

APPENDIX B

DETERMINING THE BEST ESTIMATE OF A SLOPE FACTOR FOR CARBON TETRACHLORIDE

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INTRODUCTION

The Environmental Protection Agency (EPA) has made available a large database of information on chemical toxicity and carcinogenicity in its Integrated Risk Information System (IRIS). IRIS contains information about chemicals supporting both identification of hazards and dose-response assessment, but the EPA warns of the limitations of IRIS beyond these applications. The limitations include the numerous uncertainties of risk assessment, including extrapolation from animal to human risk, the linearity drawn between high and low dose-response relationships, differences in potential endpoint between humans and animals, and the complication of synergistic effects ([EPA 1997](#)). Nonetheless, the values found in IRIS are frequently used quantitatively in both risk assessments and dose reconstructions, and taken by many as a definitive predictor of cancer incidence or some other human endpoint.

During the course of Phase II of the Historical Public Exposures Studies at Rocky Flats, chemical carcinogens were recognized as an important source of risk to the public, particularly carbon tetrachloride. As a risk assessment for exposures to carbon tetrachloride became necessary, the IRIS information on slope factors and unit risk for exposures to carbon tetrachloride was retrieved and reviewed. It became immediately apparent that the amount of quantitative information available on the risk due to human and animal exposures to this chemical is limited.

The slope factor for carbon tetrachloride was the parameter of primary concern. The slope factor is defined by the EPA as the slope of the dose-response curve in the low-dose region. It

reflects the potency, or ability of a carcinogen to produce cancer (EPA 1995). An EPA convention for the reporting and use of slope factors is, however, to use the upper bound of the uncertainty about the slope of the dose-response curve as the slope factor instead of using the median estimate of the slope of the linear portion of the curve.

Part of the goal of the Phase II work is to provide the public with estimates of the range of risk to which they may have been exposed, including upper and lower bound on that risk. Using the upper bound for the slope factor of a carcinogen such as carbon tetrachloride as the sole estimator of risk from Rocky Flats exposures seemed to contradict that goal. After discussions with the Health Advisory Panel about using the EPA's upper bound slope factor, we decided to review the data contributing to the slope factor for carbon tetrachloride and decide if a distribution of slope factor could be determined. This distribution will then be used in the risk assessment instead of the upper bound, adding a greater degree of realism to the retrospective dose reconstruction for carbon tetrachloride at the Rocky Flats Plant.

EPA METHODS

The methodology involving the EPA calculation of slope factor for carbon tetrachloride was carefully reviewed. The process, as well as the data used, is reviewed below.

Linearizing Cancer Incidence Data

The reference documents that detail the process of determination of slope factor for carbon tetrachloride by the EPA calculate and deal primarily with the unit risk. The EPA defines unit risk as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent of concentration of $1 \mu\text{g m}^{-3}$ in air or $1 \mu\text{g liter}^{-1}$ in water. This is based upon a 70 kg body weight and a breathing rate of $20 \text{ m}^3 \text{ day}^{-1}$ or water consumption of $2 \text{ liters day}^{-1}$ (EPA 1995). The intakes associated with unit inhalation or unit oral intake are considered to represent equivalent exposures, and the relationship between the two effective doses can be used to convert between oral and inhalation risk if information on one of the two is not available for the risk assessment.

Unit risk is related to slope factor, or slope of the dose response curve in the low dose region, as:

$$UR = \frac{SF \cdot BR}{BW \cdot CF} \quad (1)$$

where

UR = unit risk ($\text{m}^3\mu\text{g}^{-1}$)

SF = slope factor (kg d mg^{-1})

BR = breathing rate (m^3d^{-1})

BW = body weight (kg)

CF = correction factor ($10^3 \mu\text{g mg}^{-1}$).

Since dose-response studies on experimental animals are generally done at high doses compared to exposures received environmentally, an extrapolation from high to low doses is necessary to determine the risk at low, environmental doses. There are a variety of models

available for this extrapolation, and selection of a model is dependent upon the mechanism of carcinogenesis as well as the goodness-of-fit. When experiments result in only limited data and information, the EPA has adopted the use of the linearized multistage model as the model of convention for extrapolation purposes (EPA 1996).

The multistage model has the form:

$$P(d) = 1 - e^{-(q_0 + q_1d + q_2d^2 + \dots + q_id^i)} \quad (2)$$

where

$P(d)$ = lifetime risk (probability) of cancer at dose d

i = number of dose groups (not including the control group)

And all coefficients q_0, q_1, \dots, q_i are > 0 .

Unit risk estimates are based upon the excess risk over the background rate at dose d , to represent the effect of treatment with dose d . Excess risk is represented by:

$$P_t(d) = 1 - e^{-(q_1d + q_2d^2 + \dots + q_id^i)} \quad (3)$$

where

$P_t(d)$ = excess lifetime risk of cancer at dose d .

Equation 3 is a restatement of Equation 2, where the control, or zero dose, group exhibits no response, and there is deemed, from the given experiment, to be no background risk level, or background risk is inherent and need not be quantified. For experiments of this type, Equation 3 would be used to model the data. In experiments where the control group exhibits a response, coefficient values (q_0, q_1, \dots, q_i) must be estimated using Equation 2, where the background risk is quantitatively represented by the coefficient q_0 .

These models are exponential models that approach 100% risk at high doses. The coefficients of this polynomial are estimated by “maximizing the likelihood function of the data” (EPA 1984), which means estimating the coefficients which result in the best fit of the model to all of the cancer incidence data obtained from the experiments. At low doses, the effect of the higher-order terms in the polynomial is negligible and the response becomes linear with dose.

Because the number of cancers exhibited by an experimental population has a statistical nature, it is possible to represent the uncertainty associated with cancer incidence data. The upper bound on the uncertainty in this exhibited response is used by the EPA to determine the 95% upper bound on the unit risk. This statistical treatment of the data to extract an upper bound will be more thoroughly explained in a later section.

The results for carbon tetrachloride reported in the available literature are a maximum likelihood estimate (MLE) and a 95% upper confidence limit for the excess unit risk, $P_t(d)$, determined from the experimental cancer incidence data (EPA 1984). These are readily converted to MLE and upper-bound slope factors by accounting for the effect of body weight and breathing rate (Equation 1). In IRIS, only the upper bound slope factor value is reported, since that is accepted as a conservative estimate in light of the uncertainty and conservatism inherent in the process described above.

The preference of the upper-bound value for unit risk and slope factor has become an EPA convention. It is described as a plausible upper bound for risk, in keeping with the protective approach used in selecting the multistage model and the statistical nature of cancer incidence. Other reasons the EPA favors the use of the upper bound are the facts that the MLE does not account for estimation errors that result from small sample size, and that the MLE is too sensitive to changes in the incidence data. It is, however, inherent in the use of a point estimate that very little certainty exists about any single point chosen to represent a whole picture, whether that point is an upper bound or a median estimate.

The use of uncertainty estimates and distributions of possible values for the slope factor, however, removes this need to rely on a point estimator for lifetime risk. Selecting a single value for cancer potency seems unreasonable in light of the much more defensible method of using distributions of values for input parameters.

Animal Studies Used in Carbon Tetrachloride Analysis

Three animal studies were chosen for use by the EPA in their analysis of the cancer inducing ability of a carbon tetrachloride intake. The data sets include National Cancer Institute mouse and rat data (2 data sets), the Edwards et al. mouse data and the Della Porta et al. hamster data ([EPA 1984](#)). These studies are not individually referenced here because it was not necessary to retrieve the original studies for this slope factor analysis. Instead, the EPA document utilizing that study data is referenced since that document contained the pertinent data and was used to identify the manner in which the data were employed.

None of the studies was determined by the EPA to be ideal for estimation of risk for continuous lifetime exposure to carbon tetrachloride. The reasons for the inadequacies of the studies include no reported control group, small sample size, no statistical difference between low and high dose groups, poor dose regime, and short experiment duration. An obvious best choice between the four data sets did not exist, so the EPA decided to establish an estimate for unit risk and slope factor from each study and take the geometric mean of the four estimates to obtain an average unit risk and slope factor estimate.

Extrapolation of Animal-Based Risk to Human Populations

Once unit risk for the animal studies was established by fitting the data to the linearized multistage model, extrapolation of that risk to humans was necessary. There is little experimental evidence to support the relationship between animal risk and human risk, so models relating the two indicate the best scientific judgement based upon available evidence. Metabolic differences are probably the most significant predictor of species differences, so the preferred model representing equal toxicity of dose across species is based upon such an adjustment. It has been suggested that metabolic rate can be approximated by the 2/3 power of the ratio of body weights ([EPA 1984](#)). The equation describing the ratios for dose to body weight is:

$$d_h = d_a \left(\frac{W_h}{W_a} \right)^{2/3} \quad (4)$$

where

d_h = dose to human
 d_a = dose to animal
 W_h = body weight of human (reference = 70 kg)
 W_a = body weight of animal.

There are important species differences in uptake, metabolism, organ distribution of carcinogens, target site susceptibility, immune responses, dietary factors, and other differences that the simple body weight approximation relating equitoxic animal doses to human doses can never account for (EPA 1984). Human populations themselves differ in terms of diet, environment, activity, genetic makeup, and cultural factors. This approximation inherently carries with it a great deal of uncertainty, but that uncertainty is difficult to quantify.

There is also some evidence from other studies that metabolic rate is more closely approximated by the 3/4 power of the same ratio of weights (Peters 1983). EPA has selected the 2/3 power for use in their estimate of metabolic rate conversion, but other evidence will also be considered in our treatment of the data.

To extrapolate from animal to human dose, adjustments for the experiment duration must also be made. Unit risk refers to the risk resulting from a lifetime of exposure to the carcinogen of interest. If an animal experiment is partial lifetime, or doses are only administered for a short time period, an adjustment must be made.

First, dose is expressed as the time-weighted average dose. This relates the dosing regime and duration to the equivalent dose averaged over the entire duration of the experiment. Then if experiment duration is not equal to animal lifetime, an additional adaptation to account for missed responders in the shortened experiment must be included. This adjustment coefficient is $(L/L_e)^3$ where L is the animal lifespan and L_e is the experiment duration. The exponent value in this coefficient is the source of some uncertainty, but appears to be well supported in the literature and is consistent with the proportional hazard model (EPA 1984). Again, though EPA uses only the exponent 3, we will account for uncertainty in the exponent.

Although we recognize the limitations of using animal data to establish human risk factors, these studies are quite often the only alternative to establish some means of limiting doses to carcinogens for which controlled human experiments do not, and quite probably will not ever exist.

Adapting the Animal Study Unit Risk Values into Distributions of Slope Factors

Establishing the 95% confidence level for the unit risk is done after the linearization process and is based upon the maximized likelihood function of the animal data, as mentioned previously. In simpler terms, once the cancer incidence data from the animal experiments is fit to a model, the most likely value for slope, and thus risk, is selected. This value is based upon the coefficients in Equation 2. The coefficient q_1 , as approximated using the best fit of the multistage model to the animal incidence data, is regarded as the MLE of the slope factor. The value of q_1^* , or the 95% confidence level estimate for the slope factor, is determined with the help of the binomial theorem.

The binomial theorem is a mathematical model predicting the distribution of results of n independent trials, each of which results in one of two possible outcomes. In this case, the possible outcomes are cancer or no cancer exhibited in the study animal. For the example of this

data, let $p = P(\text{contracting cancer from the dose level})$, the probability of contracting cancer, and assume that p remains constant from trial to trial. Let Y denote the total number of cancers in the n trials. Then Y is said to have a binomial distribution:

$$P(Y = k) = \binom{n}{k} p^k (1 - p)^{n-k} \quad (5)$$

where

$P(Y=k)$ = the probability that Y is equal to some value k

k = an integer value for Y , some possible number of cancers

$\binom{n}{k}$ = the number of ways to form combinations of size k from a set of n distinct objects

with no repetitions, otherwise expressed as $\left(\frac{n!}{k!(n-k)!} \right)$, where $n! = 1 \cdot 2 \cdot 3 \cdot \dots \cdot n$.

In order to determine the 95% confidence level for the animal data, the cancer incidence data for each study were used to create binomial probabilities. Let us take the Della Porta hamster data as an example of the methods used to obtain the 95% level.

The Della Porta data had only one dose level, and the control group showed no response, so only one coefficient must be fit to the data ([Equation 3](#), $i = 1$). The Della Porta data are shown in Table 1.

Table 1. Della Porta hamster incidence data

Average daily dose (mg CCl ₄)	Responders/Tested
0 (control)	0/80
0.95	10/19

From these data, the probability of obtaining a cancer from the given dose level is 0.53, or 10/19, the observed number of cancers divided by the number of tested individuals. This probability becomes the value of p in the binomial equation. The probability is not continuous, but discrete at each value k , since the number of cancers must be a discrete value and not a fractional one. The probabilities calculated for each value of k using [Equation 5](#) are shown in [Figure 1](#).

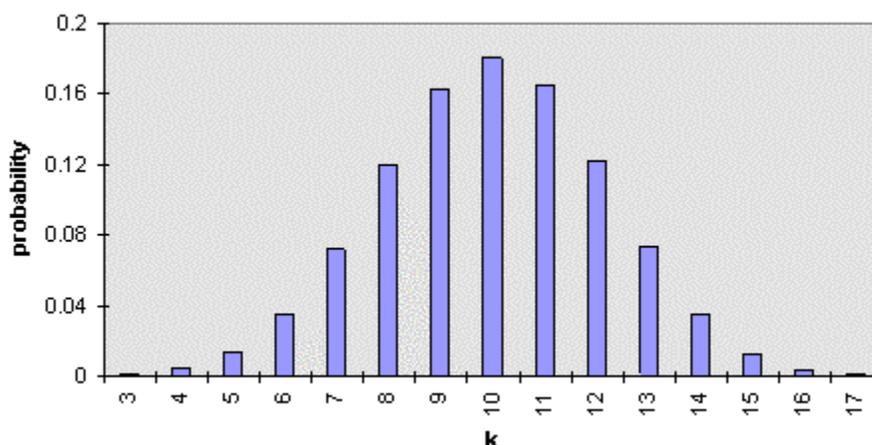


Figure 1. Binomial distribution of Della Porta cancer incidence data. Each vertical bar represents the probability of seeing k total cancer incidences out of a total of 19 exposed individuals. The total probability represented by the bars shown is $\approx 100\%$.

You can see that the most likely number of cancers out of a total of 19 tested individuals is 10, which is expected since this is the observed number of cancers in the experiment. The values about the central value of 10 are relatively normally distributed. To determine a given confidence level for this distribution, the appropriate confidence interval must be calculated. Since the distribution is two-tailed, or has a probability tail extending out on either side of the mean, the confidence interval calculates the interval about the mean that falls within the limits of the interval, leaving a portion of the distribution outside the interval on both sides. So the 90% confidence interval of a distribution represents the interval inclusive of 90% of the data, including equal amounts of data on either side of the mean. The limits of this interval are defined as the 5% and 95% confidence levels of the distribution, since 10% of the data lies outside the interval, equally divided between the sides.

For the distribution shown in Figure 1, the total probability represented is 100%. Approximately 90% of the probability is represented by the values between 7 and 13, inclusive. The limit corresponding to the 95% level is thus 13 cancers. To obtain 13 out of 19 cancers is, in the EPA definition, the probable upper limit for number of cancers at the given dose level from the Della Porta data.

To determine the upper limit for the slope factor, data fitting to the multistage model is again done, using the upper limit response of 13/19 cancers as the probability of obtaining cancer at the 0.95 mg dose level. The coefficient q_1 for the polynomial in the exponential term of [Equation 3](#) is now referred to as q_1^* , to avoid confusion and to define it as the coefficient which corresponds to an upper bound cancer incidence level. To obtain the MLE value for slope factor, or q_1 , the multistage model is fit to the response of 10/19 cancers at the 0.95 mg dose level.

The same technique is repeated for all other data sets, resulting in a value for q_1 and q_1^* for each data set. For translation to human risk, these values are converted to unit risk using techniques described earlier. The four sets of animal data then yield four sets of MLE and upper bound values for unit risk, converted to human unit risk. All EPA calculations were confirmed by RAC. The unit risk values are shown in [Table 2](#).

Table 2. EPA estimates for human oral unit risk

Data set	MLE ($\text{m}^3\mu\text{g}^{-1}$)	Upper bound ($\text{m}^3\mu\text{g}^{-1}$)
Della Porta et al. (1961)	2.1×10^{-5}	3.4×10^{-5}
Edwards et al. (1942)	7.1×10^{-6}	9.4×10^{-6}
NCI mouse (1976)	1.4×10^{-6}	1.8×10^{-6}
NCI rat (1976)	1.9×10^{-7}	3.1×10^{-7}

The conversion of these values to human risk is done as described previously, with the associated uncertainties recognized, but not quantified. The two major sources of uncertainty in the conversion to human risk are the metabolic factor and the adjustment of the experiment results to animal lifetime, as described previously ([pages 4-5](#)).

The final step toward obtaining the EPA published value is converting these oral risk values to inhalation risk. The studies used here are all risk from oral intake of carbon tetrachloride, since no inhalation cancer studies were located with adequate dose-response information. The inhalation risk is estimated from the oral risk by assuming that the same daily intake rate results in the same lifetime risk. The effective dose ($\text{mg kg}^{-1} \text{ day}^{-1}$) corresponding to $1 \mu\text{g m}^{-3}$ concentration in air was estimated and compared to the effective dose resulting from unit risk oral intake exposure of $2 \times 10^{-3} \text{ mg day}^{-1}$. The effective dose for unit inhalation intake is four times larger than that for oral exposure, so the unit risk for inhalation is estimated from the oral risk by multiplying oral unit risk by four.

The geometric mean of the inhalation unit risk value for the upper bound estimate from the four animal experiments is $3.7 \times 10^{-6} \text{ m}^3 \mu\text{g}^{-1}$ (using $k = 3$ for the power on lifetime ratio and $2/3$ power metabolic conversions). This corresponds to an inhalation slope factor of $5.2 \times 10^{-2} \text{ kg day mg}^{-1}$. These values are included in the IRIS database.

The EPA does make some attempt in the literature to estimate a possible range of values for slope factor and unit risk based upon their estimated uncertainties on the input parameters. For metabolic rate approximations, the weight ratio raised to the $2/3$ power conversion is used ([Equation 4](#)). Because the uncertainties associated with the metabolic conversion are so many and so non-quantifiable, a different predictor of metabolic rate was used to give a range to possible values for human risk after this conversion. This conversion used the simple ratio of the body weight of the animals to establish the ratio of dose and risk. The equation describing this relationship is shown below.

$$d_h = d_a \left(\frac{W_h}{W_a} \right) \quad (6)$$

where

d_h = dose to human (proportional to risk)

d_a = dose to animal (proportional to risk)

W_h = human body weight (reference = 70 kg)

W_a = animal body weight.

This equation is similar to the other metabolic conversion equation ([Equation 4](#)), but lacks the power ($2/3$) on the body weight ratio. This conversion simply applies a straight body weight

ratio to the animal dose to obtain human equivalent dose. The two ratios, body weight and (body weight)^{2/3}, yield different values for the human risk. The EPA simply reports these as a possible range for risk, implied to account for uncertainty in metabolic rate differences between species.

The lifetime adjustment uses the ratio of the animal lifetime (L) to the experiment duration (L_e) raised to the exponent m [$(L/L_e)^m$] where $m = 3$. This is the coefficient to adjust for positive responses (cancers) that would have occurred had the experiment lasted long enough for the cancers to develop. This conversion is made because unit risk represents this lifetime risk to continuous exposure.

The uncertainty in this factor is in the value of m . The value 3 is supported in part by some experimental evidence. Studies fitting the model $dt^m = \text{constant}$ to experimental data at constant risk supports values for the exponent between 2 and 4 for data on nitrosamines. The conversion to total lifetime for age-specific cancer rates in humans yield values for m of 3 or higher. The concept of time-weighted-average dose has not been verified for cancer, but is included for completeness and is represented by $m = 1$. The above values lead the EPA to believe that a representative range of values for m might be from 1 to 4. The different approximations for conversion to lifetime risk to humans give a range of human risk values for each individual data set.

The range of possible values for the upper bound to unit risk is given in the literature (EPA 1984), but is not presented to IRIS users. This range is made up of the lowest and highest estimates for unit risk from the ranges given for the individual animal experiments. This is not a very useful estimate for uncertainty, since the range does not represent a range on the geometric mean but instead a range on the individual values being averaged within that geometric mean. The information appearing in IRIS includes the upper bound values for the oral unit risk for each animal experiment, the suggested oral slope factor, and the suggested inhalation unit risk. No information on the uncertainty described above is provided to the IRIS user.

RAC MODIFICATIONS TO EPA METHODOLOGY

Once the EPA methods were reviewed and understood, we decided to determine a range and distribution of estimates for slope factor and unit risk for inhalation of carbon tetrachloride to be used in the Rocky Flats study.

It seems that the use of the upper limit for slope factor and unit risk in the IRIS database is more of a convention than a scientifically based decision. The upper bound has been shown to be more robust to changes in the incidence data than the MLE, which seems to be the primary source of confidence in the upper bound as opposed to the MLE. All estimates for risk of cancer from some known or suspected carcinogen are based on cancer incidence information. Naturally, a change in that incidence rate would have a strong effect on the median value for cancer incidence, since the assumed risk is based solely upon the information available about incidence. That does not necessarily mean that a considerably larger risk value is necessarily more reliable. It is simply larger.

The entire basis of the analysis of the incidence data and determination of the upper bound is a probability distribution. There is no reason why similar techniques cannot be applied to acquire a distribution of unit risk.

The Crystal Ball[®] uncertainty analysis software package (Decisioneering 1996) was used to calculate slope factor. The Crystal Ball[®] package is used within Microsoft Excel and allows the

user to define the distribution of possible values for an input parameter about a defined mean. This assumption cell within Excel is used as a parameter in an equation cell. This equation is contained in a forecast cell. The results of the equation are calculated using a Monte Carlo analysis. A Monte Carlo simulation uses randomly generated numbers to measure the effects of the uncertainty expressed in the probability distribution in the assumption cell. A single trial generates a random number based on the probability distribution for each assumption, recalculates the equation within the spreadsheet, and displays the result of the calculation in a forecast chart. This forecast chart represents the results of the many calculations for the series of random numbers as a probability histogram. The more Monte Carlo trials run, the more continuous this histogram appears. This histogram can then be fit to a more conventional distribution, and the statistics describing that distribution are given by the Crystal Ball® software, accounting for the uncertainty in the input variables.

Instead of defining a simple range of possible values for the unit risk estimates, the MLE and 95% estimates were used to define a distribution of values for the animal slope factor, based upon the multistage model fitting done by the EPA for the two estimates. A triangular distribution was defined with the MLE as the most likely value and the upper and lower bounds set using the 95% level as a guide for the width of the distribution.

These two values for animal slope factor, and thus the resulting animal slope factor distribution, were given in units of day mg^{-1} , instead of the more conventional kg day mg^{-1} . This indicates that the animal body weight is inherent to the slope factor and need not be adjusted for to obtain the unit risk. The unit risk for animals was calculated using a version of [Equation 1](#), which does not contain the body weight adjustment. Animal breathing rates were estimated from the available data on human unit risk and animal slope factor for each experiment, back-calculating to extract the breathing rate given all other known conversion factors. Since breathing rate is not constant for any population of subjects, the breathing rate was normally distributed about the calculated mean with a standard deviation equal to 5% of the mean.

The product of this calculation using two parameters approximated by distributions is a distribution of animal oral unit risks. To convert this to human oral unit risks for each experiment, the metabolic conversion and lifetime conversion are necessary.

The EPA's metabolic conversion uses the $2/3$ power of the ratio of body weights. Another experimentally defended conversion to approximate metabolism is the use of the $3/4$ power ([Peters 1983](#)). There is also some evidence of exponents somewhat higher and lower than these two values, but nothing so high as the 1^{st} power suggested by the EPA as an upper bound for this factor. For our uncertainty calculations, we established a distribution of values, attempting to capture the well-defended range of $2/3$ to $3/4$ along with some of the uncertainty in that range. This distribution begins at a power of $1/2$, increases to linearly $2/3$, plateaus to $3/4$, and decreases linearly to $9/10$. A diagram of the distribution is shown in [Figure 2](#).

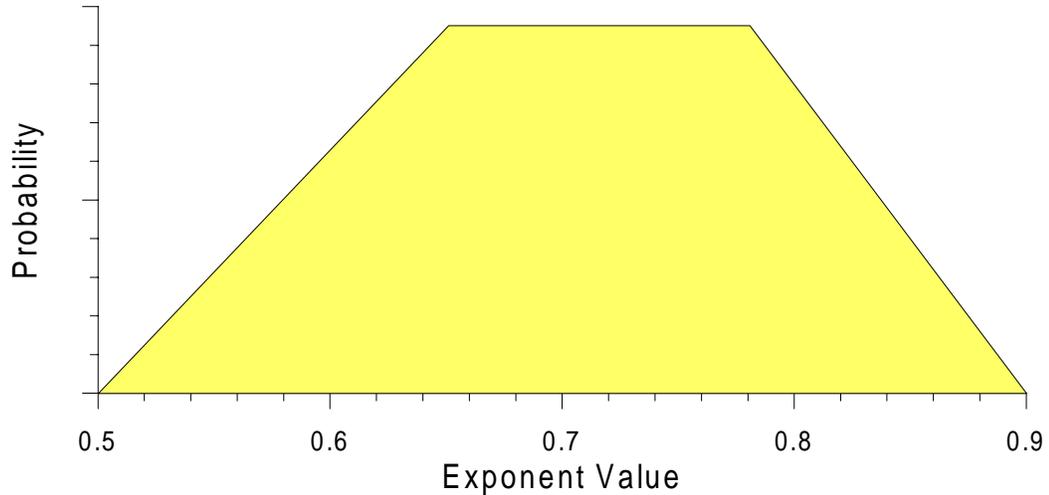


Figure 2. Probability distribution for exponent used in metabolic rate conversion factor. Vertical (y) axis is relative probability, and horizontal (x) axis is the value for the exponent. Total relative probability (under the curve) is 1.

For differences in experiment duration and animal lifetime, the conversion $(L/L_e)^m$ was used, with values for m ranging from 1 to 4, with 3 as the most likely value. This distribution is shown in Figure 3.

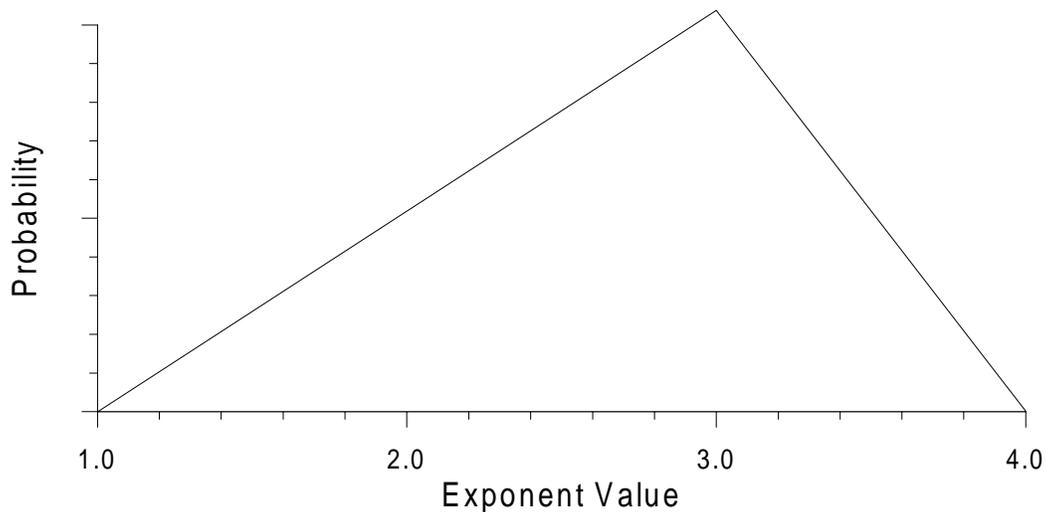


Figure 3. Probability distribution for exponent used in experiment duration/animal lifetime conversion. Vertical (y) axis is relative probability, and horizontal (x) axis is the value for the exponent. Total relative probability is 1.

These adjustments are made to the animal unit risk to convert it to human unit risk as shown in [Equation 7](#).

$$UR_h = \frac{UR_a}{\left(\frac{W_h}{W_a}\right)^k} \left(\frac{L}{L_e}\right)^m \quad (7)$$

where

UR_h = Human unit risk ($\text{m}^3 \mu\text{g}^{-1}$)

UR_a = animal unit risk ($\text{m}^3 \mu\text{g}^{-1}$)

k = exponent described in [Figure 2](#)

m = exponent described in [Figure 3](#)

And other parameters are as defined previously.

Equation 7 yields a distribution of human oral unit risk, which must be converted to inhalation unit risk for each of the four studies. As described previously, the unit risk intakes for inhalation and ingestion are converted to effective dose. The dose for a unit inhalation is four times higher than for unit ingestion, so the oral unit risk factor must be multiplied by four to produce the inhalation unit risk factor. Since this is a simple conversion, no uncertainty is associated with this part of the calculation.

To translate each of the four distributions of inhalation risk values to slope factor, [Equation 1](#) must again be employed, using the standard body weight and breathing rate for a human (70 kg and $20 \text{ m}^3 \text{ day}^{-1}$, respectively). These parameters have some uncertainty associated with them, so they are given a normal distribution with an uncertainty equal to 5% of the mean.

We are now presented with four distributions of slope factor values for human inhalation of carbon tetrachloride. Combining these distributions into a single slope factor estimate is necessary, but difficult. As discovered by the EPA, none of the four experiments is superior to the others. Neither is there a quantitative measure for comparing the experiments to each other to determine an appropriate weighting method for selecting preferentially from any of the four distributions as they are combined. The lack of a rigorous procedure for combining the four distributions to form one leaves us in a similar position to the one the EPA found itself in, so we have chosen to follow their lead and combine the four distributions using the geometric mean.

A distribution fit was done to the data produced as the final human inhalation slope factor estimate. The data were well fit by a lognormal distribution, with a geometric mean of $2.49 \times 10^{-2} \text{ kg day mg}^{-1}$ and a geometric standard deviation of 1.43. The 5% and 95% values of this distribution are $1.38 \times 10^{-2} \text{ kg day mg}^{-1}$ and $4.45 \times 10^{-2} \text{ kg day mg}^{-1}$, respectively. The EPA suggested value for slope factor of $5.2 \times 10^{-2} \text{ kg day mg}^{-1}$ appears in the distribution at about the 98% level. This suggested distribution of slope factor values will be used in the carbon tetrachloride risk calculations.

CONCLUSIONS

Values provided by the EPA in available databases for risk to humans from chemical exposures are traditionally based on upper bound, conservative estimates of the risk calculated from animal experiments with no quantitated uncertainty. For the Rocky Flats study, we have determined that an upper bound estimate yields overly conservative values for exposure based risks to carbon tetrachloride. Instead, we calculated a range and distribution of estimates for slope

factor. This range was established using the uncertainty in the translation of animal risk to human risk. We feel that this treatment of the slope factor, while deviating from the conventional EPA treatment of cancer potency, is much better for the Rocky Flats Dose Reconstruction, helping the study maintain its goal of determining best estimates of potential dose and risk with uncertainty bounds due to releases from the plant.

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