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Boron Tolerable Intake

Re-evaluation of Toxicokinetics for Data-Derived Uncertainty Factors

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ABSTRACT

Boron, which is ubiquitous in the environment, causes developmental and reproductive effects in experimental animals. This observation has led to efforts to establish a Tolerable Intake value for boron. Although risk assessors agree on the use of fetal weight decreases observed in rats as an appropriate critical effect, consensus on the adequacy of toxicokinetic data as a basis for replacement of default uncertainty factors remains to be reached. A critical analysis of the existing data on boron toxicokinetics was conducted to clarify the appropriateness of replacing default uncertainty factors (10-fold for interspecies differences and 10-fold for intraspecies differences) with data-derived values.

The default uncertainty factor for variability in response from animals to humans of 10-fold (default values of 4-fold for kinetics and 2.5-fold for dynamics) was recommended, since clearance of boron is 3- to 4-fold higher in rats than in humans and data on dynamic differences—in order to modify the default value—are unavailable. A data-derived adjustment of 6-fold (1.8 for kinetics and 3.1 for dynamics) rather than the default uncertainty factor of 10-fold was considered appropriate for intrahuman variability, based on variability in glomerular filtration rate during pregnancy in humans and the lack of available data on dynamic differences. Additional studies to investigate the toxicokinetics of boron in rats would be useful to provide a stronger basis for replacement of default uncertainty factors for interspecies variation.

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Index Entries: Boron; tolerable intake, uncertainty factor; toxicokinetics.

INTRODUCTION

Boron compounds are widely distributed in the environment; those components present in the soil may be taken up by plants or released to surface and groundwater resulting in food and drinking water being the major sources of exposure. Boron is also important commercially, and its use as a component of pesticides, soaps and cleaners, and cosmetics may also contribute to potential exposures. In animal studies, reproductive and developmental effects have been observed with a decrease in fetal weight being considered the more sensitive endpoint (also referred to as the critical effect) *(1,2)*.

With the increasing emphasis on the use of data-derived uncertainty factors, the International Programme on Chemical Safety (IPCS) developed a Tolerable Intake value *(2)* using uncertainty factors based on a data-derived scheme *(3)*. Based on this effort, the default uncertainty factor for experimental animal to human variability of 10-fold was replaced with a value of $10^{0.5}$ (or 3.1-fold) to reflect the overall qualitative similarity between the kinetics of boron in humans and rats. The uncertainty factor for average to sensitive humans was replaced with a value of $10^{0.9}$ (or 7.9). Modification of these two uncertainty factors led to an overall uncertainty factor of $10^{1.4}$ (or 25) compared to the default value of 100.

More recently, a meeting of a Working Group on Chemical Substances in Drinking Water was convened to address several parameters, including boron, for the World Health Organization's "Guidelines for Drinking Water Quality." This group evaluated the boron database to identify the critical effect and to assess the adequacy of the database for the replacement of the default uncertainty factors by more appropriate data-derived values. In order to further develop the assessment, a meeting attended by M. Dourson, B. Meek, E. Ohanian, and A. Renwick (an ad hoc joint panel) was held in September 1997 in Cincinnati, OH, to evaluate the data relevant to the derivation of uncertainty factors for boron. This report describes the outcome of this latter meeting.

METHODS

The science behind the use of uncertainty factors has progressed considerably over the past years. Increased knowledge of inter- and intraspecies sensitivity and mechanism of action 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 uncertainty factors (UFs) for standard defaults, as described by Dourson et al. *(4)*.

Renwick *(5,6)* has examined the nature of the UFs generally applied for intraspecies and interspecies extrapolations. He has proposed the subdivision of each of these UFs into subfactors to allow for separate evaluations of toxicokinetics and toxicodynamics *(5,6)*. 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 specific target organ concentration or target organ dose. The advantage to such a subdivision is that default UFs for these components can be replaced where data are available. For example, if data are sufficient to support 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 *(6)* examined in detail the relative magnitude of toxicokinetic and toxicodynamic variations between and within species for a number of chemicals and pharmaceuticals. The 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 has modified the approach set forth by Renwick *(5,6)*, by suggesting 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) because the underlying data showed the variations in kinetics and dynamics to be more similar than not for this latter factor *(4)*.

RESULTS

The ad hoc joint panel reevaluated the adequacy of the existing data on kinetics for developing data-derived uncertainty factors for both inter- and intraspecies differences for boron. Each of these studies was reviewed in detail to determine its contribution to the database for replacement of the default uncertainty factor for interspecies variation. The 19 toxicokinetic studies that were evaluated are listed in Table 1 *(7–25)*. Of these studies, six human studies and five animal studies were considered to contribute meaningfully to this database, although confidence in the data was considered low for some of these. Lack of confidence in these data related primarily to limited information about time of sampling or lack

Table 1
B Toxicokinetic Studies

Author	Year	Comments[a]
Human Studies		
Barr et al.	1993	included
Gordon et al.	1973	clear overdose; calculated clearance implausible
Hunt et al.	1997	included
Jansen et al.	1984	included
Job	1973	included
Linden et al.	1986	clear overdose; no relevant data for clearance rate determination
Litovitz et al.	1988	no individual data on intake or blood concentrations
Nielsen	1996	included
O'Sullivan and Taylor	1983	included
Wiley	1906	inadequate methodology
Wong et al.	1964	intake not quantified; time between intake and blood sampling unknown, calculated clearance rates for 3 subjects were not comparable
Animal Studies		
Bai and Hunt	1996	included
Chapin et al.	1997	included
Ku et al.	1993	included
Ku et al.	1991	included
Nielsen et al.	1992	blood concentrations were the same with and without supplementation, animals fasted overnight before sampling
Magour et al.	1982	profile of boron concentrations in selected tissues inconsistent with other studies
Price et al.	1997	included
Vanderpool et al.	1994	no relevant data for clearance rate determination

[a]Comments refer to whether or not clearance was estimated from data in the study and, thus, whether or not a study was included in Fig. 1 or 2.

of kinetic analysis. Eight studies were excluded completely. In general, human studies were excluded based on lack of quantified intake or reports of acute boron overdoses, which precluded adequate analysis of boron kinetics and prediction of steady-state conditions. Three of the animal studies were excluded from further analysis owing to difficulties in interpretation of the data.

The ad hoc joint panel agreed that in view of the lack of metabolism of boron in experimental animals and humans and the similarity in absorption and elimination, interspecies variation in kinetics relates principally to renal clearance rates. Table 2 provides an evaluation of the literature on boron absorption and elimination *(26,27)*. Over a wide range of doses, the percentage of the boron dose absorbed ranged from 64% to 98% and elimination ranged from 67% to 98% in the human studies. Similar results were reported in the rat. These data indicate that boron is nearly completely absorbed and does not tend to accumulate in humans and animals. Table 3 provides the data on blood boron levels as a function of administered dose. This relationship is presented in Fig. 1, which provides a plot of the blood concentration versus administered dose for humans, nonpregnant rats, and pregnant

Table 2
B Absorption and Elimination

Species	Route	Dose mg/kg-day	%Absorption	%Elimination	Reference
human	diet	0.0054	81-92	81-92	Hunt et al., 1997
human	diet	0.049	87-89	89-92	Hunt et al., 1997
human	i.v.	1.4-1.5	NA	99	Jansen et al., 1984
human	drinking water	1.4	≥91	≥91	Job, 1973
human	diet	ND	83-98	83-98	Kent and McCance, 1941
human	diet	0.05	84	84	Nielsen, 1996
human	drinking water	1.9	94	94	Schou et al., 1984
human	oral	2.5	92	92	Schou et al., 1984
human	oral	~26	83	86	Wiley, 1906
human	oral	~17	83	86	Wiley, 1906
human	oral	~23	64	67	Wiley, 1906
human	oral	~17	83	86	Wiley, 1906
human	oral	~22	75	78	Wiley, 1906
human	oral	ND	84	87	Wiley, 1906
rat	oral	0.02	95	99	Vanderpool et al., 1994

Table 3
Blood B Levels as a Function of Dose in Humans and Rats

Dose mg/kg-day	Human ng/ml	Rat ng/ml	Route	Reference
0.01	22 (2)[a]		drinking water	Barr et al., 1993
0.02	34 (10) plasma		diet	Nielsen, 1996
0.02	68 (34)		drinking water	Barr et al., 1993
0.04	52 (15)		drinking water	Barr et al., 1993
0.049	95 (56) plasma		diet	Hunt et al., 1997
0.06	53 plasma		diet	Nielsen, 1996
0.08	347 (163)		drinking water	Barr et al., 1993
0.2		200	diet	Chapin et al., 1997
0.3	585 (166)		drinking water	Barr et al., 1993
0.35		229 (143)	diet	Price et al., 1997
0.4	450 (87)		drinking water	Barr et al., 1993
0.5	659 (337)		drinking water	Barr et al., 1993
0.5		110	diet	Bai et al., 1996
0.65		300	diet & gavage	Bai et al. 1996
1.4	3000 (633)		drinking water	Job, 1973
1.7		800	diet	Chapin et al., 1997
3.3		564 (211)	diet	Price et al., 1997
6.3		975 (261)	diet	Price et al., 1997
8.4		2400	diet	Chapin et al., 1997
9.6		1270 (298)	diet	Price et al., 1997
13		1530 (546)	diet	Price et al., 1997
25		2820 (987)	diet	Price et al., 1997
26		6700 (1000) serum	diet	Ku et al., 1993
38		10300 (600) serum	diet	Ku et al., 1993
52		13300 (700) serum	diet	Ku et al., 1993
68		17300 (2200) serum	diet	Ku et al., 1993
95		16000 (710) plasma	diet	Ku et al. 1991

[a]Values in parentheses represent the standard deviation.

rats. Based on this information, boron clearance was calculated [clearance (mL/kg/h) = dose (mg/kg/h)/blood concentration (mg/mL)] and the resulting analysis is provided in Table 4. The mean clearance rate for the rat studies was 163 mL/kg/h and the mean clearance rate

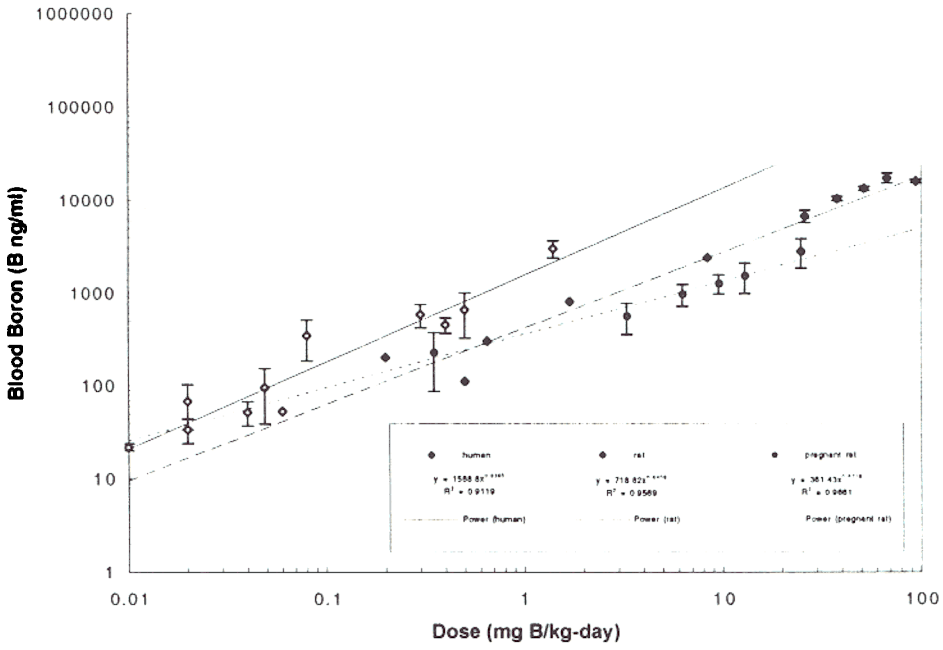

Fig. 1 Blood B concentration in humans, rats, and pregnant rats as a function of B dose (uncertain data removed).

from human studies was 41 mL/kg/h, therefore, rats have an approximately 4-fold higher boron clearance rate than humans as indicated in Fig. 2. This 4-fold difference is similar to what one would suspect based on analysis of other chemicals *(6)*.

The ad hoc joint panel also recommended a change in the uncertainty factor for intraspecies variation. Figure 1 provides some indication that blood boron levels may vary with pregnancy based on the seeming difference between pregnant and nonpregnant rats; however, the difference in kinetics of boron during pregnancy is likely due to an increase in the glomerular filtration rate (GFR). This observation is of particular interest, since the critical effect used to derive the tolerable intake (TI) is decreased fetal weight. Data describing clearance of boron in pregnant humans are not available, but an increase in GFR is a recognized physiological adaptation in pregnancy. Available data from studies of GFR in healthy pregnant females were pooled; the mean GFR was 144 (32 mL/min (± the standard deviation) during late pregnancy was determined *(28–30)*. In order to estimate the degree of intraspecies variation in this factor, the ratio of the mean GFR (i.e., 144) and the mean GFR minus two standard deviations (i.e., 2 × 32) from the mean (i.e., 144 – 64 = 80) was calculated: 144 ml/min ÷ 80 ml/min = 1.8. Thus, this factor was used directly as the adjustment for intra-human variability in kinetics.

Table 4
Blood B Clearance as a Function of Dose in Humans and Rats

Dose mg/kg-day	Clearance ml/kg/hour			Reference
	Human	Rat	Pregnant rat	
0.01	18			Barr et al., 1993
0.02	23			Nielsen, 1996
0.021	13			Barr et al., 1993
0.042	33			Barr et al., 1993
0.042	92			Nielsen, 1996
0.049	21			Hunt et al., 1997
0.15 (peak)		94		Bai and Hunt, 1996
0.28	20			Barr et al., 1993
0.317		240		Nielsen et al., 1992
0.35	32			Barr et al., 1993
0.45	28			Barr et al., 1993
0.5 (peak)		189		Bai and Hunt, 1996
0.65 (peak)		152		Bai and Hunt, 1996
1.4	51			Job, 1973
1.5 (peak)	54			Jansen et al., 1984
1.7		92		Chapin et al., 1997
3.3			417	Price et al., 1997
6.3			350	Price et al., 1997
8.4		140		Chapin et al., 1997
9.6			385	Price et al., 1997
13.3			426	Price et al., 1997
20	97			O'Sullivan and Taylor, 1983
25			409	Price et al., 197
26		162		Ku et al., 1993
38		154		Ku et al., 1993
52		163		Ku et al., 1993
68		164		Ku et al., 1993
95		247		Ku et al., 1991
Mean	40 (28)[a]	163 (49)	397 (31)	

[a]Values in parentheses represent the standard deviation

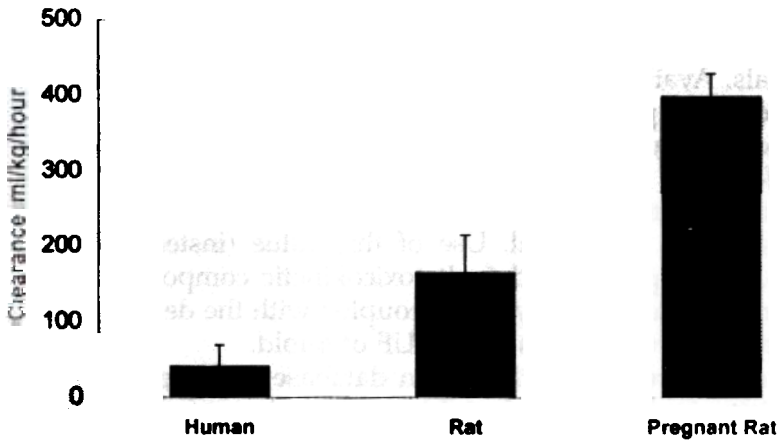

Fig. 2 B clearance in humans, rats, and pregnant rats.

DISCUSSION

The estimate of a Tolerable Intake value requires determination of a critical effect level and application of uncertainty factors to ensure this critical effect level captures the variability in dose-response for the human population. In this article, the available toxicokinetic data for boron were analyzed in detail to determine if they were adequate to replace default values with data-derived values for inter- and intraspecies variation. The ad hoc joint panel analysis supports the idea that differences in blood boron levels between rats and humans at equivalent doses reflects differences in clearance of this compound and that metabolism, absorption, and overall elimination are nearly the same among species. Calculation of the mean clearance rates for boron indicate that clearance is approximately 4-fold higher in rats than humans. This is the same as the default value for the toxicokinetic component of interspecies variation proposed by Renwick *(6)* and adopted by IPCS *(3)*, which is not unexpected since species differences in renal function contributed to the selection of the default factor of 4 *(6)*. When a subset of the data with greater confidence was used, a 3-fold difference was estimated. Since the lower clearance rate observed in humans would tend to increase boron body burden relative to rats, it appears premature to modify the default UF for toxicokinetics from animals to humans. As no data were available to modify the default UF of 2.5 for animal to human toxicodynamics, a total UF of 10 is recommended for animal to human variability.

The ad hoc joint panel also analyzed the data for intraspecies susceptibility. Figure 1 indicates a potential difference in clearance of boron between pregnant and nonpregnant rats. Variations in the toxicokinetics of boron are principally a function of differences in renal clearance, which increases during pregnancy, as reflected in the pregnant versus nonpregnant animals. Available data are inadequate; however, to make any comparison between pregnant rats and pregnant humans. Although the clearance of boron in pregnant humans has not been studied, data are available for GFR in this population. Analysis of the available literature indicates that a factor of 1.8 accounts for the difference in GFR for the average to susceptible individual. Use of this value (instead of the default value of 3.1) to replace the default toxicokinetic component of the intrahuman variability uncertainty factor coupled with the default value for the toxicodynamic portion yields a total UF of 6-fold.

The original review of the boron database had identified reports of boron toxicity in infants and children. A review of the available case reports indicated that these reports provide poor characterization of exposure and patient outcome. In O'Sullivan and Taylor *(15)* effects were reported at relatively low doses, 9 to 33 mg/kg/d, but these doses were still at least an order of magnitude greater than the recommended TI, which was based on effects in neonatal or young animals.

In summary, based on the ad hoc joint panel analysis, it was recommended that the default factor for interspecies variation of 10-fold be retained for derivation of the guideline for boron in drinking water. A toxicokinetic study in rats would be useful to compare to the available human study of Jansen et al. *(10)* and would provide a better basis for a data-derived uncertainty factor. It was also recommended that the default value for the uncertainty factor for human variability be replaced with one derived on the basis of the available information on the variability in GFR for the population relevant to the critical effect, pregnant females. Based on the available data, a factor of 6 was considered appropriate. Thus, the overall factor was 60.

The use of a data-derived uncertainty factor for a boron TI illustrates the power of utilizing the types of toxicokinetic information of a complete database, when available. Uncertainty factors for intraspecies and interspecies variability are both comprised of toxicokinetic and toxicodynamic components. Being able to define mathematically the contribution of each component of the UF and applying it to the calculation of the TI more accurately defines the TI and allows the risk assessor to estimate the safe level with more precision. Use of a reduced UF is consistent with the methodology of several regulatory bodies, such as the IPCS *(3)* or other groups such as Health Canada *(31)* or the US EPA *(32)*. For example, reduction of UFs used in the derivation of inhalation Reference Concentrations is performed routinely, particularly the reduction of interspecies variability when using animal data that has been dosimetrically modeled. The reduction of the intraspecies UF for boron is consistent with the practice of these groups. Such reductions should be undertaken when the appropriate data are available. Boron provides an example for reduction of the intraspecies UF for oral exposure.

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