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Using Human Data to Develop Risk Values[1]

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ABSTRACT

One of the criticisms of industry-sponsored human subject testing of toxicants is based on the perception that it is often motivated by an attempt to raise the acceptable exposure limit for the chemical. When Reference Doses (RfDs) or Reference Concentrations (RfCs) are based upon no-effect levels from human rather than animal data, an animal-to-human uncertainty factor (usually 10) is not required, which could conceivably result in a higher safe exposure limit. There has been little in the way of study of the effect of using human vs. animal data on the development of RfDs and RfCs to lend empirical support to this argument. We have recently completed an analysis comparing RfDs and RfCs derived from human data with toxicity values for the same chemicals based on animal data. The results, published in detail elsewhere, are summarized here. We found that the use of human data did not always result in higher RfDs or RfCs. In 36% of the comparisons, human-based RfDs or RfCs were lower than the corresponding animal-based toxicity values, and were more than 3-fold lower in 23% of the comparisons. In 10 out of 43 possible comparisons (23%), insufficient experimental animal data are readily available or data are inappropriate to estimate either RfDs or RfCs. Although there are practical limitations in conducting this type of analysis, it nonetheless suggests that the use of human data does not routinely lead to higher toxicity values. Given the inherent ability of human data to reduce uncertainty regarding risks from human exposures, its use in conjunction with data gathered from experimental animals is a public health protective policy that should be encouraged.

Key Words: human data; reference dose; reference concentration.

INTRODUCTION

We assessed the value of using human data in the assessment and management of risk using contemporary risk assessment methods. Human data as used here include

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all types of epidemiologic studies as well as controlled laboratory experiments. Although the use of such data has a long and successful history with environmental contaminants and the development of drugs and commercial chemicals, issues associated with such use have attracted increased attention among both scientists and policy makers (*e.g.*, USEPA 2000a; Russo 2000; SOT 2000; Dourson *et al.* 2001). Specifically, is information from human studies the best way to judge the potential public health risk from chemicals in our environment? Should scientists ignore available human data that might suggest a lower or higher risk value? Answers to these and related questions are complicated and not necessarily straightforward.

A key issue is whether the use of animal versus human data systematically leads to different toxicity values. That is, if animal and human data are both available, and toxicity values (Reference Doses, RfDs; or Reference Concentrations; RfCs) are calculated from these data using standard procedures, do the different sources of information yield the same values? If not, does either human or animal data consistently produce lower RfDs and RfCs? We addressed this question through an analysis comparing toxicity values derived from both animal and human data sources.

DESCRIPTION OF THE STUDY AND ITS RESULTS

In order to do this assessment, we chose a complete listing of U.S. Environmental Protection Agency's (USEPA) established noncancer risk values, that is, RfDs and RfCs, based on human data as found in its IRIS database (USEPA 2000b). RfDs and RfCs found in IRIS have gone through an extensive and rigorous development process, including internal peer review and unanimous acceptance within the USEPA. IRIS is not the only source of such information, of course (see, for example, www.tera.org/iter), but IRIS was used because it is convenient, reasonably robust, objective and respected (although many of the risk values are now outdated). These human-based RfDs and RfCs were compared to estimates from readily available experimental animal data, mainly from IRIS, based on the USEPA dose-response assessment methods (Barnes and Dourson 1988; Dourson 1994; USEPA 1994; Jarabek 1994, 1995).

Our choice of appropriate experimental animal toxicity data to develop a RfD or RfC for comparison with an existing human value depended primarily on the availability of the experimental animal data. Confidence in the resulting comparison depends in part on the confidence one has in the human-based RfD or RfC (see IRIS for confidence statements for each risk value), and on the relevance of the results in animals to the critical effect shown in humans. In descending order of importance, experimental animal data were selected to match:

- The dose-response curve of the critical effect in the human study [*e.g.*, comparison of the dose-response curves of red blood cell cholinesterase (RBC) inhibition]; or

- The Benchmark Dose (BMD), No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL) of the critical effect in the human study (*e.g.*, comparison of RBC cholinesterase inhibition NOAELs).

If matching data were not available, then these criteria were selected:

- A BMD, NOAEL or LOAEL of a closely related effect found in animals compared to the critical effect in humans (*e.g.*, comparison of any clinical signs of cholinesterase inhibition); or

- The most sensitive effect found in animals was compared to the critical effect in humans (*e.g.*, comparison of cholinesterase inhibition with liver toxicity).

We recognized that pharmacokinetics and pharmacodynamics (discussed in Dourson *et al.* 2001) may impact the comparisons and conclusions drawn from these comparisons. Furthermore, the available experimental animal data may not include a species relevant to humans, and any such comparisons of these animal data with the human data may not be sufficiently predictive of effects in humans. Therefore, these comparisons of established human-based RfDs and RfCs with those estimated from available animal data should be considered along with information on pharmacokinetics and pharmacodynamics in determining the usefulness of human data.

We developed animal-based RfDs and RfCs directly from the existing information on USEPA's IRIS, and not from a thorough review of the original literature. In some cases, USEPA's IRIS states an alternative RfD or RfC based on animal studies, and these alternative values were used instead of estimating them. Occasionally, animal versus human risk values were compared using information from ATSDR, USEPA and Health Canada as described on the International Toxicity Estimates for Risk database (*ITER* 2001). Please note that these animal-based RfDs and RfCs that were derived have not undergone a rigorous peer review. Thus, the animal-based RfDs and RfCs that were provided should only be considered as interim, subject to change with additional data and/or analysis.

In all cases, the experimental animal-based RfDs and RfCs we developed assumed no relevant human data were available. Therefore, the default uncertainty factor of 10-fold (for RfDs) or three-fold (for RfCs) was used for experimental animal to human extrapolation. Recent data and analysis by the USEPA and others allow the use of specific human and animal toxicity, toxicokinetic, and toxicodynamic data to affect the value of this and other uncertainty factors (Renwick 1993; IPCS 1994; Dourson 1994; Dourson *et al.* 1996; Renwick and Lazarus 1998; Meek *et al.* 2001).

In the development of the animal-based RfDs and RfCs, we used the same database uncertainty factor and modifying factor as found in USEPA's IRIS with one exception [the footnote for nitrite in Table 1 of Dourson *et al.* (2001) explains this exception]. This decision is reasonable because the use of these factors, and the choice of other potential factors such as that recommended under the Food Quality Protection Act, reflects confidence in the overall database (USEPA 1999), which is the basis of both animal- and human-based RfDs and RfCs.

Figure 1 shows a frequency plot of human- to experimental animal-based RfD or RfC ratios from Tables 1 and 2 of Dourson *et al.* (2001). For RfDs, 8 out of 22 comparisons (36%) are the same within the limits of their corresponding precision.[2] For 5 out of 22 comparisons (23%), the RfDs based on human data are lower than the corresponding RfDs based on animal data by more than 3-fold. For 9 out of 22 comparisons (41%), RfDs based on animal data are lower than those based on human data by more than 3-fold. An animal-based RfD could not be estimated for

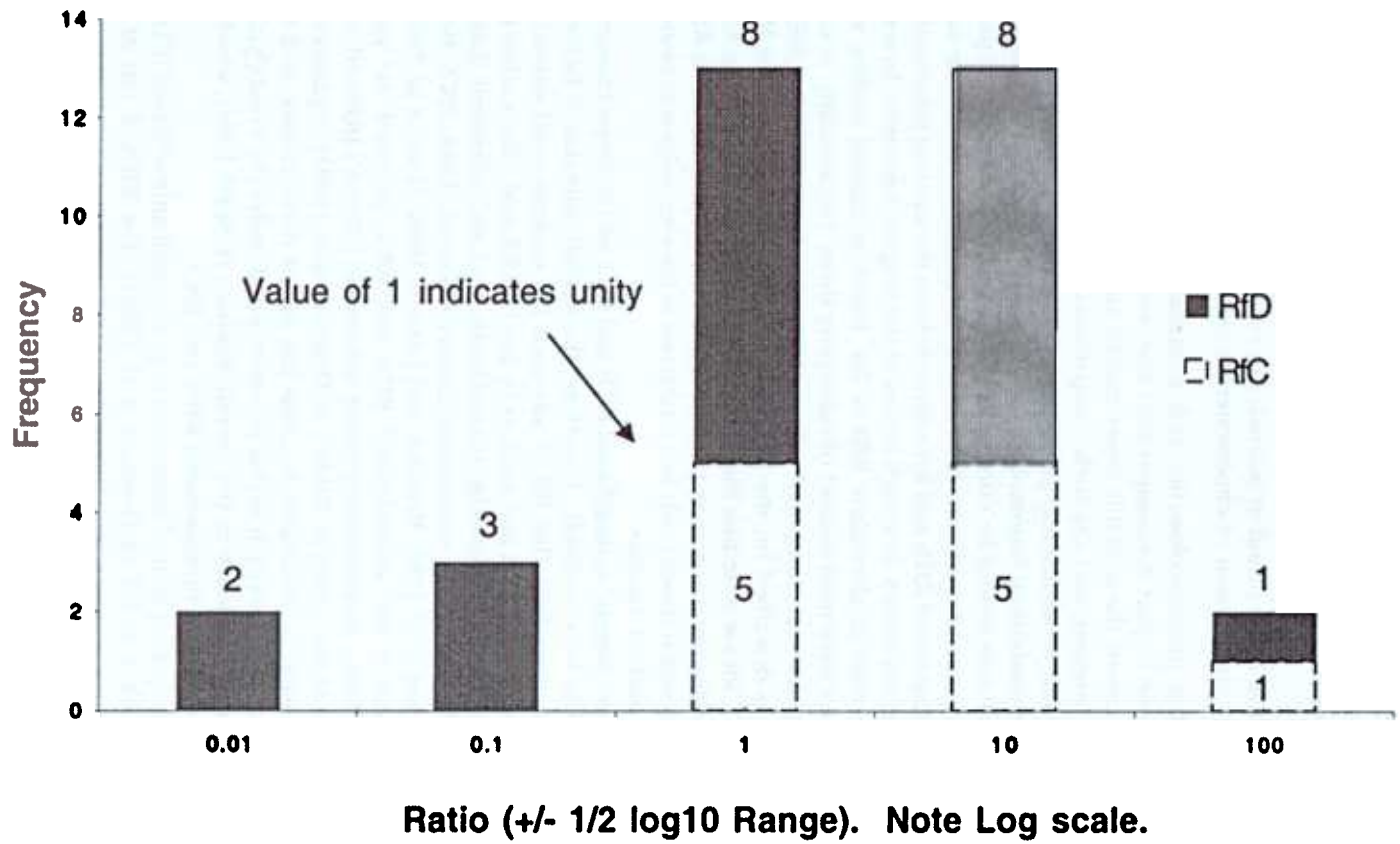

Figure 1. **Frequency of human to animal based RfD and RfC ratio from Tables 1 and 2.** Ranges defined by logarithmic midpoints (e.g., $0.3<1\leq3$). Value of 1 indicates that animal-based and human-based risk values are the same.

6 out of 28 times, since animal information was judged to be either insufficient or irrelevant. For RfCs, 5 out of 11 comparisons (45%) are the same within the limits of their corresponding precision.[2] In no cases were the RfCs based on human data lower than the corresponding RfCs based on animal data by more than 3-fold. For 6 out of 11 comparisons (55%), RfCs based on animal data are lower than those based on human data by more than 3-fold. An animal-based RfC could not be estimated for 4 out of 15 times, since animal information was judged to be either insufficient or irrelevant.

Differences in the ratios of the human to the experimental animal RfD or RfC can also be shown as the number that were above or below a value of 1 without regards to any considerations of precision. Here values below 1 indicate that human data resulted in a lower RfD or RfC than animal data. For RfDs this frequency is 9 out of 22 (or 41%). For RfCs this frequency is 3 out of 11 (or 27%). Collectively, this frequency is 12 out of 33 (or 36%). This percentage represents the number of times a human-based RfD or RfC was lower than a corresponding animal-based RfD or RfC.

We also noted reasons why certain risk values could not be based on animal data. This occurred with a frequency of 6 out of 28 (21%) for RfDs and 4 out of 15 (27%) for RfCs. Table 1 shows the stated reasons derived from Dourson *et al.* (2001). For 40%, the stated reason is a scientific judgment that the animal data are not relevant to the development of a risk value for humans as further explained in individual chemical files on IRIS (USEPA 2000b). For 60%, the animal data were not sufficiently described on USEPA's IRIS to develop a risk value.

DISCUSSION

We focus on the dose response assessment differences between humans and experimental animals as shown in Dourson *et al.* (2001). At first examination, a significant number of USEPA's human-based RfDs or RfCs are lower than those calculated from experimental animal data for which a 10-fold uncertainty factor for experimental animal to human extrapolation was used. This occurs in 36% (12 out of 33 comparisons) of all the comparisons performed, if no precision issues are considered, and occurs in 15% (5 out of 33 comparisons) if precision is considered to be "perhaps an order of magnitude."

This observation leads us to two questions. The first is whether the 10-fold factor is sufficient to protect human health for those animal-based RfDs and RfCs for which human data are lacking to corroborate the nature or dose response pattern of the critical effect. The data shown in Figure 1 can be used to address this question, in part. In doing so, however, a more rigorous evaluation of the animal-based RfDs and RfCs is suggested than that shown by Dourson *et al.* (2001). This is because these estimations of RfDs or RfCs from experimental animal data have not undergone the same rigor in development and review as those made with the human data on IRIS (USEPA 2000b).

The second question is whether the public's health is protected if one excludes the use of human-based RfDs and RfCs, and uses instead those based on animal data. It seems counterintuitive and poor public policy to disregard the use of human data

Table 1. Description of reasons why an animal-based RfD or RfC is not possible or appropriate (data from Dourson *et al.* 2001).

Chemical Name (as on USEPA's IRIS)	Specie/Type of study	Critical Effect(s)
Beryllium RfC	**Human occupational and community exposure**	
	Animal Data	**No laboratory animal model fully mimics all features of human CBD.**
Cadmium RfD	**Human chronic exposures from a variety of studies**	**Significant proteinuria**
	Animal Data	**Insufficient information exists in the IRIS file to make any determination of an RfD**
Chromium (acid mists and aerosols) RfC	**Human subchronic occupational**	**Nasal septum atrophy**
	Animal Data	Experimental animal studies have not reported on nasal mucosal effects following inhalation exposures.
Fluorine (soluble fluoride) RfD	Human epidemiology	Objectionable dental fluorosis
	Animal Data	Insufficient information exists in the IRIS file to make any determination of RfD
Hydrogen cyanide RfC	Human occupational	CNS symptoms & thyroid effects
	Animal Data	Insufficient information exists in the IRIS file to make any determination of RfC
Manganese RfC	Human occupation exposure	Impairment of neurobehavioral function
	Animal Data	IRIS states that animal toxicity data qualitatively support the human studies used as a basis of the RfC; quantified comparisons were not provided
Manganese RfD	Human data of several types	No LOAEL given, CNS effects appear to occur at higher doses
	Animal Data	IRIS states that human data are superior to any data obtained from animal toxicity studies as the basis of an RfD, since the physiologic requirements for manganese vary among species
1,1,2-Trichloro-1,2,2-trifluoroethane RfD	Human occupational exposure	Psychomotor impairment
	Animal Data	Insufficient information exists in the IRIS file to make any determination of RfD
Warfarin RfD	Human experimental	Increased prothrombin time
	Inappropriate	IRIS states "Because of marked differences in the susceptibility of different species to the effects of warfarin, it would be inappropriate to derive an RfD from studies on lower animals."
Zinc and Compounds RfD	Human experimental diet supplement	Decrease in erythrocyte superoxide dismutase concentration in adults
	Animal Data	Insufficient information exists in the IRIS file to make any determination of RfD

that suggest a lower RfD or RfC than the animal data, either because of greater sensitivity to the critical effect or different critical effect.

In contrast, this analysis also shows that a significant number of RfDs or RfCs, which were calculated from experimental animal data with a 10-fold uncertainty factor for experimental animal to human extrapolation, are lower than the human-based values. This observation also leads us to a question. How many animal-based RfDs and RfCs, for which human data to corroborate the nature or dose response pattern of the critical effect are lacking, err in a direction that is unnecessarily low or overly conservative in the goal to protect human health? Unfortunately, because this work did not include in-depth and direct comparison of any dose-response curves of the critical effect between humans and experimental animals because of the general unavailability of such data, an answer to this question awaits additional analysis.

Although this analysis indicates that animal data can lead to either a higher or a lower risk value than human data, human data often have provided information that reduces uncertainty or identifies a completely different critical effect than seen in experimental animal (*e.g.*, beryllium or chromium, see Table 1). Olson *et al.* (2000) also show that human toxicities often have no relationship to those found in experimental animals. In some cases, the USEPA and others judge that the animal data are not a reliable basis of the RfD or RfC and a ready comparison is not available or recommended (*e.g.*, manganese, warfarin). It is for these reasons, in part, that the USEPA gives higher priority to human studies (Barnes and Dourson 1988; Dourson 1994; USEPA 1994; Jarabek 1994, 1995). Other organizations have the same preference in developing their hazard identification and dose response assessments (*e.g.*, Meek *et al.* 1994; IPCS 1994).

A recommendation that might follow from these observations is that an evaluation of data from humans, when available and judged to be sufficient, is essential to the development of RfDs and RfCs. Such data seem preferable to using a UF of 10 for experimental animal to human extrapolation, and often identify effects not seen in animal studies. Furthermore, if the premise that human data are more reliable and relevant for a human risk assessment is accepted, then it follows that human data should be used without bias as to whether their use results in a higher or lower RfD or RfC. A major criterion for replacing animal data with human data should be quality; the human data should be of no lesser quality than the animal data that they will replace. Focus should be placed on a comparison of the quality of the human data to the animal data and the relevance and uncertainty for human health of each.

The ratios of human to animal based RfDs and RfCs found in Figure 1 should only be considered as a first approximation of the value of human data in the determination of a RfD or RfC for protection of the public's health. This is because the estimation of the RfD or RfC based on the human study found on USEPA's IRIS (or elsewhere) was from:

- A thorough analysis of the available data based on a review of original studies,
- The development of a risk assessment document, and
- Debate in one or more internal ATSDR, USEPA, or Health Canada peer review meetings, and, in at least the case of the USEPA, unanimous acceptance.

In contrast, the animal-based RfDs and RfCs developed by Dourson *et al.* (2001) and briefly shown here were generally based on summary information primarily found on USEPAs' IRIS or *ITER* (2001). These animal-based RfDs and RfCs generally did not have the benefit of the development of a risk document, nor extensive peer review. A more comprehensive analysis of animal-based RfDs and RfCs would have meant a comparable level of analysis and peer review.

Dourson *et al.* (2001) made comparisons between human and animal data on the basis of the RfD or RfC. In other words, the comparisons were made after uncertainty factors were applied to the NOAEL, LOAEL, BMD, or BMC. The range of uncertainty factors that is used with the NOAELs, LOAELs, BMD, or BMC in Dourson *et al.* (2001) reflects the variety of data types and databases for different chemicals. Although this approach is consistent with the goal to evaluate how well human data, used with contemporary risk assessment practices, protect human health, another procedure would be to compare biologically similar endpoints between the experimental animal species and humans.

Dourson *et al.* (2001) defined several criteria for comparing the existing human-based RfDs and RfCs with the animal-based RfDs and RfCs, and clearly indicated the hierarchy of the available data. The lowest criterion was the comparison of RfDs and RfCs based on NOAELs for unrelated effects. This is the least preferred comparison because the human and animal data tell us different things about the toxicity of the chemical in question, but this comparison was used often because these were the only data available. The choice between a NOAEL or BMD (or their corresponding inhalation counterparts) for the same or related critical effect were the next best criteria in the comparison of human and animal-based RfDs and RfCs. Dourson *et al.* (2001) also made this choice quite often. Unfortunately, data were not sufficient to match any dose response curves of the critical effect between human- and experimental animal-based RfDs and RfCs. Matching such curves is recognized as being an almost ideal criterion, but because many data are needed for such comparison, it is also the least likely criterion to be fulfilled.

CONCLUSIONS AND FUTURE DIRECTIONS

Within the limits of this analysis shown briefly here and more extensively elsewhere (Dourson *et al.* 2001), it is concluded that the direct use and interpretation of human data, in conjunction with data gathered from experimental animals, is a public health protective policy that should be encouraged.

Additional analysis of the results present here and by Dourson *et al.* (2001) could be done. For example, RfDs and RfCs based on human data were used from USEPA's IRIS. Other organizations also have similar risk values based on human data, and these values might also be compared with those based on experimental animal data. In addition, further research might explore whether commonalities exist among target tissue or mode of action for those chemicals for which animal- and human-based RfDs and RfCs differ quantitatively. Thirdly, one could explore the implications for the health-protectiveness of the vast majority of the RfDs and RfCs based on animal data, without any human data to act as a check.

Future collaborations with other interested scientists for resolution of these and other issues would be worthwhile.

FOOTNOTES

[1] Excerpted from Michael Dourson, Melvin Andersen, Linda Erdreich, and Judith MacGregor. 2001. Using human data to protect the public's health. Regulatory Toxicology and Pharmacology. 33: 234–256.

[2] These frequency values are based on ratios that fall within a 10-fold range of each other, for example 0.3 mg/kg-day< RfD ≤ 3 mg/kg-day. The use of such a range is consistent with the definition of RfDs and RfCs in that "uncertainty spans perhaps an order of magnitude," and thus their expected level of precision. However, the precision of risk values has never been explicitly addressed in the USEPA risk values (see Felter and Dourson (1998) for more discussion of this), and therefore the range used here is only for demonstration. Other, equally valid, ranges may be determined.

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