Human and Ecological Risk Assessment: Vol. 5, No. 5, pp. 973-983 (1999)

Replacing the Default Values of 10 With Data Derived Values: A Comparison of Two Different Data-Derived Uncertainty Factors for Boron

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ABSTRACT

A "safe" or sub-threshold dose is often estimated for oral toxicity of substances in order to protect humans from adverse health effects. This dose is referred to by several terms: reference dose (RfD), tolerable daily intake (TDI), and acceptable daily intake (ADI). Similarly, tolerable concentration (TC), and reference concentration (RfQ are commonly used terms for a "safe" concentration for inhalation. The process of deriving these doses generally involves identifying a no observed, or lowest observed adverse effect level (NOAEL or LOAEL) in animals, or humans, and application of uncertainty factors to account for the extrapolation from laboratory animals to humans and/or from an average human to a sensitive human. Public health agencies have begun to consider using a data derived approach, which uses available toxicokinetic and toxicodynamic data in the determination of uncertainty factors, rather than relying on the standard default values. Recently two different tolerable daily intake risk values were derived by two different World Health Organization (WHO) work groups. The International Programme on Chemical Safety, and the Working Group on Chemical Substances in Drinking Water both used the approach developed by Renwick (1993); however, the two groups interpreted and used the available data differently. The result was a difference of over twofold in the total uncertainty factor used. This review compares and contrasts the two approaches used by these WHO work groups.

INTRODUCTION

To protect humans from a toxicant, a "safe" or sub-threshold dose is often estimated which is commonly referred to as a tolerable daily intake (TDI),

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1080-7039/99/$.50

reference dose (RfD), or acceptable daily intake (ADI). Similar approaches, such as reference concentration (RfQ and tolerable concentration (TC) are used to estimate a "safe" inhaled concentration. The estimation of these doses involves identification of a critical effect in animals (or preferably humans if data are available), determination of a lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL), and application of uncertainty factors (UF) to the LOAEL or NOAEL (Dourson *et al.,* 1996). Recently, a number of agencies are considering a data derived uncertainty factor approach proposed by Renwick (1993), where each UF is divided into sub-factors to allow for separate evaluations of differences in toxicokinetics and toxicodynarnics. These groups include Health Canada (Meek *et al.,* 1994) and the International Programme on Chemical Safety (IPCS, 1994).

The IPCS suggests that the UF for interspecies extrapolation should be subdivided unequally into fourfold (toxicokinetics) and 2.5-fold (toxicodynamics), and the UF for intraspecies extrapolation should be split evenly (3.16-fold for both toxicokinetics and toxicodynamics). The toxicokinetic considerations for the data derived factors include absorption, distribution, metabolism, and excretion of a toxicant. When the comparison data are available for any of these components, the default sub-factor can be replaced with the corresponding factor determined from the available data.

Boron compounds are widely distributed in the environment. The major sources of human exposure are food and drinking water. In animals, boron exposure results in reproductive and developmental effects. Decreased fetal weight is the most sensitive effect. Recently, the IPCS and Working Group on Chemical Substances in Drinking Water (WGCSDW) estimated boron tolerable daily intake risk values for World Health Organization's guidelines for exposure limit or drinking water quality. Both groups used the data derived uncertainty factor approach in developing their boron risk values. Although risk assessors agreed on the use of decreased fetal weight in exposed rats as the critical effect, the two groups applied different UFs for interspecies and intraspecies differences based on a different consideration of the available data. While the IPCS used a total UF of 25 for interspecies and intraspecies variations, the WGCSDW considered an UF of 60 to be more appropriate. We compare the judgments made by the two groups in each of the UF components to illustrate how the same database was used to derive UFs that are different. Based on the comparison, some of the important issues in the data derived "safe" dose approach are discussed.

RESULTS

The IPCS derived an UF of 25, which differs from the UF of 60 used by the WGCSDW to derive the tolerable intake. As summarized in Table 1, the difference is due to different judgments concerning the data related to interspecies and intraspecies differences in elimination of boron. A summary of the available data on elimination is followed by comparison of the UFs proposed by the IPCS and the WGCSDW.

Table 1. Comparison of the justification of uncertainty factors used.

	IPCS	Justification	WGCSDW	Justification
Total of UF	25		60	
Interspecies	3.2 ($10^{0.5}$)		10	
Absorption		Absorption of borates is complete (95% in several mammal species including humans and rats.		As for IPCS
Distribution		Distribution occurs by passive diffusion, through body fluids, bone selectivly uptakes boron (>4 times higher than serum) for rats and humans.		As for IPCS
Metabolism		Metabolism is thermodynamically unfavorable in biological systems. Therefore there is no difference between species due to metabolism.		As for IPCS
Elimination		Route of elimination and terminal half life are similar in humans and rats.	4	It was determined that clearance at steady state kinetics is three to four times faster in rats than humans. To be included in the calculation blood samples should be taken at steady state conditions because of the short half-life of boron. Elimination calculated from overdosed individuals based upon blood boron is physiologically impossible.
Total kinetics (default is 4)	1.3 ($10^{0.1}$)	The task group judged that in light of the similarites in kinetics the default value could be reduced from the default of $10^{0.5}$ to $10^{0.1}$.	4	The group judged that the interspecies differences in kinetics were dominated by elimination. A factor of 4 was deemed appropriate.
Dynamics (default is 2.5)	2.5 ($10^{0.4}$)	Due to lack of data the default of 2.5 was retained	2.5	As for IPCS
Intraspecies	7.9 ($10^{0.9}$)		5.7	
Absorption		Data for intrahuman variability are limited.		As for IPCS
Distribution		Data for intrahuman variability are limited.		As for IPCS
Metabolism		There is no metabolism.		As for IPCS
Elimination	Not addresed		1.8	It was determined that differences in elimination are dominated by the glomerular filtration rate. Data from primigravidas indicates a 1.8 fold variation between the average pregnant woman and two standard deviations below that. Glomerular filtration at, for example 3 standard deviations below the average is not physiologically compatible with vital life function.
Total kinetics (default is 3.2)	2.5 ($10^{0.4}$)	The task group judged that since no variability due to metabolism is expected, that the default of $10^{0.5}$ can be reduced to $10^{0.4}$.	1.8	See note under elimination above.
Dynamics (default is 3.2)	3.2 ($10^{0.5}$)	There were no data to support a reduction of the default value.	3.2	As for IPCS

Interspecies Variation

As summarized by Dourson *et aL,* (1998), over a wide range of doses, most of the ingested boron is absorbed and excreted in urine. In humans, at the dose range of 0.0054 mg/kg per day to 2.5 mg/kg per day, the percentage of the boron dose absorbed ranged from 81 to 98%, and elimination ranged from 81 to 98% (Hunt *et aL,* 1997;Job 1973; Kent and McCance, 1944; Nielsen, 1996; Schou *et aL,* 1984). Similar kinetics were also seen in a rat study at 0.02 mg/kg/day (Vanderpool *et aL,* 1994). The percentage of boron absorbed was 95% and elimination was 99%. These data indicate that boron absorption was similar across species and was nearly completely absorbed. Therefore, both the IPCS and WGCSDW determined that no adjustment was necessary for interspecies variation in boron absorption.

Boron distributes evenly throughout the body fluid by passive diffusion. In rats fed a diet containing 68 mg boron/kg body weight/day (in the form of boric acid) for 7 days, increased boron concentrations in blood were observed. Boron concentrations were comparable in almost all tissues examined, including liver, kidney, muscle, colon, brain, testis, epididymis, seminal vesicles, prostate, and adrenals (Ku *et aL,* 1991). Most of the tissues reached steady state by day 3 to day 4 (12 to 30 mg boron/kg tissue). Adipose tissue accumulated only 20% as much boron as other tissues (3.78 mg/kg tissue). Bone boron levels continued to increase throughout the seven days, with the highest level of 47.4 mg/kg tissue, indicating greater boron accumulation in the bone than the other tissues. In humans, similar tissue distribution with bone accumuladon was also reported (Ward 1993; Shuler *et aL,* 1990; Alexander *et aL,* 1951; Forbes *et aL,* 1954). To compare blood boron concentrations in humans and rats, the IPCS group summarized the dose-response data from rats exposed to boron via diet or drinkingmwater and from humans exposed via diet, drinkingwater, or accidental ingestion (WHO, 1998). The ratios of rat blood boron values to a regression line for human blood boron values are as low as 0.7 and as high as 6, with the majority of values in the range of 2 to 3. Based on the aforementioned information, the IPCS considered the distribution in rats and humans to be quantitatively similar and recommended no adjustment for interspecies variation in distribution. Similar to the IPCS decision, no adjustment was proposed by the WGCSDW.

Metabolism of inorganic borate by biological systems is not thermodynamically feasible due to the excessive energy required to break the boron-oxygen bond (Emsley, 1989). Therefore, the similar boron species in the systemic circulation are expected across biological species. Considering the lack of metabolism, both the IPCS and WGCSDW concluded that it is unlikely that there is any difference between animals and humans in boron metabolism. Thus, neither group proposed any adjustment for variation in boron metabolism.

Two commonly used parameters to measure elimination are terminal halflife and clearance. The half-life of boron appeared similar between species. In human volunteers given boric acid via either intravenous or oral routes, the

half-life for elimination was the same by either route at approximately 21 hours Uansen *et aL,* 1984; Schou *et aL,* 1984). A comparable elimination half-life in people poisoned with boric acid was also reported by Litovitz *et al.,* (1988), where the elimination half-life appeared to be 13.4 hours. Information on halflife in animal studies is not readily available, but it can be estimated from the published rat study *(Ku et al.,* 1991). Assuming first-order kinetics, the half-life in rats would be 14 to 19 hours with an average of 16.5 hours. The IPCS determined that no adjustment was necessary for variation in boron elimination because the average elimination half-life of human volunteer studies and poisoning case reports was about 17.2 hours, which is comparable to the halflife of 16.5 hours in rats.

In contrast to the similarity in elimination half-life between humans and rats, differences in the estimated clearance rate were observed (Dourson *et al.,* 1998). By using kinetic data from studies and reports with data on blood boron concentrations at steady state (excluding studies and reports with clear overdose, inadequate intake information, and/or no relevant data for clearance rate), a boron clearance rate can be estimated (Figure 1). Based on the steady~ state blood boron concentrations and the corresponding oral doses, boron clearance rates were calculated (clearance [ml/kg/hl = dose [mg/kg/hl/ blood concentration [mg/ml]) where the mean clearance rate was 40 ml/kg/ hour in humans, and 163 ml/kg/hour in rats. This indicates that rats have an approximately fourfold higher boron clearance rate than humans. Based on this information, the WGCSDW proposed a factor of 4 for the variation in elimination. The IPCS group did not evaluate the data on the clearance rate.

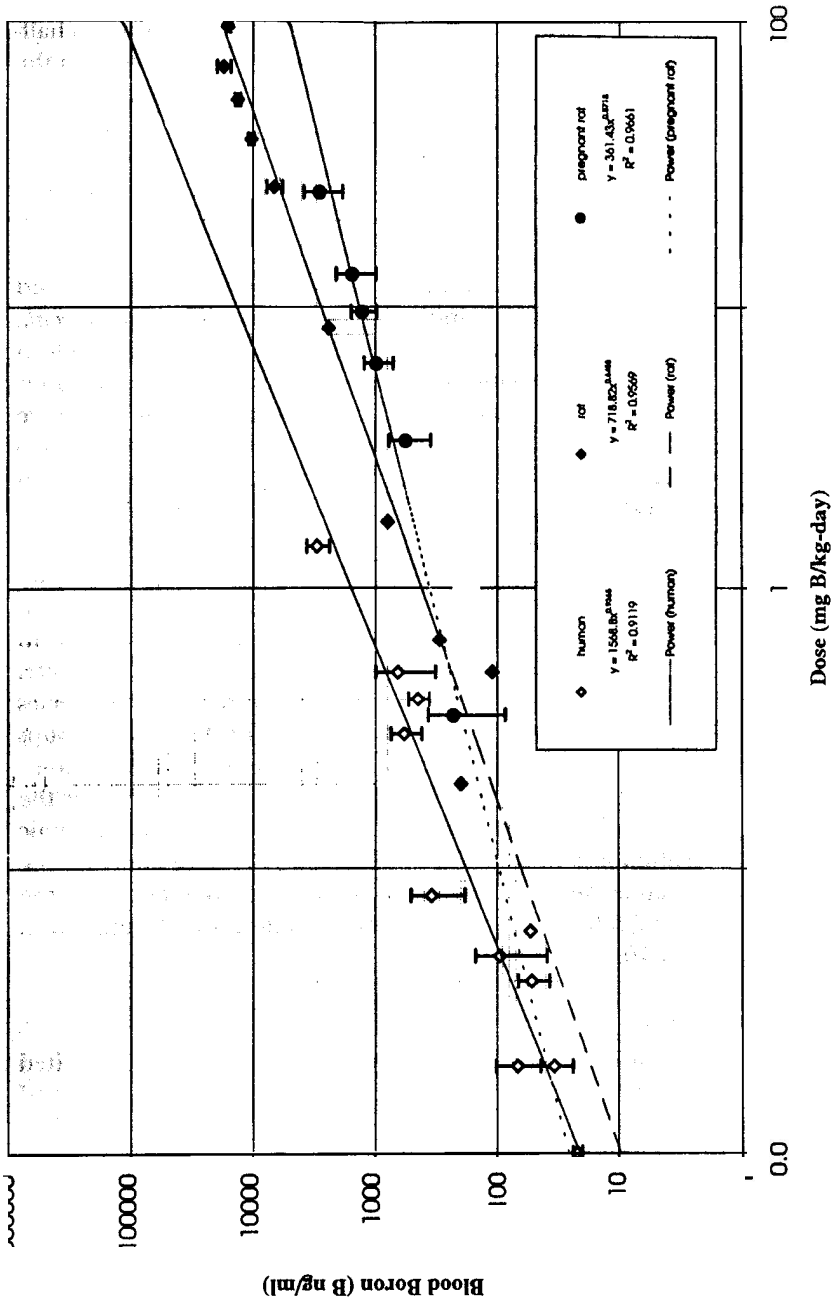
No data were available to support an UF other than 2.5 for interspecies variation in toxicodynamics. Therefore, both the IPCS and WGCSDW groups suggested using a default value of 2.5 to account for the dynamic variation.

As the result (see Table 1), the IPCS used a sub-factor of 1.3 (100-1) for the toxicokinetic variation and a default value of 2.5 (100.4) for the toxicodynarnic variation, which resulted in an interspecies UF of 3.2 (100-1). In contrast, the WGCSDW used a data-derived sub-factor of 4 for the toxicokinetic variation and a default value of 2.5 for the toxicodynarnic variation, which resulted in an interspecies UF of 10.

Intraspecies Variations

Intraspecies variation in boron absorption and distribution is very limited (Nielsen, 1995). In addition, the absence of boron metabolism in humans and experimental animals provide further support for consideration of a reduction in the default UF of 3.2 (100-5). Based on this information and without addressing the variation in elimination, IPCS judged that 2.5 (100.4) was appropriate for intraspecies variation in toxicokinetics.

While the WG4CSDW found data on boron absorption, and distribution limited, it did evaluate the variation of clearance rates in pregnant women and estimated an intraspecies variable, which was used in the UF derivation. When the boron clearance rates in pregnant rats and non-pregnant rats were esti-


Blood Boron (B ng/ml)
100000
10000
1000
100
10
1
0.0
Dose (mg B/kg-day)
pregnant rat
y = 361.43x^0.8716
R² = 0.9661
rat
y = 718.82x^0.8466
R² = 0.9569
human
y = 1568.8x^0.7845
R² = 0.9119
Power (pregnant rat)
Power (rat)
Power (human)

mated, the mean clearance rate was 163 ml/kg/hour in non-pregnant rats and 397 ml/kg/hour in pregnant rats (Dourson et al. 1998). These data correspond to increased glomerular filtration (GFR) during pregnancy, because renal excretion is the only means of boron elimination at steady state. As the critical effect caused by boron oral exposure is decreased fetal weight, which is directly related to boron exposure in the mother, the variation in boron elimination rate in pregnant women is a critical factor. Because no information on boron clearance in pregnant women is available, the variation of boron clearance rate in pregnant women was estimated based on the available information on GFR during human pregnancy. The data on GFR in pregnant women from three studies (Dunlop *et* at, 1981; Krutzen *et* at, 1992; Sturgiss *et* at, 1996) were pooled, and the mean GFR and its standard deviation were determined as 144 mL/min and 32 ml/min, respectively. The intraspecies variation in boron elimination was estimated by dividing the mean GFR (144) by the difference (144-2 x 32) between the mean and two standard deviations, which resulted in a ratio of 1.8. The WGCSDW used this ratio as the adjustment for intra-human variability in kinetics.

There are no human data on toxicodynarnics to support the use of a value different from the default of 3.2 or 100.5 . As a result, both the IPCS and WGCSDW judged the default of 3.2 is appropriate for intraspecies toxicodynamic variations.

As summarized in Table 1, the IPCS used 2.5 (100.4) for the variation in toxicokinetics and a default value of 3.2 (100.5) , resulting in an UF of 7.9 (100") for intraspecies variation. Compared to the IPCS, the WGCSDW used a subfactor of 1.8 for the variation in toxicokinetics and a default value of 3.2 for the variation in toxicodynarnics, which resulted in an UF of 6 for intraspecies variation.

DISCUSSION

Although both the IPCS and WGCSDW groups used the data derived uncertainty factor approach in deriving the UFs for both interspecies and intraspecies variations, they applied different values for several of these UFs based on different uses of the available data. For interspecies variation, considering the lack of metabolism of boron in experimental animals and humans, and the similarity in absorption and distribution, both IPCS and WGCSDW considered that interspecies variation in kinetics relates primarily to elimination of boron. Based on the similarity of boron elimination half-life in both humans and animals, the IPCSjudged that only limited adjustment was needed for variation in boron elimination; therefore, a total of 1.3 (100-1) was chosen to replace the default value of 4.0 (100.6) for interspecies kinetic variation. Combined with the suggested default value of 2.5 (100.4) for dynamic variation, a total of 3.2 (100-5) was chosen as the UF for interspecies variation. In contrast, the WGCSDWjudged that a factor of four should be used for kinetic variation based on the information that the boron clearance rate was fourfold higher in

rats than in humans. As the result, the UF for interspecies variation, including kinetics and dynamics, was determined to be 10 (4 x 2.5), which is the same as the default value.

The two groups also considered the data on elimination for intraspecies variability differently which resulted in a difference in UFs. The fact that there is no metabolism of boron by humans and animals limited a potential intraspecies variable. Therefore, the IPCS judged that the default UF of 3.2 (100 .5) should be lowered to a value of 2.5 (100.4) for variability in kinetics and a total of 8.0 (100.9 = 100-4 X 100.5)) should be used as the UF for intraspecies variation. No data related to elimination were used in the derivation of this factor. In contrast, the WGCSDW recommended a factor of 1.8 for kinetic variation based on variation of GFR in pregnant women, which is directly related to renal elimination of boron. As a result, a total of 5.7 (1.8 x 3.16 default for dynamic) was chosen as the UF for intraspecies variability.

Two parameters, elimination half-life and clearance rate, in toxicokinetics are commonly used to describe the toxicant's elimination. Of these two parameters, clearance is more important than elimination half time in comparison of toxicant elimination. As discussed by Renwick (1991), clearance (CI) determines the average plasma steady~state concentration (CP.) (CI = Dose/CP.), and is inversely proportional to toxicant plasma concentration, which is directly related to the systemic dosing of the toxicant. On the other hand, elimination half-life (TI/2) is determined not only by clearance or plasma steady~state concentration, but also by apparent volume of distribution (V) (TI/2 = 0.693 x V/Cl = 0.693 x V x CP./dose). Because the information on apparent volume of distribution is not readily available in most of the studies, a direct comparison of elimination half-life only provides us with limited information on internal dosing of the toxicant. Therefore, clearance is a more useful parameter in comparing toxicant elimination. Whenever information on clearance is available or can be calculated, it should be used to compare the variation in toxicant elimination. For boron, a comparison of elimination halflife and clearance rate produced different results. Clearance data were used by WGCSDW and half-life data were used by the IPCS, resulting in selection of different UFs.

The uncertainty factor for intraspecies variation is intended to cover the variability between the average human, and the sensitive human. Before the most sensitive population is identified, the variation in both kinetics and dynamics within the whole population should be considered in order to cover the response in an unidentified sensitive population. In the case of boron, the toxicity database is large and the critical effect has been identified as decreased fetal weight. Thus, the most sensitive population (pregnant women who are directly exposed to boron), has been identified. Therefore, the only consideration for the estimation of intraspecies variability was the variation within this sub-population. This led to a more precise adjustment in the corresponding UF.

The variation in elimination could also be estimated based on variations in physiological parameters. Using GFR to estimate the variation in boron elimi-

nation is a good example of developing a data derived LJF by using available physiological data and scientific judgment. Since no data on boron elimination in pregnant women were available, WGCSDW used an alternative approach where GFR variation was evaluated instead because boron is excreted entirely through the urinary route. By evaluating the GFR variation, the variability of elimination in the pregnant women could be estimated; therefore, a data-derived UF could be established.

To estimate tolerable intakes with greater precision, risk assessors should consider use of data-derived Us. When more than one parameter is available to describe a specific area of variation, judgment concerning use of a particular parameter must rely on careful examination of all available toxicological and physiological information. The WGCSDW has used more of the available science than the IPCS in their respective development of the TDI.

SUMMARY

Although both the IPCS and WGCSDW used the data derived uncertainty factor approach in deriving the UFs for both interspecies and intraspecies variations, they applied different values for each of these UFs based on different uses of the available data. Both groups considered that interspecies and intraspecies variations in boron toxicity relate primarily to elimination of boron. Considering interspecies variation, the IPCS suggested a sub-factor of 1.3 for kinetics, based on similar boron $T_{1,2}$ in humans and rats, which resulted in an UF of 3.2. Based on data about boron clearance. The WGCSDW used a sub-factor of 4 for kinetics, which resulted in an UF of 10. For intraspecies variation, the IPCS used sub-factor of 2.5 based on a lack of boron metabolism resulting in an UF of 7.9. In contrast, the WGCSDW used a sub-factor of 1.8 to account for variation in GFR in sensitive human population, and derived an UF of 5.7. Based on these considerations, the IPCS derived a total UF of 25, while the WGCSDW derived a total UF of 60. In comparison of toxicant elimination, clearance is more important than elimination half time. The variation in elimination could also be estimated based on physiological data such as GFR.

Based on the use of variability in GFR in humans to estimate intraspecies variability and the use of clearance to estimate interspecies variability in boron elimination, the authors conclude that the WGCSDW has used more of the available science than the IPCS in the development of the TDI. More importandy, these comparisons show the need for the development of criteria for data use in the judgment of uncertainty factors.

ACKNOWLEDGMYWr

The authors wish to gratefully acknowledge Jacqueline Patterson of Toxicology Excellence for Risk Assessment for her assistance in the development of this paper.

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