such as NOEL, NOAEL, AEL or FEL, or others, as appropriate. These categories are then regressed

on the basis of dose and, if required, duration of exposure. The result is a graph of probability of a given category of effect with dose or concentration, which is useful in the analysis of potential risks above the TI, especially for comparisons amongst chemicals.

Depending on the extent of the available data on toxicity, additional estimations regarding the percentage of individuals with specific adverse effects are possible. Such estimations require, however, an understanding of the mechanisms of toxicity of the critical effect, knowledge of the extrapolation between the experimental animal and man, and/or incidences of specific effects in humans.

Similar to the BD, categorical regression utilizes information from the entire dose-response curve, resulting in more precise estimates of risk when compared to the current approach (NOAEL-based TIs). However, categorical regression requires more information than the current TI method, and the interpretation of the probability scale can be problematic.

APPENDIX 4

BODY WEIGHT AND VOLUMES OF INTAKE FOR REFERENCE MAN

 (based on ICRP, 1974, unless otherwise indicated)

Body weight, kg

```
    Adult male      =  70
    Adult female    =  58
    Average         =  64[a]
```

Daily fluid intake (milk, tap water, other beverages), ml/day

 Normal conditions:

```
    Adults              =  1000-2400, representative
                              figure = 1900[b] (excluding
                            milk: 1400[c])
    Adult male          =  1950
    Adult female        =  1400
    Child (10 years)    =  1400
```

 High average temperature (32°C):

```
        Adults                =   2840-3410

   Moderate activity:

        Adults                =   3700
```

Respiratory volumes

8-h respiratory volume, litres

```
        resting:              Adult man        = 3600
                              Adult woman      = 2900
                              Child (10 years) = 2300
        light/non-occupational
        activity:             Adult man        = 9600
                              Adult woman      = 9100
                              Child (10 years) = 6240
```

Daily inhalation volume, m^3

(8-h resting, 16-h light/non-occupational activity)

```
        Adult male        =  23
        Adult female      =  21
        Child (10 years)  =  15
        Average adult     =  22
```

```
Proportion of time
spent indoors[c]          = 20 h/day

Amount of soil ingested[c]  = 20 mg/day
```

Dietary intake[d]

```
        Cereals             =  323 g/day (flour and milled rice)
        Starchy roots       =  225 g/day (sweet potatoes, cassava
                               and other)
        Sugar               =  72 g/day (includes raw sugar,
                               excludes syrups and honey)
        Pulses and nuts     =  33 g/day (includes cocoa beans)
        Vegetables and fruits =  325 g/day (fresh equivalent)
        Meat                =  125 g/day (includes offal, poultry
                               and game in terms of carcass weight,
                               excluding slaughter fats)
        Eggs                =  19 g/day (fresh equivalent)
        Fish                =  23 g/day (landed weight)
        Milk                =  360 g/day (excludes butter; includes
                               milk products as fresh milk
                               equivalent)
        Fats and oils       =  31 g/day (pure fat content)
```

[a] WHO uses 60 kg for calculation of acceptable daily intakes and
     water quality guidelines (WHO, 1987, 1993).
[b] WHO uses a daily per capita drinking-water consumption of 2 litres
     in calculating water quality guidelines (WHO, 1993)
[c] From Health and Welfare Canada (1992)
[d] Based on average of estimates for 7 geographical regions

        (ICRP, 1974)

RESUME

        Des valeurs guides devraient être établies dans les Critères
d'hygiène de l'environnement (CHE) de l'IPCS pour l'exposition aux
produits chimiques présents dans l'environnement. Ces valeurs guides
pourront être modifiées par les autorités nationales et locales
lorsque celles-ci fixeront leurs normes et limites pour les différents
milieux. L'élaboration des valeurs guides pour les produits chimiques
comporte les étapes suivantes:

1. Evaluer et résumer les données relatives à la toxicité pour
l'homme et l'animal et à l'exposition humaine qui offrent un intérêt
particulier pour le calcul des valeurs guides. Ces données devraient
de préférence être présentées sous la forme d'un texte explicatif
résumant les points cruciaux, complété par des graphiques.

2. Ces données pourront servir à calculer une dose tolérable (DT)
pour les différentes voies d'exposition dans le cas des effets pour
lesquels on considère qu'il existe un seuil. Le calcul consiste
généralement à appliquer des facteurs d'incertitude aux doses sans
effet indésirable observé (DSEIO) établies par l'étude la plus
pertinente pour les effets critiques. En ce qui concerne les effets
pour lesquels il n'existe pas de seuil, la relation dose-réponse devra
être caractérisée aussi complètement que possible.

3. Estimer la proportion de la dose totale provenant des différents
milieux (atmosphère à l'intérieur des locaux, air ambiant, nourriture,
eau, etc.) dans une situation donnée, en prenant comme base de calcul
un ensemble cohérent de données sur les volumes théoriques absorbés
par l'"homme de référence" de la Commission internationale de
protection contre les radiations (CIPR) et des concentrations
représentatives de l'environnement général. En l'absence de données
adéquates sur les concentrations dans les différents milieux, on
pourra utiliser des modèles mathématiques pour estimer la répartition
entre ces milieux.

4. Attribuer une proportion de la DT aux différents milieux (d'après
les résultats de l'estimation décrite à l'étape 3 ci-dessus) de façon
à déterminer la dose ou l'exposition attribuable à chaque milieu.

5. Etablir des valeurs guides pour les doses attribuées à chaque
milieu en tenant compte éventuellement du poids corporel, du volume
absorbé et de l'efficacité de l'absorption (efficacité d'absorption
 relative lorsque la valeur guide est calculée à partir de la DT
établie pour une autre voie d'exposition). Dans les monographies de
la série CHE, les valeurs guides devraient être établies pour un
scénario d'exposition clairement défini, fondé sur les données
applicables à l'homme de référence de la CIPR, données qui ne sont pas
nécessairement représentatives des conditions nationales ou locales
d'exposition. Normalement, les valeurs guides seront calculées pour
une population générale représentative, soumise à des conditions
d'exposition également représentatives. Elles devront être adaptées
au niveau national et local en fonction des circonstances.

6. La base de calcul des DT et des valeurs guides devrait être
clairement expliquée dans les monographies de la série CHE (pour le
niveau de détail exigé, voir les exemples de l'appendice 1).

RESUMEN

        En los monografías de la serie Criterios de Salud Ambiental (EHC)
del IPCS deben formularse valores orientativos para la exposición a
sustancias químicas presentes en el medio ambiente, valores que las
autoridades nacionales y locales pueden modificar al determinar sus
límites y normas aplicables al medio. Los pasos previstos para
cualquier sustancia química son los siguientes:

1. Evaluar y resumir la información referente a la toxicidad en los
animales y el hombre y la exposición en el hombre, seleccionando la
más pertinente para el cálculo de los valores orientativos. El
esquema más apropiado para presentar los datos pertinentes con miras
al cálculo de los valores orientativos es un texto que describa
sucintamente los datos críticos, complementado con los gráficos
oportunos.

2. Calcular a partir de esos datos una Ingesta Tolerable (IT) para
las diversas vías de exposición y para los distintos efectos que se
considere que tienen un umbral. Ello entraña el uso de factores de
incertidumbre, aplicados por lo general al nivel sin efectos adversos
observados (NOAEL) para los efectos críticos referidos en el estudio
más pertinente. En el caso de los efectos sin umbral, se
caracterizará en la medida de lo posible la relación dosis-respuesta.

3. Estimar la proporción de ingesta total que tiene su origen en los
diversos medios (p. ej., aire de espacios interiores y ambiental,
alimentos y agua), sobre la base de las exposiciones calculadas para
un conjunto coherente de volúmenes supuestos de ingesta (utilizando el
hombre de referencia de la Comisión Internacional de Protección contra
las Radiaciones (CIPR)) y de concentraciones representativas en el
medio ambiente general para una determinada situación. Si no se
dispone de datos suficientes sobre las concentraciones en diversos
medios, pueden emplearse modelos matemáticos para estimar la
distribución por esos medios.

4. Asignar una proporción de la IT a diversos medios de exposición
(basándose en la exposición estimada conforme a lo explicado en el
paso 3 precedente) para determinar la ingesta o exposición en cada
medio.

5. Formular valores orientativos a partir de las ingestas asignadas a
cada medio, teniendo en cuenta (si es necesario) el peso corporal, el
volumen de ingesta y la eficiencia de absorción (la eficiencia de
absorción *relativa* cuando para calcular el valor orientativo se
utilice la IT correspondiente a otra vía de exposición). En los
monografías de la serie EHC se formularían valores orientativos para
unas condiciones de exposición claramente definidas, basadas en los
datos del hombre de referencia de la CIPR y no necesariamente
representativas de las condiciones de exposición nacionales o locales.
Se calcularán comúnmente valores orientativos para una población

general representativa y unas condiciones de exposición
representativas. Los valores orientativos se deberán adaptar a nivel
nacional y local según proceda en función de las circunstancias
locales.

6. En los monografías de la serie EHC se deberán detallar claramente
los fundamentos del cálculo tanto de la IT como de los valores
orientativos (respecto al grado de detalle, véanse los ejemplos

presentados en el apéndice 1).

See Also: 6/1/2007
   Toxicological Abbreviations