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Bayesian methods for uncertainty factor application for derivation of reference values

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ABSTRACT

In 2014, the National Research Council (NRC) published *Review of EPA's Integrated Risk Information System (IRIS) Process* that considers methods EPA uses for developing toxicity criteria for non-carcinogens. These criteria are the Reference Dose (RfD) for oral exposure and Reference Concentration (RfC) for inhalation exposure. The NRC Review suggested using Bayesian methods for application of uncertainty factors (UFs) to adjust the point of departure dose or concentration to a level considered to be without adverse effects for the human population. The NRC foresaw Bayesian methods would be potentially useful for combining toxicity data from disparate sources—high throughput assays, animal testing, and observational epidemiology. UFs represent five distinct areas for which both adjustment and consideration of uncertainty may be needed. NRC suggested UFs could be represented as Bayesian prior distributions, illustrated the use of a log-normal distribution to represent the composite UF, and combined this distribution with a log-normal distribution representing uncertainty in the point of departure (POD) to reflect the overall uncertainty. Here, we explore these suggestions and present a refinement of the methodology suggested by NRC that considers each individual UF as a distribution. From an examination of 24 evaluations from EPA's IRIS program, when individual UFs were represented using this approach, the geometric mean fold change in the value of the RfD or RfC increased from 3 to over 30, depending on the number of individual UFs used and the sophistication of the assessment. We present example calculations and recommendations for implementing the refined NRC methodology.

1. Introduction

Uncertainty factors (UFs) were developed in the 1980s by U.S. Environmental Protection Agency (USEPA) scientists based on margins of safety for determining acceptable daily intakes (ADIs) (Dourson and Stara, 1983; Barnes and Dourson, 1988; Dourson, 1993, 1996; Dourson et al., 1996). The development and use of uncertainty factors comprise an attempt to address the lack of specificity in margins of safety and are designed to address specific areas of uncertainty, thus enabling the development of data-derived values to replace default values of generally 10-fold (Dourson et al., 1996). The goal for any toxicity guidance value such as the Reference Dose (RfD), Reference Concentration (RfC) or Tolerable/Acceptable Daily Intake (TDI/ADI) is not only protection of human health consistent with the societal consensus for such protection but also avoidance of an overprotective level that could conceivably lead to excessive regulation (Simon, 2011). This balance notwithstanding, the needs of regulation are immediate and these exigencies are the basis for the continued regulatory embrace of default values for UFs and their use in the derivation of reference values (RfVs).

The individual UFs used in EPA toxicity assessments address five distinct areas of uncertainty. Historical publications by EPA staff in the 1980s provide much of the basis for four of the UFs, excluding UF-D, applied for database deficiencies (Dourson and Stara, 1983; Barnes and Dourson, 1988; Dourson and DeRosa, 1991). Subsequent publications introduced the basis for this latter database factor, generally the absence of evidence regarding developmental

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Abbreviations

ADI	Acceptable daily intake
BMD	Benchmark dose
DDEF	Data-derive extrapolation factor
NRC	National Research Council
POD	Point of departure
RfD	Reference dose
RfC	Reference concentration
RfV	Reference value
PBPK	physiologically-based pharmacokinetic
TDI/ADI	Tolerable/Acceptable daily intake
UFs	Uncertainty factors
UF/EF	uncertainty/extrapolation factor
LOAEL:	Lowest observed no adverse effect level
NOAEL	No observed adverse effect level
UF-L:	LOAEL-to-NOAEL uncertainty/extrapolation factor
UF-S	Subchronic-to-chronic uncertainty/extrapolation factor
UF-A	interspecies uncertainty/extrapolation factor
UF-A-TD	toxicodynamic component of the interspecies uncertainty/extrapolation factor
UF-A-TK	toxicokinetic component of the interspecies uncertainty/extrapolation factor
UF-H	intraspecies uncertainty/extrapolation factor
UF-H-TD	toxicodynamic component of the intraspecies uncertainty/extrapolation factor
UF-H-TK	toxicokinetic component of the intraspecies uncertainty/extrapolation factor
UF-D	uncertainty/extrapolation factor for database deficiencies

and reproductive toxicity (DART) (Dourson et al., 1992, 1996; Dourson, 1993). All five areas of uncertainty are discussed in USEPA's *Review of the Reference Dose and Reference Concentration Processes* (USEPA, 2002b). The purposes of the individual UFs were to address these five areas of uncertainty and, according to this document, were:

> *… (1) the variation in sensitivity among the members of the human population (i.e., inter-individual variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation when the database is incomplete*. (USEPA, 2002b)

Before the publication of EPA's 2002 document, any uncertainties not explicitly addressed by the five different UFs had been addressed by the use of a modifying factor (MF). However, the EPA 2002 document recommended discontinuation of the use of MFs (USEPA, 2002b). In IRIS assessments developed today, all five individual UFs are multiplied together and the composite UF applied to the point of departure (POD) by arithmetic division, generally as the final step in the RfV development process.

Over time, the understanding of UFs as individual factors rather than their combination has continued to grow. Each individual UF consists of an adjustment and the uncertainty associated with the adjustment; here, we identify the central value of a UF distribution as a measure of adjustment and the variance as a measure of uncertainty. In many of the IRIS derivations considered here, EPA has chosen the UFs for specific reasons. Even Lehman and Fitzhugh (1954) recognized their composite 100-fold UF was intended to deal with several distinct areas of uncertainty (Dourson and Stara, 1983). However, the encoding of distinct areas of uncertainty as individual factors rather than as an overall or composite factor is an important distinction and is not fully recognized in NRC (2014).

The use of an overall composite UF or "safety factor" masks the compounding conservatism inherent in the use of several UFs set at default values and each intended to provide a highly protective toxicity value (Burmaster and Harris, 1993; Burmaster and Anderson, 1994; Cullen, 1994; Simon, 2011; Tatum et al., 2015). The compounded conservatism in the use of many high-end values will yield an overestimate of risk and the actual risk is likely to be much lower or even non-existent. Indeed, a highly conservative policy-based assessment seems at odds with principles of transparency and the use of science as a basis for societal decision-making (Dourson and Stara, 1983; Lewis et al., 1990).

Although we use the familiar abbreviation UF in this paper, these factors are also called extrapolation or adjustment factors and, ideally, their values, whether chemical-specific or default, will be based upon actual data (e.g., WHO-IPCS, 2005, 2014; Chiu and Slob, 2015; USEPA, 2014).

The conceptual basis of the application of UFs using the standard deviations of Bayesian prior distributions is described in the recent *Review of EPA's Integrated Risk Information System (IRIS) Process* from the National Research Council (NRC, 2014). Here we consider the NRC methodology in terms of both the mean and variance of these distributions, provide several illustrations of this application, and explore ways that these methods could be applied currently to the development of RfVs within the IRIS program or in other similar hazard assessment programs in public and private sectors. The World Health Organization International Programme on Chemical Safety (WHO-IPCS) recently released the *Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization* that also endorsed probabilistic approaches; the methods and practices described here are consistent with both the NRC report and the WHO guidance (WHO-IPCS, 2014; Chiu and Slob, 2015). We also provide a brief narrative on the considerations and best practices for the use of Bayesian methods for development of quantitative uncertainty estimates in RfVs that could be put into practice immediately.

1.1. Chemical-specific adjustment factors and data-derived uncertainty factors

In 2005, the WHO-IPCS released *Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability*: *Guidance Document for Use of Data in Dose/Concentration Assessment* (WHO-IPCS, 2005). In this guidance, UFs are called chemical-specific adjustment factors (CSAFs). Over a decade in development, this document was introduced to provide methods for the incorporation of quantitative data on toxicokinetics or toxicodynamics into the development of RfV/TDI values by modifying the default value of 10 for each CSAF. Since 1994, Health Canada has been using a data-derived procedure based on the developing WHO-IPCS guidelines (Meek et al., 1994). In 2014, the U.S. Environmental Protection Agency issued a similar document, *Guidance for Applying*