

Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment

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The science behind the use of uncertainty factors has progressed considerably. Increased knowledge of inter- and intraspecies sensitivity, mechanisms of action, and detailed evaluation of data bases can support the use of data-derived uncertainty factors, which ultimately results in a risk assessment with greater confidence. Papers that highlight available data for each of several areas of uncertainty are discussed, indicating that choice of the appropriate factor requires scientific judgement on a case-by-case basis. Case studies from EPA and Health Canada risk values illustrate the use of data in chemical specific risk assessments to support the selection of uncertainty factors other than the default value of 10-fold. In the case studies, the types of data that have been used to support a change in the default value are explicitly reviewed, as well as why the data support a different uncertainty factor, how the uncertainty was reduced, and what assumptions have been satisfied or replaced. Incorporation of all available scientific data into the risk assessment process fosters increased research and ultimately reduces uncertainty. The results of this review support the use of data-derived uncertainty factors when appropriate scientific data are available. © 1996 Academic Press, Inc.

INTRODUCTION

Health organizations throughout the world utilize a "safe" dose concept in the dose-response assessment of noncancer toxicity. This safe or subthreshold dose has often been referred to by different names, such as acceptable daily intake (ADI) (Lu, 1988; Truhaut, 1991; Lu and Sielken, 1991), tolerable daily intake (TDI) or tolerable concentration (TC) (Meek *et al.*,

1994; IPCS, 1994), minimal risk level (MRL) (Pohl and Abdin, 1995), reference dose (RfD) (Barnes and Dourson, 1988; Dourson, 1994), and reference concentration (RfC) (EPA, 1994; Jarabaek, 1994). The approaches used by these various health organizations share many of the same underlying assumptions, judgments on critical effect, and choices of uncertainty (or safety) factors.

Few chemicals have been adequately studied in humans to accurately identify a subthreshold dose directly. Therefore, scientists typically rely on existing human epidemiologic and animal laboratory data to estimate subthreshold doses for humans. In estimating a subthreshold dose for a given chemical, scientists first review all toxicity data, judge what constitutes an adverse effect, and determine the critical effect. The critical effect is the first adverse effect that occurs as dose or concentration increases. Not all effects are adverse effects, and the judgment of what constitutes an adverse effect is sometimes difficult.

Scientists then determine the appropriate uncertainty (or safety) factors to apply to the No-Observed-Adverse-Effect Level (NOAEL) or Lowest-Observed-Adverse-Effect Level (LOAEL) for the critical effect, based on considerations of the available toxicity, toxicodynamic, and toxicokinetic data. Uncertainty factors (UFs) used in the estimation of subthreshold doses are necessary reductions to account for the lack of data and inherent uncertainty in these extrapolations. For example, when human data are not available, many subthreshold doses are based upon the results of toxicity studies in experimental animals.

Health organizations and regulatory bodies accommodate areas of uncertainty similarly. For example, most agencies use a 100-fold default factor to address the extrapolation of a NOAEL found in a chronic (lifetime) animal study to the subthreshold dose for humans (Table 1). Invariably, this 100-fold default factor reflects a 10-fold factor for experimental animal-to-human extrapolation and a 10-fold factor for extrapolation of an average human NOAEL to a sensitive human NOAEL. The resulting dose is considered to be synony-

The opinions expressed in this paper are those of the authors and do not necessarily represent the views of ILSI.

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TABLE 1
Description of Typical Uncertainty and Modifying Factors in the Development
of Subthreshold Doses for Several Groups^a

Uncertainty factors (UFs) ^b	Guidelines ^c	Agency				
		Health Canada	IPCS	RIVM	U.S. ATSD R	U.S. EPA
		UF value				
Interhuman (or intraspecies)	Generally use when extrapolating from valid results from studies of prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among humans and is thought to be composed of toxicokinetic and toxicodynamic uncertainties.	1-10	10 (3.16 × 3.16)	10	10	10
Experimental animal to human	Generally use when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to humans and is also thought to be composed of toxicokinetic and toxicodynamic uncertainties.	1-10	10 (2.5 × 4.0)	10	10	10
Subchronic to chronic	Generally use when extrapolating from less than chronic results on experimental animals or humans. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs or LOAELs to chronic NOAELs or LOAELs.			10	NA ^d	≤10
LOAEL to NOAEL	Generally use when extrapolating an LOAEL to a NOAEL. This factor is intended to account for the experimental uncertainty in developing a subthreshold dose from an LOAEL, rather than a NOAEL.			10	10	≤10
Incomplete data base to complete	Generally use when extrapolating from valid results in experimental animals when the data are "incomplete." This factor is intended to account for the inability of any single study to adequately address all possible adverse outcomes.	1-100	1-100	NA	NA	≤10
Modifying factor	1-100 Generally use upon a professional assessment of scientific uncertainties of the study and data base not explicitly treated above (for example, the number of animals tested).	1-10	1-10	NA	NA	0 < to ≤10

^a Source: Dourson (1994), Jarabek (1994), IPCS (1994), Meek *et al.* (1994), Pohl and Abdin (1995), and Rademaker and Linders (1994).
^b The maximum uncertainty factor used with the minimum confidence data base is generally 10,000. See text for discussion.
^c Professional judgment is required to determine the appropriate value to use for any given UF. The values listed in this table are nominal values that are frequently used by these agencies.
^d ATSDR (Agency for Toxic Substances and Disease Registry) develops MRLs for specified durations of exposure, and generally does not extrapolate among durations. Therefore, an uncertainty factor for extrapolation between subchronic and chronic exposures is not used.

mous with an estimate of a subthreshold dose. Other areas of uncertainty include extrapolations of subchronic-to-chronic exposure, LOAEL to NOAEL, and incomplete data base. The major assumptions underlying each of these UFs are described in Table 2.

Numerous scientists have investigated the accuracy and limitations of default UFs. Dourson and Stara (1983) demonstrated that the 10-fold default values tend to be protective from the standpoint of the behavior of the average chemical. As UFs increase in number,

TABLE 2
Major Assumptions for Individual Uncertainty Factors^a

Factor	Assumptions
Interhuman	Assumes that there is variability in response from one human to the next and that this variability may not have been detected in the study, usually due to small sample size; may also assume that subpopulations of humans exist that are more sensitive to the toxicity of the chemical than the average population.
Animal to human	Assumes that results seen in experimental animals are relevant to humans and that humans are more sensitive than animals at a given mg/kg day dose or mg/m ³ concentration; this UF may also account for assumptions about specific toxicokinetic and toxicodynamic properties.
Subchronic to chronic	Assumes that an effect seen at subchronic exposures will be seen at lower doses after chronic exposures; may also assume that effects may only be seen after an experimental group is exposed chronically.
LOAEL to NOAEL	Assumes that the chosen LOAEL is reasonably close to the projected NOAEL in an experiment, and that the use of this uncertainty factor will drop the LOAEL into the range of the expected NOAEL.
Incomplete data	Assumes that the critical effect can be discovered in a reasonably small selection of toxicity studies.

^a This list of assumptions is not exhaustive.

the potential for overprotection increases substantially. Most agencies that estimate these subthreshold doses recognize this increasing protectiveness as a limitation, and they combine several areas of uncertainty together within a single 10-fold value. Subthreshold doses are considered by risk assessment scientists to be below the population threshold for many, if not all, chemicals. However, the exact degree to which these doses or concentrations are below the population threshold is not generally known. For example, EPA considers an RfD or RfC to have uncertainty spanning perhaps an order of magnitude. This consideration has several interpretations, the most common one being that an RfD of 1 mg/kg/day might have a range of 0.3 to 3 mg/kg/day, indicating a one-half order of magnitude both above and below the RfD. However, as the composite uncertainty factor grows larger with increasingly weaker data bases, the imprecision of the resulting subthreshold dose also grows larger.

The purpose of this paper is to review the scientific basis that underlies specific uncertainty factors, briefly discuss three novel approaches to data-derived uncertainty factors, provide illustrative case studies where regulatory agencies have utilized uncertainty factors that are other-than-default values of 10-fold, and provide a basis for the use of data-derived uncertainty factors whenever sufficient data are available.

RESEARCH INTO THE VALIDITY OF UNCERTAINTY FACTORS

Research into specific areas of uncertainty has been reported, most of which supports the conservative nature of the 10-fold default values generally used in non-cancer risk assessments. Zielhuis and van der Kreek (1979), Dourson and Stara (1983), McColl (1990), and Kroes *et al.* (1993) highlight available data for each of several areas of uncertainty, indicating that although

default values of 10-fold are often used, the choice of appropriate factors reflects a case-by-case judgment by experts. These publications also indicate that UFs tend to be protective, i.e., the composite uncertainty factor tends to be a conservative estimate which results in the estimation of a dose that is likely to be without adverse effects in sensitive individuals for a lifetime of exposure. This section briefly reviews the latest research that support the use of these factors. A more in-depth treatment of this subject is provided in the report of TERA (1996).

Interhuman Variability

Whenever possible, data on humans are used to conduct noncancer risk assessment, thereby avoiding the problems inherent with interspecies extrapolation. If sufficient data on sensitive individuals exist, the subthreshold dose can be estimated directly, i.e., without the need of an uncertainty factor. If adequate data on sensitive humans do not exist, an uncertainty is encountered that must be addressed—most often with a 10-fold factor. This uncertainty factor assumes that variability in response from one human to the next occurs and that this variability may not have been detected in the study, usually due to small sample size. This factor may also assume that subpopulations of humans exist that are more sensitive to the toxicity of the chemical than the average population.

Dourson and Stara (1983) describe an analysis of acute toxicity data in experimental animals on 490 chemicals from Weil (1972), which suggested that for about 92% of the chemicals a 10-fold factor would yield an adequate reduction from a median response. They concluded that a 10-fold factor to account for interhuman variability was indirectly supported, but that since experimental animals are generally less heterogeneous when compared to humans, the 10-fold factor

was not necessarily conservative. Calabrese (1985) found considerable differences among human subjects in their capacity to metabolize foreign substances, and concluded that a 10-fold factor provided protection for about 80–95% of the population. This conclusion, however, was based on the supposition that the 10-fold factor was to account for the total range of human variability. Hattis *et al.* (1987) analyzed 101 data sets of individual toxicokinetic parameters for 49 specific substances (mostly drugs) in groups of five or more healthy adults. These data suggested that a 10-fold uncertainty factor accounted for about 96% of the variation in these toxicokinetic parameters. However, these data also measured the total range of human variability in this experiment, and not the median to sensitive human variability. Sheeman and Gaylor (1990) compared the LD₅₀ ratios of adult to newborn mammals for 238 chemicals as a measure of intraspecies variability. The median ratio was 2.6 (adult to newborn). About 86% of the values were less than a 10-fold ratio, similar to observations by Dourson and Stara (1983).

In general, the default value of 10 for interhuman variability appears to be protective when starting from a median response, or by inference, from a NOAEL assumed to be from an average group of humans. However, when NOAELs are available in a known sensitive human subpopulation, or if human toxicokinetics or toxicodynamics are known with some certainty, this default value of 10 should be adjusted or replaced accordingly.

Animal to Human

If adequate toxicity data on humans do not exist, then experimental animal data are used as the basis of the assessment, and an uncertainty factor of 10 is routinely applied to the NOAEL. The basic assumptions for this uncertainty factor are that the results seen in experimental animals are relevant to humans, that toxicokinetic and toxicodynamic differences exist among species, and that humans are more sensitive than animals at a given mg/kg/day dose or mg/m³ concentration. A number of authors have tried to quantify this area of uncertainty by investigating the ratios between animals and humans, and between different animal species for a number of parameters.

For example, Brown and Fabro (1983) identified the lowest effective dose to cause teratogenicity in animals and humans for eight chemicals. Ratios (animal-to-human) vary from 1.8 to 50, with a geometric mean of 7. For the chemicals examined, these authors state that humans appear to be more sensitive, although the difference is generally less than an order of magnitude. Dourson and Stara (1983) showed an interspecies adjustment factor calculated as the cubed root of the ratio between the assumed average human body weight (70 kg) and animal weight. Assuming that such an adjust-

ment could account for all of the differences in animal to human extrapolation, then a 10-fold factor accounts for many of the experimental animal to human differences. Ford (1990) suggests that kinetic and metabolic data, when available, should be used in the assessment of the likely human health hazard of reproductive toxicants from animal toxicity data. Calabrese *et al.* (1992) and Hoel *et al.* (1975) have recommended that an uncertainty factor for animal-to-human extrapolation and a technique for dose normalization be considered separately. In this case, the adjustment based on body weight might account for toxicokinetic differences; toxicodynamic differences would be addressed by a separate factor. An example of this recommendation which might be worked into the existing subthreshold dose methods is provided in the Renwick (1993) approach discussed in the next section.

Perhaps the most promising research in the area is that of physiologically based pharmacokinetic (PBPK) modeling. Such modeling can serve as the basis for replacing the toxicokinetic component of the traditional 10-fold uncertainty factor for interspecies extrapolation in noncancer risk assessment. The use of PBPK models for this purpose is likely to grow (Jarabek, 1995a,b). Agencies such as Health Canada, IPCS, and EPA have positions reflecting the use of reduced interspecies UF when dosimetric adjustments, toxicity data, or comparative toxicokinetics are available.

Less-Than-Chronic Studies to Chronic

The subchronic-to-chronic UF is based on the assumption that an effect seen at shorter durations will also be seen after a lifetime of exposure, but at lower doses. This factor also assumes that effects may only be seen after an experimental group is exposed chronically. In fact, several investigators have examined subchronic-to-chronic ratios of NOAELs and LOAELs, and the average differences between subchronic and chronic values are only 2 to 3, while some small percentage of chemicals have ratios that exceed 10-fold (McNamara, 1976; Dourson and Stara 1983; Woutersen *et al.*, 1984; Aida *et al.*, 1992; Kadry *et al.*, 1995). Lewis (1993) showed an analysis of subchronic-to-chronic NOAEL ratios based on peer-reviewed literature or information from the U.S. National Toxicology Program. Criteria for inclusion in their analysis were rigorous. Of 54 chemicals considered, only 18 chemicals were analyzed. Of these, 78% had ratios of 3.5 or less. All but one of these ratios (17/18, or 94%) had ratios of 10-fold or less. Unpublished work in EPA (Swartout, 1995) encompasses more chemicals than described above, but the criteria for inclusion are not as rigorous. Despite this lack of rigor, however, the mean of these unpublished ratios lies between 2- and 3-fold with approximately 95% of the ratios with values of 10-fold or less.

The data shown here suggest that the routine use of a 10-fold default factor for this area of uncertainty should be examined closely. For example, short-term (2 weeks) and subchronic (90 days) NOAELs are often available for comparison, which can give an indication of the possible differences in the subchronic NOAEL and the expected chronic NOAEL. When such data are not available, a 10-fold uncertainty factor may not be unreasonable, but it should be considered as a loose upper-bound estimate to the overall uncertainty.

LOAEL to NOAEL

If a LOAEL exists on which to base the estimation of a subthreshold dose, the uncertainty in the NOAEL must be addressed. Analysis of several data bases suggest that a factor of 10 or lower is adequate and that use of data does support a lower factor with certain chemicals. For example, Dourson and Stara (1983) describe ratios of LOAELs to NOAELs of either subchronic or chronic exposures based on data from Weil and McCollister (1963). Ninety-six percent of these ratios had values of 5-fold or less. Kadry *et al.* (1995) also evaluated the uncertainty factor for LOAEL to NOAEL extrapolation for several chlorinated compounds. Ratios were 1.4 to 8.9 for methylene chloride, 2 to 5 for pentachlorophenol, 2 or 4.2 for monochlorobenzene, 3.3 or 10 for chlorpyrifos, and 1.6 or 2.2 for 1,1-dichloroethane. The authors conclude that 91% of these ratios were 6-fold or less; all of them were 10-fold or less.

The results of the research on LOAEL to NOAEL extrapolation are neither extensive nor unexpected. Experiments are seldom designed with doses in excess of 10-fold apart, leading to the common statement that these ratios depend more on dose spacing than inherent toxicity. The choice of dose spacing, however, often reflects the judgment on the likely steepness of the dose-response slope, with steeper slopes resulting in tighter dose spacing. The data indicate that when faced with a LOAEL and not a NOAEL, the choice of uncertainty factor should generally depend on the severity of the effect at the LOAEL. More severe effects should be judged to need a larger uncertainty factor because the expected NOAEL is further away from the LOAEL. Less severe effects would not require a large factor, because, presumably, the LOAEL is closer to the unknown NOAEL.

Data Base Insufficiencies

If data are only available from one chronic study on which to base the estimation of a subthreshold dose, the question may be asked whether data from chronic studies in other species or data from different types of bioassays (such as reproductive or developmental toxicity) would yield lower NOAELs. If so, an uncertainty exists that must be addressed. The default approach to address this uncertainty is by dividing by a

3- or 10-fold uncertainty factor, based on the assumption that the critical effect can be discovered in a reasonably small selection of toxicity studies.

Dourson *et al.* (1992) examined the use of this factor through an analysis of frequency histograms of NOAEL ratios for chronic dog, mouse, and rat studies, and reproductive and developmental toxicity studies in rats. On average, chronic rat and dog studies yielded similar NOAELs; reproductive and developmental toxicity studies were somewhat less sensitive, but still yielded useful information. These authors concluded that more than one bioassay is needed to develop a high confidence estimate of a subthreshold dose, and that if one or more bioassays are missing, then a factor should be used to address this scientific uncertainty. This analysis is supported by the work of Heywood (1981, 1983) and others that show different target organs among species more than 50% of the time. The results of both these investigators suggest the use of an uncertainty factor to account for missing bioassays. However, the quantification of this uncertainty factor requires additional work.

DATA-DERIVED UNCERTAINTY FACTORS

The science behind the use of uncertainty factors has progressed considerably over the past years. Increased knowledge of inter- and intraspecies sensitivity, mechanism of action, and detailed evaluation of data bases has led to improvements that allow for the incorporation of more scientific data into the dose-response assessment of noncancer toxicity, and permit the use of factors other than the standard default values. Several novel approaches have been proposed for substituting scientifically derived UFs for standard defaults. Three methods are described below.

Lewis, Lynch, and Nikiforov (1990)

Lewis *et al.* (1990) developed an alternative methodology for establishing guidelines for determining acceptable atmospheric emissions, although it is acknowledged that this approach is equally applicable to other routes of exposure. This model, hereafter referred to as the Lewis-Lynch-Nikiforov (LLN) model, is described by the authors as having three distinguishing features:

1. Emphasis is placed on the separation of expert/scientific judgments from policy/value judgments, with the former requiring professional experience and training and the latter reflecting societal values.
2. Focus is placed on providing a plausible estimate of the true risk from a defined exposure, rather than providing a boundary estimate which is not likely to underestimate risk (e.g., the approach of regulatory agencies). The level of uncertainty associated with a

TABLE 3
Adjustment Factors of the Lewis, Lynch, and Nikiforov (1990) Model

AF ^a	Description	Range of values	Most likely value	Default value
<i>S</i>	Scaling factor to account for known quantitative differences between species and between experimental conditions and those likely to be encountered by humans	>0	NS ^b	
<i>I</i>	Intraspecies variability	1-10	1-3 ^c	10
<i>R</i>	Interspecies extrapolation	>0-10	NS	10
<i>Q₁</i>	Degree of certainty that the critical effect observed in laboratory animals is relevant to humans	0.1-1		1
<i>Q₂</i>	Subchronic to chronic extrapolation	1-10	1-3	10
<i>Q₃</i>	LOAEL to NOAEL extrapolation	NS	2	10
<i>U</i>	Accounts for residual uncertainty in estimates of <i>S</i> , <i>I</i> , and <i>R</i>	1-10	NS	10
<i>C</i>	A "nonscientific, judgmental 'safety' factor"	1-10	≤3	1

^a AF, Adjustment Factor.

^b NS, Not Stated by authors.

^c Most likely value based on study of high quality

given assessment is expressed separately from the maximum likelihood value of risk.

3. Scientific consensus on adjustment factors is valued over independent assessments.

With regard to the first point, the LLN approach makes a careful distinction between factors used to adjust, for example, an animal NOAEL to a human NAEL (No-Adverse-Effect Level), and those factors that are applied to incorporate a "margin of safety." The adjustment factors are considered to be rooted in science and the determination of the appropriate magnitude of these factors is within the purview of the risk assessor. The margin of safety, however, is considered to be outside of the scientific realm and should, according to LLN, be left to risk managers and policy makers.

The areas for which adjustment factors (the preferred term by LLN) are suggested are quite similar to those used by others,

$$NAEL_{\text{human}} = \frac{NOAEL_{\text{animal}} S}{IRQ_1Q_2Q_3UC}$$

where the terms are described in Table 3.

Renwick (1993)

Renwick (1991, 1993) has examined the nature of the uncertainty factors generally applied for intraspecies and interspecies extrapolations. He has proposed the division of each of these UFs into subfactors to allow for separate evaluations of differences in toxicokinetics and toxicodynamics. The toxicokinetic considerations include absorption, distribution, metabolism, and excretion of a toxic compound, and therefore address differences in the amount of the parent compound or active metabolite available to the target organ(s). The toxicodynamic considerations are based on variations

in the inherent sensitivity of a species or individual to chemical-induced toxicity, and may result from differences in host factors that influence the toxic response of a target organ to a specified dose. The advantage to such a subdivision is that components of these UFs can be addressed where data are available (e.g., if data exist to show similar toxicokinetic handling of a given chemical between laboratory animals and humans, then the interspecies extrapolation factor would need to account only for differences in toxicodynamics).

Renwick (1993) examined in detail the relative magnitude of toxicokinetic and toxicodynamic variations between and within species. He found that toxicokinetic differences were generally greater than toxicodynamic differences, resulting in a proposal that the 10-fold overall uncertainty factor be subdivided into factors of 4 for kinetics and 2.5 for dynamics. The International Programme on Chemical Safety (IPCS, 1994) has adopted the principles set forth by Renwick (1991, 1993), but has suggested that while the UF for interspecies extrapolation be subdivided unequally into 4-fold (toxicokinetics) and 2.5-fold (toxicodynamics), the UF for intraspecies extrapolation should be split evenly (3.16-fold for both kinetics and dynamics).

Probabilistic Approaches

Swartout *et al.* (1994) and Baird *et al.* (1996) have investigated the probabilistic nature of uncertainty factors. The premise behind this research is that data exist to support a range of values for each default uncertainty factor. Expression of the likely probability of the numeric value of each uncertainty factor is based on actual toxicity data on groups of chemicals for which RfDs have been developed. This type of evaluation lends much more credibility to the use of the uncertainty factor approach, as it acknowledges the inherent

variability of these factors. This research can be further refined by using data on similar chemicals.

Data-derived distributions for each of the uncertainty factors have been published by Baird *et al.* (1996). Those used by Swartout *et al.* (1994) in developing RfDs are being further refined. The most likely distribution for each of these uncertainty factors will be log-normal, although data may support alternative distributions. The assumptions upon which Swartout *et al.* (1994) establish these distributions include:

- an UF of 10 represents the 95th percentile
- an UF of 3 (half-log) represents the 50th percentile
- the UF for interspecies subchronic-to-chronic and LOAEL-to-NOAEL extrapolations are bounded by values of 1 and 50
- the UF for interspecies extrapolation is bounded by values of 0.2 and 50.

For RfDs that have more than one area of uncertainty, the respective individual distributions are multiplied using Monte Carlo techniques to develop an overall distribution reflecting total uncertainty. This is then applied to the NOAEL or LOAEL to develop a probabilistic RfD.

CASE STUDIES

The following research and case studies are drawn from a large sample of EPA and Health Canada risk values where uncertainty factors other than a default value of 10-fold were used in the estimation of a RfD, RfC, TDI, or TC. In the case studies, we explicitly review the types of data that have been used to support a change in the default value, why the data support a different UF, and what assumptions have been satisfied or replaced or how the uncertainty was reduced.

Survey of Existing Risk Assessment Values

It is a common perception that the estimation of these subthreshold values used for regulatory purposes invariably use default values and rarely, if ever, actual data. However, cases can be found where regulatory and health agencies have chosen to deviate from default values when adequate data are available.

To illustrate this, the published information of Health Canada for 24 TDIs or TDCs and the readily accessible information of EPA for 393 RfDs or RfCs on its Integrated Risk Information System (IRIS) were searched for examples in which factors other than a default value of 10-fold were used in the derivation of a subthreshold dose. Table 4 shows the percentage of instances where individual default factors of 10-fold have been reduced, based on the availability of specific data within that area of uncertainty, knowledge of the mechanism of toxicity, a combination of both, and/or informed professional judgment. Percentages for the

use of these data-derived factors varied between 3.6 and 47%.

The highest proportion (36/38) of replacement of the traditional 10-fold factor with specific data has occurred with the interspecies factor for EPA's RfCs. As described by EPA (1994) and in the published literature (Jarabek *et al.*, 1989, 1990; Jarabek, 1994; Jarabek, 1995b), dosimetric adjustments are routinely used to estimate human equivalent concentrations from experimental animal exposures in developing RfCs. In doing so, the traditional factor of 10-fold for extrapolation from experimental animal to humans is reduced to 3-fold by EPA.

Other factors are much less often replaced with specific data. But, as shown in Table 4, the replacement of default uncertainty factors with those reflecting specific data, knowledge of the chemical's mechanism of toxic action, and/or informed professional judgment is far from unusual.

Five case studies in which default UFs were replaced with data-derived UFs are described briefly below. These examples allow a more complete picture of various situations in which data can be and have been used to replace the default values of 10-fold.

Aroclor 1016

The RfD for Aroclor 1016 is 7×10^{-5} mg/kg/day (EPA, 1996). The critical effect forming the basis for this RfD is reduced birth weights in a rhesus monkey reproductive and developmental bioassay (Barsotti and van Miller, 1984), followed through several postexposure experiments (Levin *et al.*, 1988; Schantz *et al.*, 1989, 1991). The NOAEL and LOAEL for this study are judged by EPA to be 0.007 and 0.03 mg/kg/day, respectively.

EPA (1995) applied a total UF of 100 to the NOAEL, which represents a composite of four distinct half-log areas of uncertainty:

- A 3-fold factor for within-human variability; the default for intraspecies variability is a 10-fold UF. This UF was reduced to 3-fold for Aroclor 1016 because the data indicate that infants exposed transplacentally represent a sensitive subpopulation. In particular, infants exposed *in utero* were often affected in the absence of any maternal toxicity.
- A 3-fold factor for animal-to-human extrapolation; the default for interspecies extrapolation is a 10-fold UF. This UF was reduced to 3-fold for Aroclor 1016 because of the similarity in toxic responses and metabolism of PCBs between monkeys and humans and the general physiologic similarity between these two species.
- A 3-fold factor for subchronic-to-chronic extrapolation; the default for this extrapolation is a 10-fold UF. A reduced factor of 3-fold is used because the chosen study was longer than subchronic but less than chronic.

TABLE 4
Frequency of Data-Derived UF Rather than Standard Default Values

Organization (number of values) ^a	Area of uncertainty: Interhuman (intraspecies)	Interspecies	Subchronic to chronic	LOAEL to NOAEL	Data base deficiency	Modifying factor
Health Canada (24 TDIs or TDCs)	0/24	0/24	1/9	2/8	NA	4/13
U.S. EPA, RfCs (46 RfCs)	2/46	36/38	11/20	9/21	23/32	1/46
U.S. EPA, RfDs (346 RfDs)	13/346	3/320	9/52	15/127	25/71	13/346
Overall frequency (%)	3.6	10	26	17	47	4.4

^a Frequency counts do not always add to the total number of subthreshold assessments because not every assessment had uncertainty in each area.

- A 3-fold factor for data base gaps was applied; the data base for Aroclor 1016 is fairly complete, but the issue of male reproductive effects is not directly addressed in any study, and a multigeneration study is absent.

- EPA considers the modifying factor for Aroclor 1016 to be 1; this is the default value.

EPA (1996) rated the series of critical studies for Aroclor 1016 at medium confidence. The investigators evaluated sensitive endpoints of PCB toxicity in maternal animals over a period of 6 years, but essentially only three groups of monkeys were examined. The data base for Aroclor 1016 examined monkeys, mice, rats, and mink. However, EPA only rated it at medium confidence due to limited chronic toxicity and reproductive data. The critical effect for Aroclor 1016 is consistent with those of other PCBs, and the available human toxicity data (although these data are problematical; see for example, Swanson *et al.*, 1995). The degree of confidence in the RfD is also considered to be medium.

Boron

The RfD for boron is 9×10^{-2} mg/kg/day (EPA, 1996). It has undergone extensive deliberations in the past couple of years and is the one example in this study in which all of the recent data have not been utilized; to do so would likely result in a reduced uncertainty factor. The critical effect forming the basis for the current RfD is testicular atrophy seen in a 2-year dietary study in dogs (Weir and Fisher, 1972). The NOAEL and LOAEL for this study are judged by EPA to be 8.8 and 29 mg/kg/day, respectively.

The total UF applied to the NOAEL is 100, which includes:

- a 10-fold factor for intraspecies variability (this is the default value);
- a 10-fold factor for interspecies differences (this is the default value);
- although this was only a 2-year study in dogs,

which does not represent a lifetime exposure, EPA generally accepts this duration in this species as a chronic study; therefore, an UF of 1 was applied for subchronic-to-chronic extrapolation.

- As summarized by EPA (1996), the data base for boron is complete, so a data base uncertainty factor of 1 is appropriate.

- EPA considers the modifying factor for boron to be 1; this is the default value.

Subsequent to the 1989 verification of this RfD, several developmental toxicity studies have been performed for boron which appear to be a more appropriate basis for an RfD (Price *et al.*, 1996). Three developmental studies are available which reveal decreased fetal body weight to be the critical effect for boron. Allen *et al.* (1996) applied benchmark dose (BMD) methodology to the recent developmental studies and determined the 95% lower bound on the dose associated with a 5% decrease in mean fetal body weight to be 10.3 mg/kg/day.

The appropriate uncertainty factors to use with this benchmark dose have been debated. Specifically, it has been suggested (IEHR, 1995) that a total UF of 30 is appropriate: 3 for interspecies extrapolation and 10 for intraspecies extrapolation. The reduced UF proposed for interspecies extrapolation is based on a separation of this factor into 3-fold components for toxicokinetics and toxicodynamics. An argument has been made that a factor of 1 should be used for the kinetic portion because of extensive data on the toxicokinetics of boron showing similar handling in multiple species, including humans. Toxicodynamic differences between humans and laboratory animals, particularly with regard to developmental effects, are not known and therefore this remains an area of uncertainty. Murray (1995) also conducted a risk assessment of boric acid and borax in drinking water that uses not only the newer developmental toxicity studies, but also reduced uncertainty factors based on considerations similar to those of IEHR (1995). The ECETOC (1995) and the European

Commission (1996) made very similar recommendations.

While separation of the 10-fold UF for interspecies extrapolation into separate factors for toxicokinetics and toxicodynamics has been promoted in peer-reviewed risk assessment literature (as discussed above), it is not yet standard practice in the development of EPA's RfDs. A movement toward such a separation is apparent, however, with EPA's RfCs where only a 3-fold factor (for toxicodynamic differences) is deemed necessary for interspecies extrapolations.

Di(2-Ethylhexyl)Phthalate (DEHP)

The RfD for DEHP is 2×10^{-2} (EPA, 1996). The critical effect forming the basis for this RfD is a statistically significant increase in relative liver weight from a 1-year dietary study in female guinea pigs (Carpenter *et al.*, 1953). A NOAEL was not evident in the study; the LOAEL is judged by EPA to be 19 mg/kg/day. No treatment-related effects were seen on mortality, body weight, kidney weight, or gross pathology and histopathology of the kidney, liver, lung, spleen, or testes at either 19 or 64 mg/kg/day.

As summarized by EPA (1996), the data base for DEHP also includes a 2-year dietary study in rats and a reproductive study in mice. The NOAEL from the rat study was 60 mg/kg/day, and the LOAEL was 195 mg/kg/day, based on retarded growth and increased kidney and liver weights. The data from the guinea pig study suggests that this species is more sensitive than rats to DEHP toxicity. Reproductive and developmental toxicity were observed for DEHP, but only at doses about an order of magnitude higher than that chosen as the LOAEL from the guinea pig study.

EPA's (1996) total uncertainty factor applied to this LOAEL was 1000, which includes:

- a 10-fold factor for interspecies variation (this is the default value);
- a 10-fold factor for intraspecies variation (this is the default value);
- a 3-fold factor for LOAEL-to-NOAEL extrapolation. The only effect observed in guinea pigs at the lowest dose of 19 mg/kg/day was increased relative kidney weight which was not accompanied by any histopathological effects. This was also the only effect observed at a 3-fold higher dose and therefore is considered by EPA to be a minimal LOAEL, requiring less than a 10-fold UF for LOAEL-to-NOAEL extrapolation.
- A 3-fold for "less than chronic"-to-chronic extrapolation (the duration of this study was 1 year—more than subchronic, yet not reflective of a lifetime exposure). Therefore, EPA judged that less than a 10-fold UF is appropriate for extrapolation to a chronic exposure.
- The data base for DEHP is complete, so that an UF of 1 is applied for this area; and

- EPA considers the modifying factor to be 1; this is the default value.

Methyl Mercury

The RfD for methylmercury (MeHg) is 1×10^{-4} mg/kg/day (EPA, 1996). It is based on a benchmark dose (BMD) calculated from two human epidemiologic studies that identified developmental neurologic abnormalities in infants exposed *in utero* as the critical effect. Because the critical exposure time was *in utero*, the mothers' intake of MeHg was used as the appropriate dose. Since data on the actual dietary intakes of MeHg were not available, the average daily dietary intake was calculated using maternal hair concentrations. The hair concentrations were converted to an analogous blood concentration, which was then back-extrapolated to an oral intake.

The total uncertainty factor applied to the benchmark dose for MeHg was 10, which includes:

- a 3-fold factor for interhuman variability; a 3-fold (rather than 10-fold) UF was appropriate for interhuman extrapolation because the RfD is based on effects in a sensitive subpopulation (i.e., the developing fetus). This, in effect, accounts for variability in toxicodynamics; the toxicokinetic portion of the interhuman UF, however, is maintained (hence the 3-fold factor) because of known variation in the biological half-life of MeHg, and variation in the hair/blood ratio of Hg.
- A 3-fold factor for data base insufficiency, particularly the lack of a two-generation reproductive study and lack of data on the effect of exposure duration on resulting developmental effects and adult paresthesia (critical effect in adults);
- although this was a subchronic exposure to the mothers, the exposure to the developing fetus was in essence chronic, and therefore a UF other than 1 for subchronic-to-chronic exposure is not necessary; this is standard practice in EPA when the critical effect is developmental toxicity.
- EPA considers the modifying factor for MeHg to be 1; this is the default value.

The final point of interest with regard to the choice of UFs for MeHg is related to the use of a BMD rather than a NOAEL or LOAEL. The suitability of the dose-response data for MeHg for statistical modeling allowed the determination of a BMD. In this case, the use of the BMD is preferred over attempting to determine a NOAEL, which would be difficult to estimate since the human data provide a continuum of exposure levels (as opposed to actual dose groups used in experimental animal testing). The BMD was determined by modeling exposure vs effect using both Weibull and polynomial models. Exposure was determined from maternal hair concentrations, as described previously. Effects were considered to be any childhood neurological abnormal-

ity, with the BMD estimated to be the lower 95% confidence limit on the dose that was correlated with an incidence rate of 10% above background.

Work by Faustman *et al.* (1994) and Allen *et al.* (1994a,b) was cited as supporting the use of a 10% benchmark dose for quantal developmental data as being roughly equivalent to a NOAEL. Therefore, in deciding the appropriate application of UFs for MeHg, the calculated BMD was in fact considered to be equivalent to a NOAEL.

certainty, and subsequently tainty, became commonpl While several publications the use of these 10-fold fact ment that their routine a overly conservative risk ase

It has been recognized wi estimate RfDs and RfCs a data or judgments regardin tainty can be used to replac

APPLICATION TO FUTURE RISK ASSESSMENTS

It is generally recognized that default values currently used by risk assessors are health protective from the standpoint of the behavior of the average chemical (e.g., Dourson and Stara, 1983). In fact, based on new data being generated and analyzed, some of these factors may be overly conservative. As a result, data-based uncertainty factors are justified when such data exist, a fact reflected in the greater use of data-based uncertainty factors by health agencies such as EPA.

The use of uncertainty factors in the risk assessment process was initiated because data were generally not available to indicate how humans as compared with laboratory animals would react to an exposure, and to protect more sensitive members of the general population. Ten-fold default factors for these two areas of un-

basis for a quantitative risk assessment. The science of risk assessment has evolved to the point that it is appropriate to reconsider both the identification of certain effects as critical and the routine application of a 10-fold UF to a LOAEL for such effects.

Another area in which gains are being made in UFs is the movement toward analyzing the complete data base for a chemical rather than just those studies conducted by the route of exposure being assessed. For example, if the oral toxicity data base does not include any studies on developmental or reproductive toxicity, a UF will generally be applied for this data gap. However, if studies by the route of inhalation exist to show that developmental or reproductive effects are absent, or that other systemic toxicity precedes any developmental or reproductive toxicity, then this data gap may be filled (unless, of course, the systemic handling of the chemical is significantly different following these two different routes of exposure), or perhaps if data from a second route of exposure indicate that the toxicity following chronic exposure is not much different than that following subchronic exposure, then a 3-fold UF is more appropriate to use for subchronic-to-chronic extrapolation for the route of interest. Many more examples may be offered as demonstrated in the case studies described in this paper.

Default uncertainty factors have been indispensable to the development of risk assessment methods. However, these methods have been evolving over many years, and now ask many more in-depth questions of the entire data base for a chemical. While the composite UF for a chemical was typically limited to 100 two decades ago, it may now be as high as 10,000 for a chemical with a poor data base. While such a high UF may be appropriate and necessary in some cases, in others it may be modified by incorporation of nontraditional toxicity information (e.g., mechanistic data) into individual UFs resulting in the reduction of the composite UF. Indeed, ultimately the goal of risk assessment is just that—to be able to describe the risk, or lack of risk, posed by various exposures with as little uncertainty as possible.

CONCLUSIONS

Health agencies generally recognize that default values currently used by risk assessors are somewhat protective from the standpoint of the behavior of the average chemical, and may in fact be overly conservative based on new data being generated and analyzed. As a result, these agencies are using other-than-default uncertainty factors on a more regular basis. The state of the art is sufficiently advanced that every effort should be made to use all of the available scientific information in establishing appropriate UFs.

The default position has been the use of a 10-fold uncertainty factor. We have provided a basis for con-

cluding that the default should be to embrace the use of data-derived uncertainty factors. Only in situations where there is truly inadequate data should the use of a 10-fold default factor be the first choice. This shift to the use of data-derived uncertainty factors is already occurring, and risk assessors should become more comfortable using the existing data to select UFs, even in the presence of significant data gaps. Moreover, as biologically based dose-response models and hazard identification guidelines are developed for target organs of interest, this work must be integrated into the present risk assessment process to provide continuity and reduce uncertainty.

We encourage the growing use of other-than-default, or data-derived, uncertainty factors by risk assessors whenever sufficient data are available. In addition, we hope that utilization of all available scientific information, resulting in the use of uncertainty factors other than default values, will foster better research into noncancer risk assessment.

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