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Past and Future Use of Default Assumptions and Uncertainty Factors: Default Assumptions, Misunderstandings, and New Concepts

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INTRODUCTION

Several reports exist on the scientific underpinnings of uncertainty factors (*e.g.*, Dourson and Stara 1983; McColl 1990; Kroes *et al.* 1993; Calabrese and Baldwin 1995; Dourson *et al.* 1996; Kalberlah and Schneider 1998). Several of these reports highlight available data for each of several areas of scientific uncertainty, and Dourson *et al.* (1996) show examples from the USEPA and Health Canada where data have been used to support the selection of uncertainty factors values other than default. Many of the underlying assumptions and choices of uncertainty factors in noncancer risk assessment are similar among these health agencies worldwide. Such similarity is one foundation of global harmonization of risk assessment methods, a formidable task undertaken by the International Programme on Chemical Safety (Sonich-Mullin 1995; IPCS 1994, 2001, 2005).

Uncertainty factors are not precise (Felter and Dourson 1998). The underlying data that support these factors demonstrate large variability. However, the incorporation of all available scientific data into the risk assessment process fosters increased research and ultimately reduces uncertainty. This, in turn, supports the use of Chemical Specific Adjustment Factors (CSAF), resulting in noncancer risk assessments in which greater confidence can be placed. Examples where research has reduced the use of default factors are readily found (*e.g.*, Jarabek 1995; Zhao *et al.* 1999; Dourson *et al.* 2001; Gentry *et al.* 2002; USEPA 2005).

The USEPA's scientists led the way in the early part of this willingness to step forward with data instead of default values for standard uncertainty factors (*e.g.*, Dourson and Stara 1983; Hattis *et al.* 1987; Jarabek *et al.* 1989; Dourson *et al.* 1992; USEPA 1994). More recent efforts by Health Canada (Meek *et al.* 1994), the International Programme on Chemical Safety (IPCS 1994), and others have culminated in an interim guidance document in this area (IPCS 2001, 2005), based in part on the seminal work of Renwick (1993).

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Since 1980, the science behind default assumptions[1] and uncertainty factors has progressed considerably. This is due to increased knowledge of toxicokinetics, toxicodynamics, mechanisms of toxicity, and temporal aspects of critical effect for many chemicals, and more importantly, to a willingness by risk assessment scientists to use these data, rather than defaults, for science-based decisions. U.S. Environmental Protection Agency (USEPA) scientists led the way in the early part of this willingness to step forward with data instead of default assumptions and uncertainty factors, based in part on the NAS (1983) risk assessment/risk management framework. More recent efforts by Health Canada, the International Programme on Chemical Safety, the USEPA and others have culminated in interim guidance in this area.

This article briefly describes previous default assumptions and current misunderstandings, but emphasizes how new science is being incorporated into the hazard identification and dose response assessment of noncancer (and cancer) endpoints.

DEFAULT ASSUMPTIONS

As defined by the USEPA a Reference Dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The judgment of the critical effect and its no-observed-adverse-effect-level (NOAEL) or benchmark dose (BMD) along with the appropriate uncertainty factor (UF) and modifying factor (MF) leads to the estimation of the RfD. The RfD is considered to be an accurate estimate of a dose below a toxicity threshold, because it is based on a review of all toxicity data and individual UFs are considered to be somewhat protective (Barnes and Dourson 1988; USEPA 2002).

Several major assumptions are involved in the estimation of the RfD: (1) a population toxicity threshold exists, (2) the estimate represents a subthreshold dose, and (3) prevention of the critical effect protects everyone in the population. Using default assumptions to derive the RfD has its strengths (*e.g.*, all data are reviewed for the critical effect and uncertainties are addressed with factors based on professional judgment) and weaknesses (*e.g.*, the NOAEL ignores other data, uncertainty factors are imprecise, and risk above the RfD is not estimated). These estimates of subthreshold dose rates are considered accurate, but not precise. Each uncertainty factor varies with ranges up to about 10-fold. Several factors are generally multiplied to estimate

[1]Many groups used different terms in risk assessment. The definition of several terms used when discussing default assumptions in this article are provided as: (1) adverse effects are either biochemical change, functional impairment, or pathologic lesion, which impairs performance and reduces the ability of an organism to respond to additional challenge, (2) adaptive effect enhances an organism's performance as a whole and/or its ability to withstand a challenge; an increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity, (3) compensatory effect maintains overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect, (4) critical effect is the first adverse effect or its known and immediate precursor that occur as dose rate increases, (5) severity is the degree to which an effect changes and impairs the functional capacity of an organ system (USEPA 2005).

a subthreshold dose and some factors overlap, thereby increasing variability and decreasing precision. Subthreshold doses can only be as precise as their least precise component. In the case of most of these estimates, the least precise component is the uncertainty factor. As the composite uncertainty factor grows larger, the imprecision of the resulting subthreshold doses also grows larger (Barnes and Dourson 1988; USEPA 2002).

MISUNDERSTANDINGS

There are at least five common misunderstandings in the development of these "safe" estimates. First, studies with a small number of subjects (*e.g.*, small "n") are not useful. In truth, studies with even one subject are important. For example, a well done, human study with an adverse effect at a lower dose than an RfD based on an experimental animal-based study is viewed as undermining the basis of the RfD.

The second misunderstanding is that uncertainty factors are arbitrary. Choosing to use a particular uncertainty factor is never arbitrary, but the value assigned is often imprecise. For example, no one ever uses an experimental animal to human uncertainty factor with human data, nor a less than lifetime uncertainty factor with a chronic study. Thus, the choices of particular uncertainty factors are not arbitrary.

Third, a factor of 10 is not protective enough with the most common complaint being that the human population is variable beyond a 10-fold range. This misunderstanding presupposes that risk assessment scientists always start out with resistant or insensitive individuals, which is not realistic. Analysis of past RfD assessments indicates that a factor of 10 is most often a conservative estimate (Klaassen 2001; Dourson and Stara 1983; Dourson *et al.* 2002).

The fourth misunderstanding is that animal RfDs are always protective. This is true most of the time, but not always; risk assessors should always consider all the data, including available human data. In Dourson *et al.* (2001) the frequency of human to animal based RfD ratios were analyzed. They found that 36% of the USEPA's human-based "safe" doses are within 3-fold of animal-based values, 41% of the USEPA's human-based "safe" doses are more than 3-fold higher than animal-based values, and 23% of the USEPA's human-based "safe" doses are more than 3-fold lower than animal-based values. Thus, ignoring data is not protective of human health; human and laboratory animal data together give the best picture of the overall toxicity of a chemical.

The fifth and most common misunderstanding is that RfDs do not protect children. RfDs are designed to protect children and other sensitive members of the population with the combination of interhuman and database deficiency uncertainty factors. In Dourson *et al.* (2002) an interhuman UF of either 3 or 10 was found to be protective for 67–100% of chemicals or specific populations. Studies in larger populations suggest that near 100% of the population is protected by the UF of 3 or 10. Newborns or premature infants are more often sensitive to the toxicity of parent compounds than adults, but older children are more often resistant. The use of a database uncertainty factor of either 3 or 10 protects either 92 or 98% of the potential lower NOAELs from studies in young experimental animals when compared with chronic study protocols. Overall, the likelihood that the combined interhuman and database factors protect children is very probable. Thus, the use of

an additional UF for children, such as the Food Quality Protection Act (FQPA) safety factor, is unlikely to provide greater protection for children older than 6 months of age, but for children less than this age, careful evaluation is needed for bioassays in these aged experimental animals. For example, current study protocols for systemic toxicity testing in young animals could be improved lending greater confidence in RfDs based on these studies.

NEW CONCEPTS

Over the last several years, scientists have begun using more data when choosing uncertainty factors. Scientists are using a number of approaches ranging from default UFs ("presumed protective") to those incorporating more data-derived chemical specific UFs ("biologically based protective").

The benchmark dose (BMD) is a data-derived alternative to the traditional NOAEL/LOAEL approach, the statistical lower confidence limit on the dose producing a predetermined response of an adverse effect compared with the response in untreated animals. A BMD is calculated by fitting a mathematical dose-response model to actual data. For example, the 95% lower confidence on the dose that causes a 10% increase in the number of animals developing fatty liver compared with untreated animals would be the BMD for that critical effect. The BMD is advantageous because it is not limited to the doses tested experimentally and is less dependent on dose spacing, it takes into account more of the shape of the dose-response curve, and it provides flexibility in determining biologically significant rates (*e.g.*, a 10% increase may be appropriate for one response whereas a 1% increase is appropriate for a different response). The increased use of the BMD approach gives incentive to conduct better studies, more rigorous studies result in tighter uncertainty bands, and thus, higher BMDs. The BMD approach also has limitations; it is possible to introduce error in the model prediction of BMD if the models are used to extrapolate to low doses without incorporating information on mechanism, quantal data (*e.g.*, tumor incidence or number of pups with a deformity) and continuous data (*e.g.*, changes in body/organ weight or serum enzyme levels) are handled differently, and the ability to estimate a BMD may be limited by the format of the data presented, unless the raw data from a study are available.

Another data-derived dose-response modeling approach is categorical regression, which uses meta-analytical techniques to incorporate not only information on how the incidence of response increases with dose, but also information on how the severity of response increases with dose (Haber *et al.* 2001). Categorical regression allows all the useful data to be categorized, combines data across studies or across endpoints, and provides a consistent basis for calculating risk above the RfD. However, animal to human extrapolation is still needed and transforming data into categories loses information, limiting the use of categorical regression (Haber *et al.* 2001).

Chemical specific adjustment factors (CSAF) use quantitative toxicokinetic and toxicodynamic data to inform interspecies and intraspecies UFs in dose–response assessment (IPCS 2001). A study by Renwick (1993) proposed subdividing the 10-fold interspecies and intraspecies UFs into toxicokinetic (TK) and toxicodynamic (TD) components. This concept was modified by the IPCS to result in an UF of 4 ($10^{0.6}$) for interspecies toxicokinetics, 2.5 ($10^{0.4}$) for interspecies toxicodynamics, and 3.2 ($10^{0.5}$) each for intraspecies toxicokinetics and intraspecies toxicodynamics (IPCS

1994, 2001). This approach allows the replacement of the usual 100-fold uncertainty factor with quantitative chemical-specific data relating to either toxicokinetics or toxicodynamics, which will have a direct and quantitative impact on the risk assessment outcome, thus reducing its overall uncertainty (IPCS 2001, 2005). Several factors must be taken into consideration when using a CSAF approach, the choice of the appropriate endpoint must be the critical effect based on understanding the mode of action, the metric for toxicokinetics or the measure of effects for toxicodynamics needs careful consideration in relation to the delivery of the chemical to target organ, and the available data must relate to the active form of the chemical (IPCS 2001). Also, the relevance of the population, route of exposure, dose/concentration and adequacy of numbers of subjects/samples must be considered, and impact on validity of calculated ratio addressed (IPCS 2001, 2005).

CONCLUSIONS

Estimates of "safe" doses are accurate but imprecise. They are believed to be without risk, but cannot be used to estimate risk. Many agencies are using data-derived UFs on a more regular basis rather than rely on the 10-fold default UFs. BMD, categorical regression, and CSAF ask different questions of the data, and are not alternatives to each other, nor the current "safe" dose approach. Methods of combining two or more of these methods are routinely used. For example, in its estimation of "safe" doses, Health Canada and the USEPA use both BMD and CSAF. In developing subthreshold doses, the first choice should be to use data to generate a distribution (Monte Carlo analysis) or CSAF; a second choice would be to use the default factors. CSAFs are justified when adequate and specific data exist; use of distributions and CSAFs will lead to better data and fewer uncertainties.

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