THE FUTURE OF CHEMICAL SPECIFIC ADJUSTMENT FACTORS IN RISK ASSESSMENT

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Background

Noncancer risk assessment, and specifically the use of uncertainty factors (or safety factors) to determine a "safe" dose has been the principal approach to protecting public health from chemical exposures since the 1950s by agencies throughout the world. This approach has depended heavily of the use of default uncertainty factors of 10 and is generally regarded as conservative and imprecise. However, new advances in understanding the mode of chemical action, including toxicokinetics, toxicodynamics and dosimetry have allowed reconsideration of the common use of 10-fold uncertainty factor as a primary tool to developing "safe" doses to protect public health.

For example, the use of the term "chemical-specific adjustment factor" (CSAF) was formalized in a recently finalized guidance document of the International Programme on Chemical Safety (IPCS). This document was prepared by an international group of renowned scientists to describe methods to derive CSAFs to replace default uncertainty factors based on mode of action[1] information (i.e., toxicokinetic and toxicodynamic data)[2] (IPCS 2001). Since the introduction of CSAFs, previously referred to as "data-derived" uncertainty factors (Renwick, 1991; Renwick 1993; IPCS 1994) a series of workshops has been published in *Human and Ecological Risk Assessment* (e.g., Abdel-Rahman, 2002), that have demonstrated the potential application of data-derived values for groups of chemicals and chemical-specific adjustment factors for individual compounds. The use of the "data-derived" approach has recently been proposed to extrapolate data from classes of well-studied compounds and metabolic or physiological processes to compounds with limited data (e.g., Naumann et al., 2001; Walton et al., 2001).

Data-derived factors can be used to replace default uncertainty factors to establish safe levels of exposure whenever sufficient chemical-specific data are available. The Renwick scheme provides a framework for incorporating compound-specific toxicokinetic and toxicodynamic data when deriving regulatory and advisory health-based limits such as acceptable daily intake values, tolerable intake values, reference doses/concentrations and occupational exposure limits.

When considering the use of a default factor (briefly described below) a number of criteria need to be satisfied. Renwick (1999) (IPCS, 2001) listed a number of considerations for use of compound-related data, including whether the compound itself or a metabolite is the active species, the relevance of the toxicokinetic or toxicodynamic data to the critical endpoint, and how representative the data are of the human population. Meek *et al.* (1999) and IPCS (2001) have also proposed guidelines on the use of data-derived adjustment values to replace default uncertainty factors when sufficient compound-specific data are available.

Advantages of application of chemical-specific adjustment factors include reduction of uncertainty through reliance on considerably more of the available chemical-specific data and capacity to more meaningfully protect susceptible subgroups. These chemical-specific adjustments are similar in concept to that proposed for dosimetric adjustments in the late 1980's by the U.S. EPA for the development of safe concentrations in air (Jarabek, 1995). Application of the framework for CSAFs also identifies data gaps critical to informing health protective risk assessment and management.

CSAFs vs. Default Uncertainty Factors

Risk assessors use uncertainty factors to account for what they don't know as they are trying to predict a true no-effect level for the population, including sensitive subgroups. While we are well aware of the analyses that show that the 10-fold default factors are generally protective, perhaps overly so for certain compounds (Dourson and Stara, 1983; Dourson et al., 1996), when default factors are used in the absence of data, some level of uncertainty always remains about how health-protective a recommended limit may be.

"Informed" regulatory decision-making implies that risk assessors and risk managers have brought to bear all of the information needed to arrive at the ultimate goal – a health-based limit that is protective of the intended population (e.g., general population, patients, workers). The decision to rely on default uncertainty factors or to develop chemical-specific adjustment factors (CSAFs) depends on the available data for a given compound. Use of data-informed approaches, such as CSAFs, are now being proposed as the primary approach because risk assessors should always consider all relevant data in the context of its adequacy to address kinetic and dynamic components of interindividual and interspecies differences (Dourson et al., 1996; EPA, 2002). Default uncertainty factors (which are typically 10-fold) should only be used in the absence of adequate relevant kinetic and/or dynamic data on interindividual or interspecies differences. Application of the framework to consider available data on kinetic and dynamic aspects of interspecies differences and interindividual variability is valuable even in the absence of adequate data as a basis for development of CSAFs, since data gaps are identified, which can in turn be used for focused research in critical risk assessment areas.

The distinction between uncertainty (e.g., we do not know what the answer is) and variability (e.g., we know the answer and it varies) should also be emphasized. CSAFs are used to characterize the "variability" in kinetics and dynamics in a relevant subset of the intended population. To the extent that this subset is representative of the overall population and provides quantitative information on differences (or similarities), the level of "uncertainty" should be reduced considerably. The risk assessors/risk managers should feel more confident than the health-based limit they derive will provide adequate protection for even the most susceptible individuals. There may be residual uncertainties; however, these would obvi-

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ously be less than when no data are available on potentially important differences. By focusing on toxicokinetic and toxicodynamic data for potentially susceptible subpopulations, the risk assessor consciously evaluates data for the segment of the population with the greatest need of protection.

Guidelines On Using CSAFs

Within the CSAF scheme, interindividual differences are assessed using several toxicokinetic and toxicodynamic (also referred to as pharmacokinetic and pharmacodynamic) parameters indicative of systemic exposure and pharmacologic activity of the compounds evaluated. The pharmacokinetic parameters initially chosen as measures of internal dose, depend on the expected mode of action of the compound: such as short acting from the peak plasma concentration (referred to as Cmax), or perhaps longer acting from average chemical concentration in blood (referred to as area under the curve or AUC). These are often considered the best indicators of body burden and systemic exposure since they are also direct measures of the amount of a compound in the blood.

The general guidelines (Meek et al. 2001, IPCS 2001) for evaluating pharmacokinetic and pharmacodynamic data include some important considerations for choosing CSAFs. For assessing interindividual differences in pharmacokinetics: the parameter used should be directly related to the critical effect (e.g., AUC vs. Cmax for effects following chronic exposure versus those associated with short term peak levels);
the data should be generated with the dose and route most relevant to the recommended health-based limit, and
data from human subjects should be representative of the expected variability in the population being protected (e.g., workers from ages 18-65).

For assessing interindividual differences in pharmacodynamics: the measured endpoint must be directly related to the critical effect used to derive the recommended exposure limit, a quantitative comparison of the response in tissues from average and sensitive humans given the same dose, and a sufficient number of individuals must be included to define interindividual variability.

Guidelines are also available for evaluating interspecies differences in pharmacokinetics and pharmacodynamics.

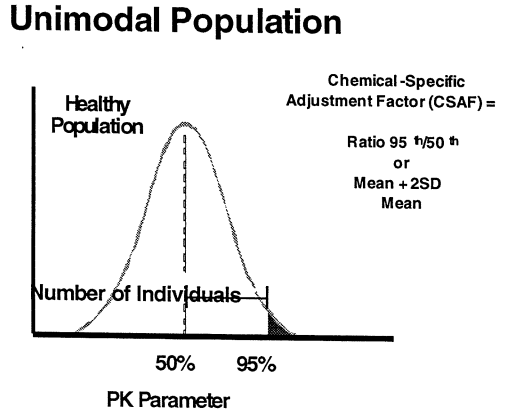

Figure 1. Derivation of a chemical-specific adjustment factor (CSAF) from a unimodal distribution.

How Are CSAFs Derived?

The method for estimating interindividual differences and deriving CSAFs relies on the ratio of the tail of the distribution to the central tendency for the pharmacokinetic and pharmacodynamic parameters of interest. The approach is based on the premise that, if a sensitive subpopulation is sufficiently different from the general population (i.e., more susceptible based on significantly higher Cmax or AUC values), its level of exposure needs to be adjusted downward to conform to the normal (average) healthy population (see Figure 1). Where sufficient information is available to quantify the distinction between these populations, the ratio of the upper tail of the most sensitive subpopulation over the mean of the healthy population is used to derive an appropriate adjustment factor (see Figure 2).[3]

Several analyses have been published to illustrate how human pharmacokinetic and pharmacodynamic data can be used to characterize interindividual differences and derive acceptable daily intake values and occupational exposure limits (Silverman et al. 1999; Naumann et al. 2001). In these evaluations, CSAFs accounting for interindividual differences in pharmacokinetics for drugs in one therapeutic class ranged from 1.2 to 3.2 for unimodal distributions. For bimodal distributions CSAFs of 2.9 for adult poor metabolizers, 6.0 for young poor metabolizers, and 3.0 for elderly patients, were calculated. CSAFs were also calculated using pharmacokinetic data from subjectss with pre-existing medical conditions, including hepatic insufficiency (CSAF=6.4), chronic renal failure (CSAF=4.9) and cirrhosis (CSAF=7.5). When combined with the default CSAF for pharmacodynamics of 3.2, the corresponding composite CSAFs ranged from 3.8 to 24.0.

A case study was also published to illustrate how CSAFs can be used to derive occupational exposure limits (OELs) using the beta-adrenergic blocking agent timolol maleate (Naumann et al. 2003). The removal of timolol maleate from the body is influenced by a genetic polymorphism in oxidative metabolism. Two distinct phenotypes have been identified: poor metabolizers and extensive metabolizers. The prevalence of poor metabolizers (up to 9 percent of selected subpopulations) is high enough to indicate careful consideration of this potential susceptibility when establishing the OEL for timolol maleate. A CSAF for kinetics of 9.8 based on AUC data was combined with a CSAF for dynamics of 1.2 to yield a composite adjustment factor of 12. This was applied to the extrapolated no-effect level for clinically significant cardiovascular effects to establish an OEL for timolol maleate that is expected to be protective of workers, including those that may be poor metabolizers.

U.S. EPA (2005b) has also developed a Reference Dose (RfD) for boron based on the principles of CSAF. In this particular case, data on boron clearance and body weight in animals and humans were used to estimate a value of 3.3 for interspecies toxicokinetic variability. Data on the glomerular filtration rate in healthy pregnant women was used to estimate a value of 2 for human toxicokinetic variability. Default values of 3.16 were used to account for interspecies and human toxicodynamic variability. Thus, EPA used a data-derived uncertainty factor of 66, rather than the default value of 100.

It should be noted that use of CSAFs does not automatically imply a reduction in the "safety factor" used in setting health-based limits. Sometimes the available data for a given compound suggest a high level of interindividual variability. While many compounds have been shown to have CSAFs less than the default value of 10, there are several examples where the data-derived value exceeds the

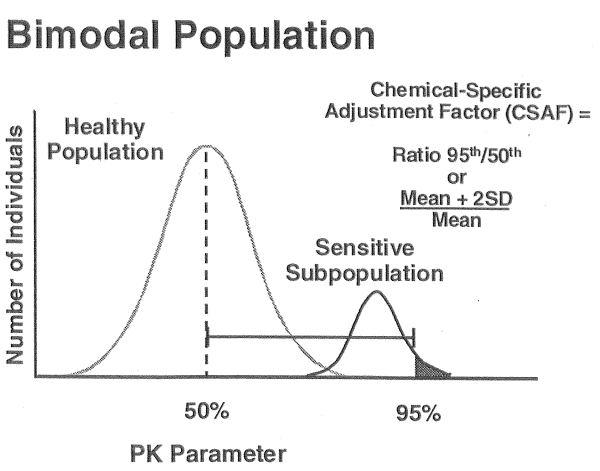

Figure 2. Derivation of a chemical-specific adjustment factor (CSAF) from a bimodal distribution.

default value. In these cases, use of a default uncertainty factor would not provide adequate protection for the sensitive subpopulation.

We believe that risk managers should now routinely ask if the available data on any chemical of concern were considered in the context of their adequacy as a basis to develop a CSAF. Acceptance of default uncertainty factors without question should be discouraged. If a CSAF is lower than the default component of the UF, then a risk manager has greater assurance that the resulting higher safe dose has more certainty, thus providing greater flexibility in a risk management decision. If the CSAF is higher then a default component of the uncertainty factor, then a risk manager has greater assurance that the lower safe dose can be used with greater scientific certainty. Ultimately, increasing use of CSAFs based on development of relevant data strives to ensure scarce resources are appropriately directed to highest priorities.

(Footnotes)

[1] Mode of action is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in a toxic event, such as cancer formation (EPA, 2005a).

[2] Toxicokinetic and toxicodynamic are defined simply as how the body handles the chemical and how the chemical impacts adversely on the relevant tissue, respectively.

[3] In practice, the evaluation of interindividual differences typically relies on papers presenting only summary statistics (e.g., mean and standard deviation) for pharmacokinetic and pharmacodynamic parameters such as AUC and a relevant measure of effect in the target tissue. A CSAF is generally calculated by dividing the mean plus two standard deviations by the mean, i.e., (Mean + 2SD)/ Mean). Occasionally, standard errors needed to be converted to standard deviations by multiplying the former by ÖN.

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