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Using Human Data to Protect the Public's Health

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The value of using human data in the assessment and management of risk is evaluated. Although the use of such data has a long and successful history with environmental contaminants and the development of drugs and commercial chemicals, recent deliberations within the Environmental Protection Agency (EPA) have questioned this practice in part. Specifically, we evaluate the degree to which reference doses (RfDs) and reference concentrations (RfCs) derived from human data on EPA's Integrated Risk Information System (IRIS) differ with RfDs and RfCs that we estimate from experimental animal data. We also use several minimal risk levels of the Agency for Toxic Substances and Disease Registry (ATSDR) and tolerable intakes of Health Canada in this comparison. Human-based RfDs are more than threefold lower than the corresponding animal-based RfDs for 23% of the comparisons. Human- based RfDs or RfCs are lower than corresponding animal-based RfDs or RfCs for 36% of the comparisons. Furthermore, for 10 of 43 possible comparisons, insufficient experimental animal data are readily available or data are inappropriate to estimate either RfDs or RfCs. We also discuss human pharmacokinetic data from volunteer studies and mechanistic studies with human tissues *in vitro* and demonstrate through a series of case discussions that utilization of such data is important when making decisions to protect exposed individuals. Moreover, physiologically based pharmacokinetic (PBPK) modeling evaluates critical information in assessing interindividual variability and identifying at-risk populations. Within the limits of our analysis, we conclude that the direct use and interpretation of human data, in conjunction with data gathered from experimental animals, are public health protective policies that should be encouraged. © 2001 Academic Press

***Key Words*: dose response; human; reference dose; reference concentration; risk; pharmacokinetics; pharmacodynamics; uncertainty factor.**

INTRODUCTION

Is information from human studies the best way to judge the potential public health risk from chemicals in our environment? Should public health agencies strive to resolve the ethical questions and identify criteria to foster the conduct of human studies that might lead to better protection of the public's health? Should scientists ignore available human data that might suggest a lower or higher risk value? What is a risk value?

These issues have been a subject of much recent discussion (e.g., EPA, 2000a; Russo, 2000; SOT, 2000) and a topic of increased attention among both scientists and policy makers. Answers to these questions are complicated and not necessarily straightforward. Perhaps the easiest question to answer is the last because it covers a narrower part of the NAS (1983, 1994) risk assessment and risk management paradigm—that of hazard identification and dose–response assessment. Conceivably it should be the first question answered, since its response lays the foundation for the other questions involving more than the underlying science. We attempt to answer this question directly below. Other questions are discussed later.

What Is a Risk Value?

In its simplest form, a risk value is a given point on the dose–response curve associated with some probability of an outcome. In many cases, risk values are chosen to be associated with a level of zero or very small risk, usually referred to as "no appreciable risk." A common example of a risk value is a reference dose (RfD). A RfD is a point on the dose–response curve for a chemical of interest that is believed to be in the region of no adverse effect and is often used by risk managers to distinguish between the region of no adverse effect and the region of adverse effect. With either interpretation, however, the RfD does not distinguish between the region of *any* effect and that of no effect, because scientists often distinguish between a chemical's ability to cause an adverse effect and its ability to cause effects that are not considered adverse. For example, risk assessors often distinguish among adaptive, adverse,

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compensatory, and critical effects.[2] In this process the concepts of severity of effect, homeostasis, and hormesis are often discussed.

Specifically, a RfD is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988). The reference concentration (RfC), where dose is expressed as a concentration, is similarly defined and applies to inhalation exposures (Jarabek, 1994, 1995). A measure or estimate of human exposure is often integrated with a risk value such as a RfD or RfC to develop a simple risk characterization, such as a maximum contaminant level goal (MCLG) in drinking water. This MCLG is then considered with other information in developing a risk management position, such as a maximum contaminant level (MCL). This MCL is enforceable and is designed to protect the public's health. EPA develops other risk characterizations and risk management decisions for other media. Such characterizations might involve more complex dose–response assessments and exposure assessments. Health organizations around the world use risk values and their associated exposure measures in similar fashion when conducting risk characterizations and arriving at risk management decisions.

In some cases, scientists postulate that a chemical may not have a distinguishable region of adverse effect and no adverse effect in the dose–response curve. In such cases, the adverse effect might occur at any dose, with more and more individuals being affected at greater doses (such as what might occur with cancer), or the adverse effect will not occur at any dose. With many chemicals this distinction is debated, because the scientific data are insufficient to provide certainty in conclusions in the area of the dose–response curve used for inference.

How Are Human Data Used?

Human data can be used in several ways in a hazard identification and dose–response assessment. For hazard identification, human data can be used alone to evaluate a finding or it may be used in concert with experimental animal data to provide weight-of-evidence that an observed association between exposure and response is actually caused by the exposure. In general, when used alone, human epidemiological data are insufficient evidence to strongly support causality (there are notable exceptions to this rule such as arsenic). In the case of human data associated with clinical studies or clinical interventions (such as for tamoxifen), the strength of the causal association is higher than with environmental epidemiological data. The main reasons for this difference pertain to limitations in the measurement of exposures in environmental epidemiological studies and the inability to control or include confounding variables that could also be associated with the observed toxicity.

In dose–response assessment, human data regarding the no-observed-adverse-effect level (NOAEL) can be used directly as the basis of a RfD or RfC. The presence of human data obviates the necessity of extrapolating from animals to humans; therefore, human studies, when available, are given first priority, with animal toxicity studies serving to complement them (Barnes and Dourson, 1988). However, using human data in this fashion requires that the human study be judged to be of at least comparable quality to an animal study that might be used to determine such a risk value. Moreover, the human study must conform to the highest standards associated with the conduct and evaluation of scientific data and include informed consent. Human data that are not directly useful as the basis of the NOAEL value can also be compared with animal data to determine the most appropriate interspecies uncertainty factor, rather than a default factor of 10 (Dourson *et al.*, 1996).

Human data can also be used as a guide to determine the appropriate toxicological end point to be considered for use in the hazard identification. In this regard, human case studies and incident reporting systems or other *in vivo* or *in vitro* experiments could be valuable when coupled with the more quantitative and better-controlled experimental animal toxicity studies. Used in this fashion, the human data can be seen to add mechanistic understanding of the critical effect determined from animals or to otherwise limit or bound the likely estimates of risk determined from the animal work in the dose–response assessment. They can also identify human effects that are not detected in animal studies, such as with the cardiac valvular defects

[2] Below are common definitions of types of effects. These effects are not always clear-cut categories, but often represent a continuum. Different individuals are expected to have different capacities for adaptive and compensatory effects.

- Adaptive effects are not considered to be adverse. They enhance an organism's performance as a whole and/or its ability to withstand a challenge. An increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity.
- Adverse effects are biochemical changes, functional impairments, or pathologic lesions that affect the performance of the whole organism or reduce an organism's ability to respond to additional environmental challenges (EPA, 2000b).
- Compensatory effects are not considered to be adverse. They maintain overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.
- Critical effects are the first adverse effects or their known precursors that occur as dose rate increases (EPA, 2000b).
- Severity is the degree to which an effect changes and impairs the functional capacity of an organ system.

associated with the use of the drugs for weight loss (FDA, 1997).

What Are the Types of Human Data?

To date, the human data that have been used in risk assessments include a wide variety of types, based primarily on the different ways in which health data on humans can be obtained. Human data range from anecdotal case reports to systematically designed epidemiological studies of an exposed cohort. Epidemiological studies use several different approaches for collecting data, including surveillance, public health statistics, geographic correlation studies, and the cohort and case–control studies designed to identify associations and sometimes to support inferences about cause and effect. Human data also include experimental exposures of individuals; these are typically short-term studies that involve doses below a hypothesized threshold of adverse effect.

Epidemiological studies are routinely based on inadvertent exposures that may occur in the workplace, by unusual natural contamination, or as the aftermath of an accident such as an explosion or industrial release. However, deliberate exposure to humans has been used for centuries to test therapeutic procedures (Lee, 1980). Human studies are routinely used in drug development to evaluate the efficacy or safety of a therapeutic or diagnostic regimen. Clinical studies, or phase I clinical trials, are designed to identify a safe dose of a potential therapeutic or preventive agent. These studies are an intrinsic part of medicine, and methods for the design and statistical analysis of these studies are discussed in most statistical textbooks (Elwood, 1998).

The human experimental studies used for agents in the environment generally measure biochemical and/or physiological changes related to the anticipated adverse response in order to obtain quantitative information, usually for comparison with animal data. Criteria for both Phase I clinical trials and experimental studies in humans of environmental exposures include voluntary participation. Exposures to environmental chemicals are intended to produce minimal or no immediate adverse effects and no irreversible adverse effects (e.g., these studies usually examine an end point in the adaptive or compensatory response range). In the case of environmental exposures, studies are designed for multiple reasons such as to aid in understanding how exposures might be measured in a general population or to provide additional information for species comparisons and reduce uncertainty. In both cases, these studies are aimed at improving health. In the case of Phase I clinical trials for drugs, studies are designed to identify dosing levels that can be tolerated without any serious or unacceptable side effects and to serve as a guide for dose selection for future studies.

Approximately 7 of 8 potential drugs fail during clinical development and are subsequently not used (DeGeorge, 1999). For the 1 of 8 that are commercially developed, it is somewhat unlikely that a healthy volunteer would subsequently develop a need for the same pharmaceutical. In contrast, experimental studies for environmental contaminants have the potential for improving the risk estimates for chemicals for which the volunteers and the rest of the general public may more likely be exposed. Such improvement may have an indirect public health benefit. For example, the use of herbicides and pesticides may indirectly benefit health if the agents reduce organisms that are disease vectors, or increase accessibility to foods needed for a healthy diet.

For evaluation in this paper all RfDs and RfCs based on human data were selected from EPA's IRIS (EPA, 2000b). The human data that formed the basis of these RfDs and RfCs were of all types, for example: case reports of argyria from exposure to silver, epidemiological studies of populations exposed to natural arsenic or to methyl mercury from environmental contamination, a surveillance epidemiology study for methemoglobinemia from nitrate exposure, population studies of fluorosis, and experimental studies of aldicarb, barium, warfarin, and zinc.

Purpose of This Research

The purpose of this research is to compare established RfDs and RfCs based on human data with those we estimate based on experimental animal data, and to show the use of human toxicokinetic and toxicodynamic information for estimating noncancer and cancer risk. We also briefly discuss the use and interpretation of human data, in conjunction with data gathered from experimental animals, as a public health protective policy.

METHODS

Methods Used for Comparison of RfDs and RfCs

We chose to use the complete listing of noncancer risk values, that is RfDs and RfCs, based on human data as found in EPA's IRIS database (EPA, 2000b). RfDs and RfCs found in IRIS have gone through an extensive and rigorous development process, including internal peer review and unanimous acceptance within EPA. IRIS is not the only source of such information, of course (see for example www.tera.org/iter), but we used IRIS because it is convenient, reasonably robust, objective and respected (although many of the risk values are outdated). We compared these human-based RfDs and RfCs with RfDs and RfCs we estimate from readily available experimental animal data, mainly from IRIS, based on EPA dose–response assessment methods (Barnes and Dourson, 1988; Dourson, 1994; Jarabek, 1994, 1995; EPA, 1994). We chose not to do a similar comparison

for cancer risk values because of the added complexity of developing risk values from experimental animal data, although such work may be pursued in the future.

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 Tables 1 and 2, which present confidence statements for risk values on IRIS), and on the relevance of the results in animals to the critical effect shown in humans. In descending order of importance, we selected experimental animal data 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, we then selected:

- A BMD, NOAEL or LOAEL of a closely related effect found in animals and compared it to the critical effect in humans (e.g., comparison of any clinical signs of cholinesterase inhibition); or
- The most sensitive effect found in animals and compared it to the critical effect in humans (e.g., comparison of cholinesterase inhibition with liver toxicity).

We recognized that pharmacokinetics and pharmacodynamics (discussed later) may impact such 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 we 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 EPA's IRIS, and not from a thorough review of the original literature. In some cases, EPA's IRIS states an alternative RfD or RfC based on animal studies, and we used these alternative values instead of estimating them. Occasionally, we compared animal versus human risk values of ATSDR, EPA, and Health Canada as described on Toxicology Excellence for Risk Assessment's (*TERA*) International Toxicity Estimates for Risk (*ITER*) database (see *TERA*, 2000). Please note that the animal-based RfDs and RfCs that we derived have not undergone a rigorous peer review. Thus, the animal-based RfDs and RfCs that we provide should only be considered as interim, subject to change with additional data and/or analysis.

In all cases, we developed the experimental animal-based RfDs and RfCs assuming no relevant human data were available. Therefore, we used the default uncertainty factor of 10-fold (for RfDs) or 3-fold (for RfCs) for experimental animal to human extrapolation. Recent data and analysis by the EPA 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; see also discussion below).

In the development of the animal-based RfDs and RfCs, we used the same database uncertainty factor and modifying factor as found in EPA's IRIS with one exception (the footnote for nitrite in Table 1 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 (EPA, 1999), which is the basis of both animal- and human-based RfDs and RfCs.

Methods for Pharmacokinetic Modeling

Making adjustments to animal results. Chemical risk assessments for cancer and noncancer end points are moving toward a common, harmonized methodology (Barton *et al.*, 1998). The basic steps in the approach are the establishment of a point of departure that may be a NOAEL, a LOAEL, or a BMD estimated from experimental data as described above. In the inhalation reference concentration methodology (EPA, 1994), the point of departure value is adjusted for differences in exposure duration to account for the fact that animals are exposed for less than 24 h per day while the exposure of interest for humans is continuous lifetime exposures. This duration-adjusted value is then corrected to take into account dosimetry differences expected between animals and human in order to provide a human equivalent concentration (HEC). These steps affect the numerator in the RfC equation. Several uncertainty factors are then applied to account for interspecies differences between test animals and humans and interindividual differences among humans. The HEC is divided by these uncertainty factors. Human pharmacokinetic and dosimetry data play potentially important roles in estimating the HEC and in assessing the magnitude of the uncertainty factors.

Mode of action and target tissue dose. The mode of action for a chemical entails the set of steps that are involved in causing toxicity following exposure to that particular chemical. Target tissue dose is the form of the chemical, i.e., parent compound, metabolite, peak

TABLE 1
Summary of U.S. EPA's RfDs on IRIS as of May 2000 Based on Human Data[1]

Chemical name (as on EPA's IRIS)	Specie/Type of study	NOAEL, LOAEL or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfD	RfD confidence	RfD ratio: Human to animal
				Total	H	A	L	S	D	MF			
Aldicarb	Human experimental gavage	0.01	Clinical signs of blood or plasma cholinesterase inhibition	10	10	1	1	1	1	1	1×10^{-3}	Medium	Either 1 (clinical signs) or 3 (plasma ChE)
	Rat developmental gavage	0.125	Clinical signs of cholinesterase inhibition	100	10	10	1	1	1	1	1×10^{-3}	Medium	
	Dog 52-week feeding	0.028[4]	Plasma cholinesterase inhibition	100	10	10	1	1	1	1	3×10^{-4}	Medium	
Arsenic, inorganic	Human epidemiology drinking water	0.0008	Skin lesions and possible vascular complications	3	3	1	1	1	1	1	3×10^{-4}	Medium	0.1
	Rat 13-week feeding[5]	2.6 (L)	Bladder hypertrophy and hyperplasia	1000	10	10	3	3	1	1	3×10^{-3}	Low	
Barium	Human experimental, epidemiological drinking water	0.21	Increased blood pressure	3	3	1	1	1	1	1	7×10^{-2}	Medium	0.4
	Rat chronic drinking water	45	Increased kidney weight	300	10	10	1	1	3	1	2×10^{-1}	Medium	
Baygon	Human experimental single dose	0.36 (L)	Mild cholinergic symptoms, RBC cholinesterase inhibition	100	10	1	10	1	1	1	4×10^{-3}	Medium	0.8
	Dog 12-month feeding	5 (L)	Cholinesterase inhibition	1000	10	10	10	1	1	1	5×10^{-3}	Medium	
Benzoic acid	Human anecdotal dietary exposure	4.4	No adverse effects observed	1	1	1	1	1	1	1	4	Medium	100[6]
	Mouse chronic exposure	40 (L)	Decreased resistance to stress	1000	10	10	10	1	1	1	4×10^{-2}	Low	
Cadmium	Human chronic exposures from a variety of studies	0.005	Significant proteinuria	10	10	1	1	1	1	1	5×10^{-4}	High	N.A.
	N.A.[7]	N.A.	Insufficient information exists in the IRIS file to make any determination of an RfD								N.A.	N.A.	
Chlorpyrifos	Human experimental capsule	0.03	Plasma cholinesterase inhibition	10	10	1	1	1	1	1	3×10^{-3}	Medium	30
	Dog 2-year feeding	0.01	Dog plasma and RBC cholinesterase inhibition	100	10	10	1	1	1	1	1×10^{-4}	Medium	
4,6-Dinitro-*o*-cyclohexyl-phenol	Human anecdotal clinical therapy	2.0 (L)[8]	Cataract formation	1000	10	1	10	10	1	1	2×10^{-3}	Low	Either 0.03 (cataract) or 0.07 (growth depression & swelling)
	Rat 6-month feeding	64 averaged	Cataract formation[9]	1000	10	10	1	10	1	1	6×10^{-2}	Low	
	Rat 6-month feeding	32 averaged	Growth rate depression, cloudy swelling of liver cells	1000	10	10	1	10	1	1	3×10^{-2}	Low	

2,4-Dinitrophenol	Human anecdotal clinical therapy	2.0 (L)	Cataract formation	1000	10	1	10	10	1	1	2×10^{-3}	Low	Either 0.02 (cataract) or 0.4 (growth depression & swelling)
	Rat 6-month feeding	130 averaged	Cataract formation	1000	10	10	1	10	1	1	1×10^{-1}	Low	
	Rat 6-month feeding	5	Growth rate depression, cloudy swelling of liver cells	1000	10	10	1	10	1	1	5×10^{-3}[10]	Low	
Ethephon	Human experimental oral exposure	0.5 (L)	Plasma cholinesterase inhibition	100	10	1	10	1	1	1	5×10^{-3}	Low	6
	Dog 2-year feeding	0.75 (L)	Plasma cholinesterase inhibition	1000	10	10	10	1	1	1	8×10^{-4}	Low	
Ethion	Human experimental short term	0.05[11]	Plasma cholinesterase inhibition	100	10	1	10	1	1	1	5×10^{-4}	Medium	8
	Dog 90-day oral exposure	0.06 (L)	Plasma cholinesterase inhibition	1000	10	10	10	1	1	1	6×10^{-5}	Medium	
Fluorine (soluble fluoride)	Human epidemiology	0.06	Objectionable dental fluorosis	1	1	1	1	1	1	1	6×10^{-2}	High	N.A.
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD								N.A.	N.A.	
Malathion	Human experimental feeding	0.23	Erythrocyte cholinesterase inhibition	10	10	1	1	1	1	1	2×10^{-2}	Medium	0.4
	Rat 2-year feeding	5	Decreased brain cholinesterase and decreased body weight	100	10	10	1	1	1	1	5×10^{-2}	Medium	
Manganese	Human data of several types	0.14	No LOAEL given, CNS effects appear to occur at higher doses	1	1	1	1	1	1	1	1.4×10^{-3}	Medium	N.A.
	N.A.	N.A.	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								N.A.	N.A.	
Methyl mercury	Human epidemiological poisoning	0.0011 (B)	Infant developmental neurological abnormalities	10	3	1	1	1	3	1	1×10^{-4}	Medium	5
	Rat developmental gavage and 26-month feeding study	0.005	Decrease in operant behavior performance, reduced body weight gains, minimal clinical signs of neurotoxicity, kidney damage	300	10	10	1	1	3	1	2×10^{-5}	Medium	
Molybdenum	Human epidemiological dietary	0.14 (L)	Increased uric acid	30	3	1	10	1	1	1	5×10^{-3}	Medium	2
	Rat 13-week feeding	2.5 (L)	Retarded weight gain	1000	10	10	3	3	1	1	3×10^{-3}	Low	
Nitrate	Human epidemiology surveys	1.6	Early clinical signs of methemoglobinemia <10%	1	1	1	1	1	1	1	1.6	High	8
	Rat 24-month drinking water	20[12]	Dilated bronchi, fibrosis, and emphysema	100	10	10	1	1	1	1	2×10^{-1}	Medium	

TABLE 1–*Continued*

Chemical name (as on EPA's IRIS)	Specie/Type of study	NOAEL, LOAEL or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfD	RfD confidence	RfD ratio: Human to animal
				Total	H	A	L	S	D	MF			
Nitrite	Human epidemiology surveys	1.0[13]	Early clinical signs of methemoglobinemial <10%	1	1	1	1	1	1	10	1×10^{-1}	High	5
	Rat 24-month drinking water	2	Dilated bronchi, fibrosis, and emphysema	100	10	10	1	1	1	1	2×10^{-2}	Medium	
Pirimiphos-methyl	Human 56-day experimental feeding	0.25	Transient plasma cholinesterase inhibition	25	10	1	2.5	1	1	1	1×10^{-2}	High	Either 2 (rat) or 20 (dog)
	Rat 2-year feeding	0.5	Plasma cholinesterase inhibition	100	10	10	1	1	1	1	5×10^{-3}	High	
	Dog 2-year feeding	0.5(L)	Brain cholinesterase inhibition	1000	10	10	10	1	1	1	5×10^{-4}	Medium	
Selenium and compounds	Human food and soil epidemiology	0.015	Clinical selenosis	3	3	1	1	1	1	1	5×10^{-3}	High	6
	Rat developmental toxicity	0.075	50% reduction in number of young reared	100	10	10	1	1	1	1	8×10^{-4}	High	
Silver	Human anecdotal studies	0.014	Argyria	3	3	1	1	1	1	1	5×10^{-3}	Low	0.2
	Rat 218-day drinking water exposure	89 (L)	Ventricular hypertrophy	3000	10	10	10	3	1	1	3×10^{-2}	Low	
1,1,2-Trichloro-1,2,2-trifluoro-ethane	Human occupational exposure	273	Psychomotor impaiment	10	10	1	1	1	1	1	3×10^{1}	Low	N.A.
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD								N.A.	N.A.	
Warfarin	Human experimental	0.029	Increased prothrombin time	100	10	1	10	1	1	1	3×10^{-4}	Low	N.A.
	Inappropriate	N.A.	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"								N.A.	N.A.	

Zinc and compounds	Human experimental diet supplement	59.7 (L)	Decrease in erythrocyte superoxide dismutase concentration in adults	3	1	1	3	1	1	1	3×10^{-1}	Medium	N.A.
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD								N.A.	N.A.	

[1] All data from which we estimate animal-based RfDs are taken from EPA's IRIS unless otherwise stated. Judgments of confidence levels for animal-based risk values were based on M. Dourson's experience with the RfD/RfC Work Group of EPA.

[2] All values are in mg/kg-day and are NOAELs unless otherwise stated: (L), LOAEL; (B), benchmark dose (BMD).

[3] Uncertainty factors are H, average human to sensitive human; A, animal to human; L, LOAEL to NOAEL: S, subchronic exposure to chronic; D, database insufficiency; MF, modifying factor to account for uncertainities not covered by the traditional factors. Note that for this exercise, the D and MF factors were considered to be the same between the animal-based RfD and the human-based RfD, since they originated from the same database with one exception (nitrite) since information on IRIS allowed a difference. These factors may or may not be the same upon reevaluation of newer toxicity data not on IRIS.

[4] Both the dog and human studies showed plasma cholinesterase inhibition at the lowest dose. For this comparison, both low doses were consider as NOAELs; if they are considered as LOAELs, the RfDs might be lower for both, but the ratio between these RfDs would be the same.

[5] Data derived from Okoji *et al.* (1999).

[6] IRIS states "that laboratory animals are inappropriate models for studying the toxicity of benzoic acid in humans . . . ," but then go on to give an RfD of 4×10^{-2} with a further comment that it "is not appropriate to use the animal data for the RfD."

[7] N.A., not applicable.

[8] Based on analogy to 2,4-dinitrophenol.

[9] IRIS states that "the subchronic dietary rat study...is not useful for the RfD derivation because experimental animals are not adequate models for the induction of cataracts in humans by low-level oral exposure to dinitrophenols, and, therefore, an RfD based on the rat data may not be adequately protective for humans." This comment is not found on the 2,4-dinitrophenol IRIS file, but applies to it as well.

[10] Value given on IRIS. Please note the comment above on 4,6-dinitro-*o*-cyclohexyl phenol.

[11] EPA's IRIS lists this value as a NOEL, but also adds an uncertainty factor for LOAEL to NOAEL extrapolation because of the proximity of this NOEL to brain cholinesterase inhibition in dogs at 0.71 mg/kg-day.

[12] Based on the toxicity of nitrite with a 10-fold increase in the NOAEL.

[13] Based on the toxicity of nitrate with an adjustment to this dose with a 10-fold MF.

concentrations, net exposures as area under the concentration curves, that is believed to be most closely associated with the toxic effects. Any narrative describing the mode of action of a compound should also convey the form of the chemical believed to be responsible for initiating the cascade of steps leading to the toxic responses. Similarly, extrapolation between species should be conducted using a dose metric that reflects this understanding of the mode of action of the compound.

For example, a mode of action statement for vinyl chloride would be: tumors associated with vinyl chloride are caused by mutational effects arising from the reaction of epoxide metabolites with DNA resulting in increases in the mutational frequency in specific cells. The dose metric for this mode of action would be a measure of the net tissue exposure of the epoxide metabolites (EPA, 2000b). For chloroform, the mode of action statement would read: tumors in the liver and kidney induced by chloroform arise due to mutations during recurrent episodes of cytotoxicity and cell proliferation associated with metabolism of chloroform to phosgene in cells with high CYP 2E1 activity. Here the dose metric would be related to peak rates of metabolism of chloroform in liver and in kidney cortex (ILSI, 1997).

Pharmacokinetic and dosimetry data in risk assessment. Several advances in dose–response assessment have occurred over the past 20 years due to increased emphasis on understanding modes of action and on determining the major biological determinants that contribute to pharmacokinetic behavior in animals and humans. Before 1980, it was common to simply collect pharmacokinetic data and analyze it empirically with mathematical models to evaluate the correspondence of the data with specific compartmental models. Sometimes the data were not analyzed at all. A difficulty with these compartmental approaches was in extrapolation of the results to important untested situations. Even when impressive fits to animal data were obtained, how confident could we be that the compounds would have similar kinetic behavior in humans? If human data were actually obtained from volunteers, how confident could we be that the data obtained from a small group of healthy individuals were representative of pharmacokinetic behaviors expected in a larger human population? These two questions led to increased emphasis on development of physiologically based pharmacokinetic (PBPK) models in which the organism is described realistically in terms of anatomy, physiology, biochemical parameters of distribution, and the physical-chemical characteristics of the test compound (Gerlowski and Jain, 1983). These particular models are more amenable to extrapolation from test animals to humans and are also amenable to establishing the importance of variability within the human population by Monte Carlo methods.

RESULTS

Comparison of Human- and Experimental Animal-Based RfDs and RfCs

Table 1 shows a comparison of all RfDs based on human data as found on IRIS (EPA, 2000b) or for several chemicals on *ITER* (*TERA*, 2000), and those we estimate from experimental animal data found on IRIS using the criteria defined above. For 36% (8 of 22 comparisons), the human- and animal-based RfDs are comparable, that is within the limits of their corresponding precision.[3] For 23% (5 of 22 comparisons), the RfDs based on human data are lower than the corresponding RfDs based on animal data. For 41% (9 of 22 comparisons), RfDs based on animal data are lower than those based on human data. An animal-based RfD could not be estimated in 6 of 28 possible comparisons, since animal information was judged to be either insufficient or irrelevant.

Table 2 shows a comparison of all RfCs based on human data as found on IRIS (EPA, 2000b) or for several chemicals on *ITER* (*TERA*, 2000), and those we estimate from experimental animal data found on IRIS using criteria defined above. For 45% (5 of 11 comparisons), the RfCs are comparable, that is within the limits of their corresponding precision.[3] In no cases were the RfCs based on human data lower than the corresponding RfCs based on animal data within the limits of precision being assumed. For 55% (6 of 11 comparisons), RfCs based on animal data are lower than those based on human data. An animal-based RfC could not be estimated for 4 of 15 times, since animal information was judged to be either insufficient or irrelevant.

Figure 1 shows a frequency plot of human- to experimental animal-based RfD or RfC ratios from Tables 1 and 2.

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 of 22 (or 41%). For RfCs this frequency is 3 of 11 (or 27%). Collectively, this frequency is 12 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.

[3] These frequency values are based on ratios that fall within a 10-fold range of each other, for example 0.3 mg/kg-day $\leq$ RfD $\leq$ 0.3 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 EPA risk values (see Felter and Dourson, 1998, for more discussion of this), and therefore the range we use here is only for demonstration. Other equally valid ranges may be determined.

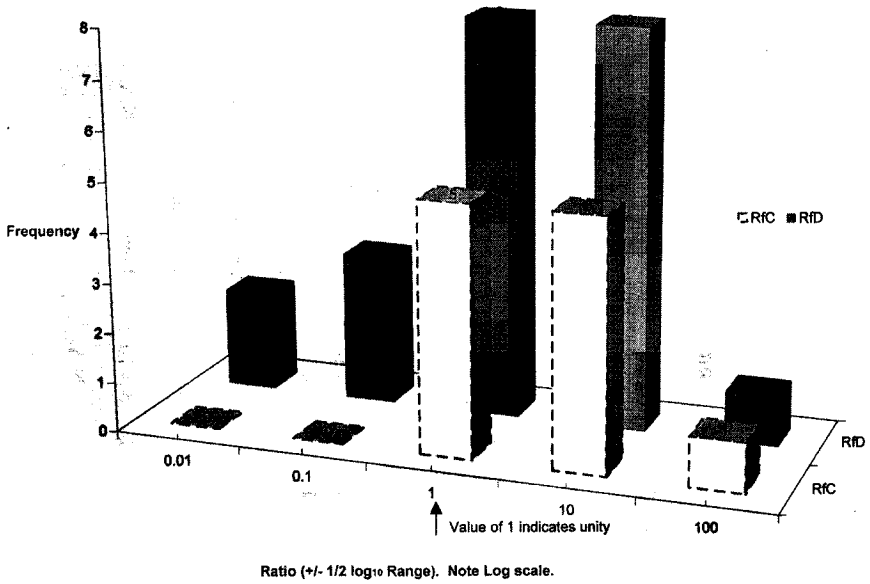

FIG. 1. Frequency of human- to animal-based RfD and RfC ratio from Tables 1 and 2. Ranges defined by logarithmic midpoints (e.g., $0.3 < 1 \leq 3$). Value of 1 indicates that animal-based and human-based risk values are the same.

Table 3 shows human to animal RfD ratios from Table 1, where experimental or anecdotal clinical human data formed the basis of EPA's assessment. The purpose of this subset analysis is to determine whether different kinds of human data allow the development of different conclusions. Eight of 15 comparisons (53%) of human to animal RfDs are less than 1. If anecdotal clinical data are excluded from these comparisons, then 3 of 10 comparisons (30%) of experimental human-based to animal-based RfDs are less than 1. Unfortunately too few comparisons exist in order to make any definitive conclusions on the relative proportions of these ratios amongst the different types of human data as described in the introduction. However, these percentages of ratios less than 1 found in Table 3 are not dissimilar from the percentage of ratios with the overall RfD database of 41% (found in Tables 1 and 2).

It is of interest to study the reasons why certain risk values could not be based on animal data. This occurred with a frequency of 6 of 28 (or 21%) for RfDs and 4 of 15 (or 27%) for RfCs. Table 4 shows the stated reasons derived from Tables 1 and 2. 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 (EPA, 2000b). For 60%, the animal data was not sufficiently described on EPA's IRIS to develop a risk value.

Comparison of Human and Experimental Animal Pharmacokinetics

Human data for risk assessment purposes include *in vitro* determinations of biochemical constants for metabolism and tissue partition coefficients, limited pharmacokinetic studies in specific human populations, and mechanistic studies using human tissues or human cells *in vitro*. The emphasis in this section is on the use of kinetic data and *in vitro* methods for assessing biological determinants of kinetics in human tissues. A Contemporary Concepts in Toxicology Workshop under the auspices of the Society of Toxicology (SOT) Task Force to Improve the Scientific Basis of Risk Assessment was held in September 1999. The report of the workshop outlining the uses of human tissues in risk assessment is in press (MacGregor *et al.*, 2000). This paper provides a larger perspective on use of human tissues for mechanistic studies.

We describe a series of examples to illustrate the use of human pharmacokinetic data in risk assessment.

Dichloromethane

Human equivalent concentrations. Occupational toxicology has historically featured the use of human volunteers for assessing the pharmacokinetics of industrial chemicals. Long before human testing was undertaken, the occupational importance and history of the compound's usage in industrial environments was established. In general, exposure standards had been established and the human exposures were conducted at exposure levels at or below existing Threshold Limit Values or equivalent occupational standards. Work with human volunteers in the 1970's established the conversion of dichloromethane (DCM; methylene chloride) to carbon monoxide and the production of relatively high levels of carboxyhemoglobin (HbCO)—from 5 to 20%—following high level exposures to this solvent. The analytical methods for measuring most

TABLE 2
Summary of U.S. EPA's RfCs on IRIS as of May 2000[1]

Chemical name (as on EPA's IRIS)	Specie/Type of study	Human Equivalent NOAEL, LOAEL, or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfC	RfC confidence	RfC ratio: Human to animal
				Total	H	A	L	S	D	MF			
Ammonia	Human occupational	2.3	Lack of evidence of decreased pulmonary function or changes in subjective symptomatology	30	10	1	1	1	3	1	1×10^{-1}	Medium	20
	Rat subchronic inhalation	1.9 (L)	Increased severity of rhinitis and pneumonia with respiratory lesions	300	10	3	3	1[4]	3	1	6×10^{-3}	Medium	
Beryllium	Human occupational and community exposure	0.0002 (L)	Beryllium sensitization and progression to chronic beryllium disease (CBD)	10	1	1	3	3	1	1	2×10^{-5}	Medium	N.A.
	N.A.[5]	N.A.	No laboratory animal model fully mimics all features of human CBD								N.A.	N.A.	
Bromomethane	Human occupational	2.2 (L)[6]	Neurological effects	100	10	1	10	1	1	1	2×10^{-2}	N.A.	4
	Rat 29-month inhalation	0.48 (L)	Degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity	100	10	3	3	1	1	1	5×10^{-3}	High	
Carbon disulfide	Human occupational	19.7 (B)	Peripheral nervous system dysfunction	30	3	1	1	3	3	1	7×10^{-1}	Medium	8
	Rat 90-day inhalation	27	Peripheral nervous system dysfunction	300	3	3	1	10	3	1	9×10^{-2}	Medium	
Chromium (acid mists and aerosols)	Human subchronic occupational	0.000714 (L)	Nasal septum atrophy	90	10	1	3	3	1	1	8×10^{-6}	Low	N.A.
	N.A.	N.A.	Experimental animal studies have not reported on nasal mucosal effects following inhalation exposures								N.A.	N.A.	
N,N-Dimethylformamide	Human occupational	7.9 (L)	Digestive disturbance and minimal hepatic changes suggest liver effects	300	10	1	3	3	3	1	3×10^{-2}	Medium	4
	Rat 4-week inhalation	25 (L)	Hepatic cell changes	3000	10	3	10^{7}	3	3	1	8×10^{-3}	Medium	
n-Hexane	Human inhalation epidemiology	73 (L)	Neurotoxicity; electrophysiological alterations	300	10	1	10	1	3	1	2×10^{-1}	Medium	0.5
	Mouse 90-day inhalation	38	Epithelial lesions in the nasal cavity	100	10	3	1	1	3	1	4×10^{-1}	Medium	

Hydrogen cyanide	Human occupational	2.5 (L)	CNS symptoms and thyroid effects	1000	10	1	10	3	3	1	3×10^{-3}	Low	N.A.	
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfC								N.A.	N.A.		
Manganese	Human occupation exposure	0.05	Impairment of neurobehavioral function		1000	10	1	10	3	3	1	5×10^{-5}	Medium	N.A.
	N.A.	N.A.	IRIS states that animal toxicity data qualitatively support the human studies used as a basis of the RfC; quantified comparisons were not provided									N.A.	N.A.	
Mercury, elemental	Human occupational	0.009 (L)	Hand tremor; increases in memory disturbances; slight subjective and objective evidence of autonomic dysfunction		30	3	1	3	1	3	1	3×10^{-4}	Medium	0.4
	Rat 72-week inhalation	0.07	No histopathological evidence of respiratory damage; higher doses caused developmental toxicity in a different study		100	10	3	1	1	3	1	7×10^{-4}	Low	
Styrene	Human occupational	34	CNS effects		30	3	1	1	3	3	1	1	Medium	50
	Mouse subchronic inhalation	74 (L)	Bronchiolar regeneration, olfactory metaplasia and degeneration, increased lung weight, increased epithelial hyperplasia of the forestomach		3000	10	3	10	3	3	1	2×10^{-2}	Medium	
Tetrachloroethylene	Human occupational	24 (L)[9]	Increased reaction times to simple neurological tests		100	10	1	10	1	1	N.A.	2×10^{-1} [8]	N.A.	0.6
	Mouse 103-week inhalation	363 (L)[11]	Reduced survival (in males), hepatotoxicity (males), lung congestion and nephrotoxicity (males and females)		1000	10	10	10	1	1	N.A.	3.6×10^{-1} [9]	N.A.	
Toluene	Human occupational	119 (L)	Neurological effects		300	10	1	10	1	3	1	4×10^{-1}	Medium	5
	Rat 2-year inhalation	79 (L)	Degeneration of nasal epithelium		1000	10	3	10	1	3	1	8×10^{-2}	Medium	
Toluene diisocyanate mixture (TDI)	Human occupational	0.002	Chronic lung function decline		30	10	1	1	3	1	1	7×10^{-5}	Medium	2
	Rat chronic inhalation	0.01 (L)	Necrotic rhinitis with epithelial atrophy, metaplasia, and inflammation		300	10	3	10	1	1	1	3×10^{-5}	Medium	

TABLE 2—*Continued*

Chemical name (as on EPA's IRIS)	Specie/Type of study	Human Equivalent NOAEL, LOAEL, or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfC	RfC confidence	RfC ratio: Human to animal
				Total	H	A	L	S	D	MF			
Xylenes	Human occupational	60.76 (L)[9]	Subjective symptoms	100	10	1	10	1	1	N.A.	6×10^{-1} [10]	N.A.	3
	Rat inhalation developmental toxicity	177 (L)[11]	Fetal toxicity	1000	10	10	10	1	1	N.A.	1.8×10^{-1}	N.A.	

[1] All data from which we estimate animal-based RfCs are taken from EPA's IRIS unless otherwise stated. Judgments of confidence levels for animal-based risk values were based on M. Dourson's experience with the RfD/RfC Work Group of EPA.

[2] All values are human equivalent concentration in mg/m^3 and are NOAELs unless otherwise stated: (L), LOAEL; (B), benchmark concentration (BMC).

[3] Uncertainty factors are H, average human to sensitive human; A, animal to human; L, LOAEL to NOAEL; S, subchronic exposure to chronic; D, database insufficiency; MF, modifying factor to account for uncertainties not covered by the traditional factors. Note that for this exercise, the D and MF factors were considered to be the same between the animal-based RfD and the human-based RfD, since they originated from the same database. These factors may not be the same upon reevaluation of newer toxicity data not on IRIS.

[4] The value of this subchronic to chronic uncertainty factor is 1; it is subsumed in the description of the uncertainty factor for database deficiencies as per IRIS.

[5] N.A., not applicable.

[6] Value is from ATSDR and the resulting risk value is a minimal risk level (MRL). Some differences exist among methods to estimate these risk values among EPA and ATSDR. Please see www.tera.org/iter/methods. Specific values of ATSDR and EPA can be found at www.tera.org/iter under "bromomethane."

[7] An evaluation of the original study within the overall database may allow a reduction in this factor to a value of 3.

[8] Specific values of ATSDR and Health Canada can be found at www.tera.org/iter under "tetrachloroethylene."

[9] Value is from ATSDR and the resulting risk value is a minimal risk level (MRL). Some differences exist among methods to estimate these risk values among EPA, ATSDR, and Health Canada. Please see www.tera.org/iter/methods.

[10] Specific values of ATSDR and Health Canada can be found at www.tera.org/iter under "xylenes."

[11] Value is from Health Canada and the resulting risk value is a tolerable concentration (TC). Some differences exist among methods to estimate these risk values among EPA and ATSDR. Please see www.tera.org/iter/methods.

TABLE 3
Summary RfDs from Table 1 Based on Experimental or Clinical Human Data

Chemical name (as on EPA's IRIS)	Specie/Type of study	Critical effect(s)	RfD	ratio: Human to animal
Aldicarb	Human experimental gavage	Clinical signs of cholinesterase inhibition, plasma cholinesterase inhibition	1×10^{-3}	Either 1 (clinical signs) or 3 (plasma ChE)
	Rat developmental gavage	Clinical signs of cholinesterase inhibition	1×10^{-3}	
	Dog 52-week feeding	Plasma cholinesterase inhibition	3×10^{-4}	
Barium	Human experimental, epidemiological drinking water	Increased blood pressure	7×10^{-2}	0.4
	Rat chronic drinking water	Increased kidney weight	2×10^{-1}	
Baygon	Human experimental single dose	Mild cholinergic symptoms, RBC cholinesterase inhibition	4×10^{-3}	0.8
	Dog 12-month feeding	Cholinesterase inhibition	5×10^{-3}	
Chlorpyrifos	Human experimental capsule	Plasma cholinesterase inhibition	3×10^{-3}	30
	Dog 2-year feeding	Plasma and RBC cholinesterase inhibition	1×10^{-4}	
4,6-Dinitro-*o*-cyclohexyl phenol	Human anecdotal clinical therapy	Cataract formation	2×10^{-3}	Either 0.03 (cataract) or 0.07 (growth) depression and swelling)
	Rat 6-month feeding	Cataract formation	6×10^{-2}	
	Rat 6-month feeding	Growth rate depression, cloudy swelling of liver cells	3×10^{-2}	
2,4-Dinitrophenol	Human anecdotal clinical therapy	Cataract formation	2×10^{-3}	Either 0.02 (cataract) or 0.4 (growth depression and swelling)
	Rat 6-month feeding	Cataract formation	1×10^{-1}	
	Rat 6-month feeding	Growth rate depression, cloudy swelling of liver cells	5×10^{-3}	
Ethephon	Human experimental oral exposure	Plasma cholinesterase inhibition	5×10^{-3}	6
	Dog 2-year feeding	Plasma cholinesterase inhibition	8×10^{-4}	
Ethion	Human experimental short term	Plasma cholinesterase inhibition	5×10^{-4}	8
	Dog 90-day oral exposure	Plasma cholinesterase inhibition	6×10^{-5}	
Malathion	Human experimental feeding	Erythrocyte cholinesterase depression	2×10^{-2}	0.4
	Rat 2-year feeding	Decreased brain cholinesterase and decreased body weight	5×10^{-2}	
Pirimiphos-methyl	Human 56-day experimental feeding	Transient plasma cholinesterase inhibition	1×10^{-2}	Either 2 (rat) or 20 (dog)
	Rat 2-year feeding	Plasma cholinesterase inhibition	5×10^{-3}	
	Dog 2-year feeding	Brain cholinesterase inhibition	5×10^{-4}	
Silver	Human anecdotal studies	Argyria	5×10^{-3}	0.2
	Rat 218-day drinking water exposure	Ventricular hypertrophy	3×10^{-2}	
Warfarin	Human experimental	Increased prothrombin time	3×10^{-4}	
	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"	N.A.	N.A.
Zinc and compounds	Human experimental diet supplement N.A.	Decrease in erythrocyte superoxide dismutase concentration in adults	3×10^{-1}	N.A.
		Insufficient information exists in the IRIS file to make any determination of RfD	N.A.	

compounds in blood and excreta were new and many had only moderate sensitivity. The work with DCM established the exposure concentrations associated with specific increases in HbCO and led to strategies for controlling DCM that insured no more than a 5% increase in blood HbCO. This early work with DCM, while quantitative, provided simple mathematical relationships to correlate specific exposures with increased HbCO; they did not really allow prediction of these values from knowledge of human metabolism, physiology, and activity levels.

In the 1980s, DCM was found to be carcinogenic in mice, shifting the end point from HbCO to the possibility that DCM might cause cancer in exposed individuals. A risk assessment for DCM was proposed, based on a PBPK model, that estimated the tissue exposures in lung and liver to metabolites of DCM (Andersen *et al.*, 1987). A variety of data indicated that the carcinogenicity in mice was most likely associated with metabolites formed by conjugation of DCM with glutathione, catalyzed by glutathione *S*-transferase (GST). This metabolic clearance pathway competes with a higher affinity, though lower capacity oxidation of DCM by cytochrome P450. The isozyme involved is now recognized to be CYP2E1. The dose metric used for analysis in the region of observation was the integrated production of the glutathione conjugate per volume tissue per day. This same dose metric was estimated for humans by using a PBPK model that included physiological parameters for humans and kinetic constants for the glutathione-S-transferase enzyme in lung and liver for both the mouse and the human. Using model substrates, activities for the human liver and lung enzymes were estimated in studies using microsomes obtained from accident victim's tissues. Later work established the activities of these enzymes toward DCM itself (Reitz *et al.*, 1989).

Controlled pharmacokinetic studies had been conducted in human volunteers using several different concentrations of DCM (Andersen *et al.*, 1991). These studies were evaluated with a PBPK model to assess the consistency of predictions based on scaling the rodent PBPK model to predict actual human data. The earlier risk assessment had simply used a model with human parameters to make predictions of the dose metrics. With moderate refinements to the portion of the model describing carbon monoxide distribution after its formation by DCM oxidation, the model predicted the blood and exhaled air time-course for DCM. For CO, the model adequately predicted blood HbCO and exhaled CO. The ability to match concentrations of DCM, HbCO, and CO in humans provides confidence that the scale-up from rats to humans is feasible. These results collectively and individually provide evidence for the correction in the numerator of the RfC, for example, that which is required for developing a human equivalent concentration. The dose metric used is the amount of HbCO formed for an occupational concern for carboxyhemoglobin or the amount metabolized in lung or liver by the glutathione-S- transferase reactions. This latter dose metric is estimated from an accurate prediction of the blood concentrations of DCM and the enzyme activities in the target tissues. These PBPK models allow estimation of the human exposure concentrations that are required to provide a tissue dose similar to that associated with the point of departure concentration in the test animal.

Human variability. The denominator of the RfC and RfD includes uncertainty factors for interspecies and intraindividual differences. The RfC methodology (EPA, 1994) indicates that the interspecies factor can be reduced when compound specific kinetic data are used to derive the human equivalent concentration. A second application of these kinetic models is to estimate the impact of variability in physiology, metabolism, etc. in pharmacokinetic variability within the human population. For this application, ranges of model parameters, such as breathing and blood flow rates, body composition, and metabolic parameters, are introduced into the model specification. The PBPK model is run multiple times during which the parameters are selected from these distributions by a sampling algorithm. The resultant output is a distribution for target tissue dose expected for a diverse population at the specified exposure concentration. By assessing the variability in this distribution of tissue doses, it becomes possible to decide if the factor of 10 for intraindividual differences is adequate or if it needs to be adjusted. Examples of use of Monte Carlo sampling of parameter distributions to assess tissue dose with DCM have focussed on standard setting for the workplace (Thomas *et al.*, 1998) and for environmental exposures (Clewell, 1996).

The work with DCM provides a template for applications of human data in risk assessment based on toxicity results in animals. Mechanistic studies usually set the foundation for assessing the dose metric that is important to estimate as a measure of tissue dose. The PBPK model indicates the important parameters that determine the dose of active forms of the compound at target tissues. Studies with human tissues, coupled with knowledge of human physiology/anatomy, provide a method to estimate human tissue doses of active compounds and a method to derive the HEC. Focused, limited, human-volunteer studies, develop *in vivo* data that allows refinement and validation of the predictions of the human PBPK model. The completed PBPK description lends itself to a refined, quantitative analysis of variability in pharmacokinetic behavior in the human population. This paradigm for use of human studies would be applicable to RfC, RfD or cancer assessments for various end points. In contrast

to the state-of-the-art in analytical chemistry in the 1970s, many of the pharmacokinetic studies in humans can now be conducted at much lower, almost tracer (or trace) levels of contaminants mitigating concerns about possible adverse effects of compounds in the human volunteers.

Vinyl Chloride

Pharmacokinetic (PK) modeling plays an increasingly accepted role in many of the efforts in the new IRIS Pilot project activities to integrate the risk assessment process for specific compounds. Vinyl chloride (VC) documentation has been completed within the last year (EPA, 2000b). The critical end points with VC are liver toxicity and liver cancer—hemangiosarcoma. VC is an animal and human carcinogen with strong site-concordance between species. Mechanistic work has firmly established a central role for an epoxide, metabolite in causing DNA adducts, mutations, and tumors. Pharmacokinetic and disposition studies have been conducted in multiple species of laboratory animals and limited pharmacokinetic uptake studies were conducted with human volunteers at low concentrations. The IRIS document with VC includes a PBPK model to assess the consistency in dosimetry between animals and humans, and provides methods for extrapolating across dose routes and between species. The human data provides a test of model predictions and reassurance that the standards set based on these model estimates of dose are likely to be sound.

Inhaled Acids and Esters

A wide variety of organic acids and esters have recently been associated with degeneration and toxicity in the nasal olfactory epithelium in rats and mice. It was unclear whether these compounds would have similar effects in humans. Within the past two to three years, PBPK models have been completed and published for several of these compounds—vinyl acetate (Plowchalk *et al.*, 1997), acrylic acid (Frederick *et al.*, 1998), and methyl methacrylate (Andersen *et al.*, 1999). Dosimetry model development with these compounds has included evaluation of uptake from the rodent airstream, parameterization of nasal models for airflow and tissue uptake, and measurement of metabolizing enzymes in epithelial tissues throughout the nose. These dosimetry models predict differences between humans and rodents and support estimation of HECs for these compounds. A workshop was held in Research Triangle Park, North Carolina, in February 1998. Participants discussed the utility of these dosimetry models for nasal dosimetry and risk assessment and continuing data needs. A major continuing data need enumerated was for human studies of scrubbing of compounds from the nasal airstream using specific breathing patterns and sampling strategies (Andersen and Jarabek, 2000). The validation of existing models by selective, carefully designed human studies was recognized as an important research priority.

Boric Acid

The most sensitive end point with boric acid in laboratory animals is developmental toxicity in the offspring of Sprague–Dawley rats (Dourson *et al.*, 1998). This inorganic acid has fairly straightforward pharmacokinetic behavior. It is not metabolized to any appreciable extent; it is primarily excreted into the urine via the kidneys; and it does not accumulate anywhere in the body. The main issue in assessing the uncertainty factors for this compound is estimation of the net tissue exposure to fetuses in rats and any differences in exposure for equivalent doses in humans. General arguments can be offered regarding the expected kinetic behavior. For instance, the volume of distribution should follow body weight (or at least lean body weight) and renal clearance should follow body weight raised to the 2/3 power (see, for example, NRC, 1986). These are theoretical arguments for generic compounds. It would be best to estimate these differences by direct determination of boric acid clearance studies in pregnant and nonpregnant females.

These renal clearance studies have recently been conducted by the University of California, Irvine (Vaziri *et al.*, 2000). Murray and Andersen (2000) provide a preliminary outline of the results of these studies, including relative areas under the blood curve and the variability observed in renal boric acid clearance in both rats and women. These studies provide data to clearly obtain compound-specific adjustment factors to replace default or rule of thumb interspecies adjustments. The work focussed attention on the need to define a dose metric for interspecies adjustment. Two possibilities are peak maternal blood levels or net fetal exposure during the critical period, which should be proportional to net area under the boric acid blood curve in maternal plasma.

Criteria Pollutants

Chemicals with extensive history of controlled human experimentation are the criteria pollutants, including ozone, sulfur dioxide, nitrogen oxides, and carbon monoxide. These byproducts of commerce and of the internal combustion engines that fuel our technical society achieve airborne concentrations quite close to frank effect levels. Human studies of dosimetry, the amounts retained in the lungs, and pulmonary function in healthy and in compromised individuals have been important in setting acceptable ambient levels for these compounds that strike a balance between safety and continuing economic activity.

Organophosphates (OPs)

In adults, at least, the main risks posed from acute exposures to OPs are associated with inhibition of tissue cholinesterases and impaired cholinergic transmission. For the thiophosphorate compounds, toxicity is complexly related to activation to the active oxon, a process that has to compete with metabolism, including hydrolysis to inactive products. How do these various processes work together in target pest species or in inadvertent target species that may be exposed to these compounds?

PBPK models have been developed for organophosphate compounds in order to integrate knowledge of various pathways in both causing toxicity or in inactivating the compounds before they can exert their biological effects (Gearhart *et al.*, 1990). The possibility exists to collect *in vitro* data with human tissues, blood, etc., to assess kinetic constants for various pathways and develop a predictive model for production and distribution of the oxon. The time course of the oxon in blood and tissues would be directly related to inhibition of the target macromolecules. These predictive models should be validated by limited studies in human volunteers. With current analytical methods, these studies can be done at dosages where there are minimal changes in any of the esterase activities in the body. The main goal of such work is not simply to assess doses that cause some minimal change in blood or plasma cholinesterase. Instead, they fulfill multiple objectives by assessing the major biological determinants of the kinetics of parent compound and oxon. As with all human studies, doses of these materials have to be carefully selected and the dosing closely supervised by a physician. However, human data are critical for making sound judgements about the use of these compounds, insuring protection of all exposed individuals, and avoiding overreliance of default approaches for animal to human extrapolation for such a widely used group of compounds.

With this information, it is possible to examine expected differences among individuals associated with metabolic polymorphisms and to ascertain if the pharmacokinetics seen in other species are expected in humans. In addition, these mechanistic PBPK models can explore whether there may be specific populations—aged, youth, or compromised individuals—who may be at greater risk. This evaluation is conducted by providing distributions of critical parameters for metabolism, physiological parameters or tissue clearance and see if particular combinations of parameters give rise to predictions of unusually large tissue doses. The distributions entered into the models could include physiological and metabolic profiles for children or for the elderly. Often the limiting factor in applying these models with distributions of parameters to estimate tissue dose/responses is our limited knowledge of parameter values in the general population or in specific groups in the general population.

DISCUSSION

Do Human Data Produce More Accurate Estimates of Risk?

This paper focuses on the dose–response assessment differences between humans and experimental animals. At first examination, a significant number of RfDs or RfCs, that we calculate from experimental animal data and where we use a 10-fold uncertainty factor for experimental animal to human extrapolation, are higher than EPA's human based values. This observation leads us to question whether the 10-fold factor is sufficient to protect human health for those animal-based RfDs and RfCs for which we lack human data to corroborate the nature or dose–response pattern of the critical effect. The data in Tables 1 and 2 and shown in Fig. 1 can be used to address this question, in part. In doing so, however, we suggest a more rigorous evaluation of the animal-based RfDs and RfCs that we calculate. This is because our 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 (EPA, 2000b).

However, our analysis also show that a significant number of RfDs or RfCs, that we calculate from experimental animal data and where we use a 10-fold uncertainty factor for experimental animal to human extrapolation, are lower than the human based values. This observation leads us to question whether, for those animal-based RfDs and RfCs for which we lack human data to corroborate the nature or dose–response pattern of the critical effect, how many of these RfDs and RfCs err in a direction that overly protects human health? Unfortunately, because our 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, answers to such questions await additional analysis.

Although our 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 end point. For example, it is generally recognized that in developing RfDs or RfCs from animal data, the availability of adequate human data reduces or even obviates the need of uncertainty factors for extrapolating from animals to humans. This is based on the presumption that such adequate human data are more accurate predictors of human toxicity than animal data. In addition, EPA (2000b) notes several times when animal data are deemed inappropriate (e.g., warfarin, manganese, see Table 4), or the effect is different in at least some

TABLE 4
Description of Reasons Why an Animal-Based RfD or RfC Is Not Possible or Appropriate (Data from Tables 1 and 2)

Chemical name (as on EPA's IRIS)	Specie/Type of study	Critical effect(s)
Beryllium RfC	Human occupational and community exposure	Beryllium sensitization and progression to chronic beryllium disease (CBD)
	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 and 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 Inappropriate	Increased prothrombin time
		IRIS states "Because of marked differences in the susceptibility of different species to the effects of warfarin, it would be inappropriate toderive 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

important aspect (e.g., arsenic, barium, beryllium and silver, see Tables 1 and 2). It is for these reasons, in part, that EPA gives higher priority to human studies (Barnes and Dourson, 1988; Dourson, 1994; EPA, 1994; Jarabek, 1994, 1995). Other organizations have the same preference in developing their hazard identification and dose–response assessments (Meek *et al.*, 1994; IPCS, 1994).

A recent text by Olson *et al.* (2000) also focuses on the hazard identification comparisons of experimental animals and humans for a series of 150 pharmaceutical compounds. These authors conclude that concordance between human and experimental animal toxicity was highest in the hematological, gastrointestinal, and cardiovascular areas and poorest for cutaneous, endocrine, and hepatobiliary and liver function abnormalities. Overall for 30% of the human toxicities, there was no relationship with toxicities seen in animals. This work supports the idea that in a significant number of times, human data would be essential for hazard identification and presumably for dose–response assessment.

Every cancer that has been first associated with a chemical in human studies, for which numerous examples exist (e.g., benzene, asbestos, chromium), supports the idea that human data result in a lower "safe" dose when compared to animal data. Animal bioassays may now be able to better predict carcinogenicity in humans than in the days prior to mandatory testing and the development of test guidelines, but other uncertainties are more likely to exist. The epidemiological data on dioxin suggest that humans are far less sensitive than animals (Hays *et al.*, 1997). In contrast, Crump *et al.* (1989) show rough similarities among human or animal studies for 23 chemicals for which adequate data were available to estimate lifetime cancer doses associated with a 25% incidence of tumor response (i.e., TD_{25}s) on the basis of mg/kg body weight dose. However, there is no reason to believe that for some other chemical the error in an assessment based on animal data would be the other way, with humans being far more sensitive (for example, see the results in Table 1 for 2,4-dinitrophenol). The question for either the cancer or noncancer end point is the same: if we ignore opportunities for collecting

human data to check our assessments, will we be basing standards on the wrong critical effect, or the wrong assumptions and consequently setting limits too high to be protective of the public's health?

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 uncertainty factor of 10 for experimental animal to human extrapolation, and often identify effects not seen in animal studies.

What Are Some of the Limitations of Our RfD/RfC Analysis?

The ratios of human to animal based RfDs and RfCs found in Tables 1 and 2 and in Fig. 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 EPA'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, EPA, or Health Canada peer review meetings, and, in at least the case of EPA, unanimous acceptance.

By contrast, the animal-based RfDs and RfCs that we develop here were generally based on summary information primarily found on EPA's IRIS or *TERA's ITER*. 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, but clearly a much more intensive involvement, than this paper allows.

We have made these comparisons between human and animal data on the basis of the RfD or RfC. In other words, the comparisons were made after uncertainty factors have been applied to the NOAEL, LOAEL, BMD, or BMC. This approach is consistent with our goal, which is to evaluate how well human data, used with contemporary risk assessment practices, protect human health. The range of uncertainty factors that is used with the NOAELs, LOAELs, BMD, or BMC in these tables reflects the variety of data types and databases for different chemicals. Therefore, we based our comparison on the RfDs and RfCs themselves, not on the NOAELs, etc. However, we acknowledge that it would be perhaps better if comparisons could be made on specific matching end points between the experimental animal species and humans, such as what has recently been done by EPA for the reassessment of dioxin (http://www.epa.gov/ncea/pdfs/dioxin/dioxreass.htm).

If high-quality animal data are available, the default uncertainty factor is likely to be 100 for RfDs (e.g., nitrite, malathion) and a 10-fold difference between animal and average human NOAEL may be expected. For the chemicals with human and animal RfDs based on the same biological end point and data type (e.g., NOAELs), a ratio close to 1 corroborates the selection of an interspecies uncertainty factor of 10-fold. For example, for aldicarb (i.e., plasma cholinesterase inhibition) and baygon, the ratios are similar only with an uncertainty factor of 10-fold. A body of ongoing research seeks to evaluate and improve the basis for the uncertainty factors (e.g., Dourson *et al.*, 1996; Renwick and Lazarus, 1998; Meek *et al.*, 2000).

This issue of power of a study to detect change is also important, but generalizations about the power of different studies, such as the idea than animal studies are always more powerful than human studies because they often have more subjects, are difficult. We suggest a case by case comparison—a large case control study may have a few hundred people; a cohort study may have thousands, some cohorts follow up the people until nearly all have died, but some epidemiology studies have only limited exposure data.

A major issue here is the power of any study, but in particular, the power of a "negative" epidemiology study. In cancer risk assessment negative epidemiology studies have been used to set upper limits on the possible risk—if a study had the power to detect a 3-fold increase and does not, it assures us that risks above 3X are unlikely. Issues of power include not only study size, but also design and exposure assessment.

We defined several criteria for comparing the existing human-based RfDs and RfCs with the animal-based RfDs and RfCs we estimate in our paper. The lowest criterion was the comparison of RfDs and RfCs based on NOAELs for unrelated effects. This is, of course, the least preferred comparison because the human and animal data tell us different things about the toxicity of the chemical in question. We made this choice quite often in Tables 1 and 2.

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. Of course, these are more preferred comparisons because the human and animal data tell us more similar things about the toxicity of the chemical in question. We also made this choice quite often in Tables 1 and 2.

Some might suggest that such comparisons should be made on the basis of the BMD rather than the NOAEL. We have no inherent problem with this suggestion (our choices here were based on availability of BMDs). However, in general, the choice of either a NOAEL or BMD as the basis of this comparison correctly depends on the available data. For example, dog studies seldom have a sufficient number of animals to do an adequate BMD,

but the value in exploring different types of effects with a larger animal should not be underestimated. NOAELs from dogs might be vastly superior to a BMD from rodents, if blood pressure was the critical effect, for example. In addition, not all effects model well. Numerous examples exist of critical effects that are masked at higher doses by effects of greater severity. The BMD can often not adequately model these critical effects and risk assessors need to depend on the NOAEL or LOAEL for guidance. Risk assessors often analyze the effects of different severity at every dose of a chemical, and recall their experiences in evaluating the results of other experiments with similar chemicals, before they make judgments of critical effect. Such judgement cannot depend only on the estimation of BMDs, nor NOAELs.[4]

Unfortunately, we did not have sufficient data in order 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.

Do Alternatives to Human Clinical Designs Exist in Reference to Pharmacokinetics?

The goal of standard setting is to establish exposure levels that are protective of human health in a variety of situations—environmental exposures, occupational exposures, and exposures to by-products of our modern society. The intellectual tools for all these exercises are similar. These exercises require interpretation of a body of data on effects in animals or in exposed individuals to assess minimally toxic levels and to apply specific factors to insure that all members of exposed populations receive adequate protection. The perceived safe level may vary for criteria pollutants, essential nutrients, and occupational toxicants. However, in all cases, considerations of similar factors become important. Pharmacokinetic models or tools are designed to determine conditions where similar doses to tissues would be attained for different species or exposure situations. These affect the numerator in the RfD or RfC process. PBPK modeling evaluates critical determinants for the pharmacokinetics and aids in assessing interindividual variability and identifying at-risk populations. These considerations affect the denominator in the RfD or RfD determination. These PK tools together with human pharmacokinetic data from volunteer studies and *in vitro* mechanistic studies with human tissues provide an optimal data set from which sound decisions can be reached for protection of exposed individuals.

[4] This is why the BMD and NOAEL need to be somewhat comparable; if they are not comparable, then the risk assessors' job of critical effect judgment becomes exceedingly difficult with data sets having both BMD and NOAEL.

PBPK approaches are important because they use scientific methods to as accurately as possible estimate and understand potential risk to humans and provide greater scientific certainty in risk characterization. The alternatives to PBPK are default assumptions, which have greater uncertainty.

If Human Data Are the Preferred Basis to Protect Human Health, Then What Does One Conclude if Human Data Lead to a Higher Risk Value Than One Based on Animal Data?

All ratios in Tables 1 and 2 that have a value greater than 1 demonstrate that the human based RfD or RfC is greater than the animal-based value. Ratios about equal to 10 would be expected if animals and humans were shown to be about equally sensitive, that is if NOAELs or LOAELs were similar (e.g., see chlorpyrifos or ethephon in Table 1). This is because the use of a 10-fold interspecies uncertainty factor with the animal NOAEL or LOAEL would result in a RfD or RfC that was about 10 times lower than a human-based RfD (and thus the ratio of human to animal-based risk value would be greater than 1). Even if the NOAEL in humans were lower than in animals, but by a factor of ~10 or less, the use of an interspecies uncertainty factor of 10-fold could result in a lower RfD or RfC based on animal data than the RfD or RfC based on human data.

Such a situation would also occur if the human data were suggesting a critical effect that the animal data were not. Table 1 shows several examples of this (e.g., nitrate, nitrite and selenium and compounds). In some cases, EPA 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). This is an example of the important role of data other than whole animal bioassays, such as pharmacokinetics and pharmacodynamics, in the overall determination of RfDs and RfCs.

What is more problematic, and potentially much more serious, is when the human data suggest a lower RfD or RfC than the animal data, either because of greater sensitivity to the critical effect, or different critical effect. This occurs in 36% (12 of 33 comparisons) of the comparisons we performed, if no precision issues are considered, and occurs in 15% (5 of 33 comparisons) if precision is considered to be "perhaps an order of magnitude." In either case, the use of animal-based RfDs and RfCs, rather than those based on human data might be considered inappropriate because the public's health does not appear to be protected.

If we accept the premise that human data are more reliable and relevant for a human risk assessment, 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. Replacement of animal data with human data should be dependent on the quality of the human data

being at a minimum comparable to the animal data it 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.

CONCLUSIONS AND FUTURE DIRECTIONS

At the outset we asked a series of questions regarding the use of human data for risk assessment.

- Is information from human studies the best way to judge the potential health risk from chemicals in our environment?

The answer is perhaps given best by the many health organizations that address this question. For example, Health Canada (Meek *et al.*, 1994), IPCS (1994), and EPA (Barnes and Dourson, 1988; EPA, 1994) each prefers the use of human data rather than animal data in the development of risk values. Based on our analysis we also agree. For example, the use of human data has led to the estimation of RfDs and RfCs on EPA's IRIS that are often lower than animal-based RfDs and RfCs that we estimate in this paper. Especially in these cases, the use of these human-based RfDs and RfCs may be better protective of the public's health.

- Should public health agencies strive to resolve the ethical questions and identify criteria to foster the conduct of human studies that might lead to better protection of the public's health?

We hope that the answer to this question is a resounding yes. Our analysis, although limited, suggests a high percentage of comparisons where the exclusive use of animal data would lead to RfDs and RfCs that do not protect the public's health. Moreover, in many cases the animal data were recognized as having greater limitations than the existing human data, as reflected in generally larger uncertainty factors than those used with the existing human data.

Perhaps what we really should be asking is how good are our best-qualified animal data for protecting human health? How can we determine when it would be better to use or develop human data rather than conducting another 2- year animal study?

- Should scientists ignore available human data that might suggest a lower or higher risk value?

The obvious answer here is no. Protecting the public's health is why we all do this work. However, it seems reasonable for scientists and regulatory agencies to further evaluate the use of human data in the development of risk values, such as RfDs and RfCs. Perhaps new criteria could be developed so that such data can be used with greater confidence.

Additional analysis of the results we present here could be done. For example, we were able to use the complete listing of RfDs and RfCs based on human data from EPA'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 commonalties exist among target tissue or mode of action for those chemicals for which animal- and human-based RfDs and RfCs differ quantitatively. None of the animal-based RfCs that we estimated was below the human-based one found on IRIS, within the limits of precision being assumed. Was this deficiency due to a small sample size or was it related to the use of dosimetry for RfCs, but not yet for RfDs? Similarly, what are 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?

We look toward future collaborations with other interested scientists for resolution of these and other issues.

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