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A Simple Procedure for Estimating Pseudo Risk Ratios from Exposure to Non-Carcinogenic Chemical Mixtures

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Abstract

Background—Non-cancer risk assessment traditionally assumes a threshold of effect, below which there is a negligible risk of an adverse effect. The Agency for Toxic Substances and Disease Registry (ATSDR) derives health-based guidance values known as Minimal Risk Levels (MRLs) as estimates of the toxicity threshold for non-carcinogens. Although the definition of an MRL, as well as EPA reference dose values (RfD and RfC), is a level that corresponds to "negligible risk," they represent daily exposure doses or concentrations, not risks.

Objectives—To present a new approach to calculate the risk at exposure to specific doses for chemicals mixtures.

Methods—The assumption in this approach is to assign *de minimis* risk at the MRL. The assigned risk enables the estimation of parameters in an exponential model, providing a complete dose-response curve for each compound from the chosen point of departure to zero.

Results—We estimated parameters for 27 chemicals. The value of k, which determines the shape of the dose-response curve, was moderately insensitive to the choice of the risk at the MRL.

Conclusions—The approach presented here allows for the calculation of a risk from a single substance or the combined risk from multiple chemical exposures in a community. The methodology is applicable from point of departure data derived from quantal data, such as data from benchmark dose analyses (BMD) or from data that can be transformed into probabilities, such as lowest-observed-adverse effect level (LOAEL). The individual risks are used to calculate risk ratios that can facilitate comparison and cost-benefit analyses of environmental contamination control strategies.

Keywords

Toxicological mixtures; risk assessment; Minimal Risk Levels; acceptable risk; benchmark dose; lowest-observed-adverse effect; point of departure

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Introduction

Non-cancer risk assessment traditionally assumes a threshold of effect, below which there is a negligible risk of an adverse effect. For carcinogens, a mix of techniques are used; some with modeling down to low exposures and others assuming a threshold (EPA). The Agency for Toxic Substances and Disease Registry (ATSDR) derives health-based guidance values known as Minimal Risk Levels (MRLs) as estimates of the toxicity threshold for non-carcinogens. By definition, an MRL is a substance-specific estimate of the daily human exposure to a substance that is likely to be without an appreciable risk of adverse, non-cancer effects over a specified duration of exposure (Pohl and Abadin 1995). The point of departure (POD) for deriving an MRL for a substance is most commonly determined from the best fit dose response curve obtained by benchmark dose (BMD) methods, such as BMDL (benchmark dose lower bound) or BMCL (benchmark concentration lower bound) which correspond to the lower limit of a one-sided 95% confidence interval on the BMD or benchmark concentration (BMC) at a given response rate, usually 10% (Crump 1984). Other techniques have been proposed (Gaylor et al. 1998; Gaylor et al. 1999; Sand et al. 2011). If sufficient data are not available for modeling a dose-response curve, the lowest-observed-adverse effect level (LOAEL) or no-observed-adverse effect level (NOAEL) is used as a POD. Uncertainty factors (UF) are used to extrapolate from the POD to the MRL. Uncertainty factors incorporate uncertainty to account for: 1) the biological differences between human and the animal species (interspecies); (2) differences between individuals within the human population (intraspecies); and 3) use of a BMD/C or LOAEL POD instead of a NOAEL POD. In addition, the risk assessor can use modifying factors (MF) under special circumstances (e.g., biological relevance). MRLs are derived for inhalation and oral routes of exposure, and for acute (1 – 14 days), intermediate (15 – 364 days), and chronic (≥365 days) durations of exposure. They all use the general equation:

$$MRL = \frac{NOAEL\ or\ LOAEL\ or\ BMDL\ or\ BMCL}{UFxMF} \quad [1]$$

MRL values can differ from reference doses (RfD) or reference concentrations (RfC) developed by the Environmental Protection Agency (EPA) for a variety of reasons and can serve as guidance values to help health assessors evaluate the human health impact of exposure to hazardous substances found in communities or at waste sites (Abadin et al. 2007). Most commonly, these differences are due to differences in scientific opinion regarding the most important finding, differences in time which can lead to the use of additional literature and differences in the factors used. Although the definition of an MRL is a level that corresponds to “negligible risk,” MRL levels represent daily exposure doses or concentrations, not risks. There would be advantages to reporting risks at MRL values including: 1) the ability to add risk of several substances to provide an overall risk associated with exposure to several chemicals at a site and; 2) communicating to communities the risk ratios from hazardous substances in their environment compared to risks associated with other exposures and risks encountered in daily life.

In this manuscript, we develop a method to evaluate whether risks from individual exposures are significantly greater than the expected risk at the MRL. This method is then used to derive aggregate risks for multiple chemical exposures and demonstrated for several example and real mixture scenarios. The method is applicable to quantal data or continuous data that can be transformed into probabilities. This method is intended for situations where there is no information to guide the choice of a specific type of model for a chemical mixture (such as a physiologically-based pharmacodynamic model to take into account competitive binding). This is similar to Tiers 0, 1 and 2 in Kortenkamp et al. (Kortenkamp et al. 2012).

Materials and Methods

Deriving the Model

To describe the risks for exposure to xenobiotics requires the use of a dose-response curve, preferably one that is in accordance with scientific theory and biological plausibility. However, in most cases, such biologically-based dose-response models are not available for most toxicants. As a default, the USEPA has chosen to use a linear function for cancer risk assessment (EPA 2005). The methodology used by the EPA can be easily applied to other endpoints while preserving the concept that these other endpoints have nonlinear behavior. We accomplish this through the use of the Weibull model (Figure 1). Note that other models could also be used in this context and we will discuss this choice further down in the text.

Derivation using the Weibull model—The Weibull model with a background risk is usually defined as:

$$P_D = \beta + (1-\beta) \times \left[1 - e^{(-\alpha D^k 2)}\right]. \quad [2]$$

where P_D is the extra risk at a specific dose D, α is the slope factor, D the dose or concentration, e is Euler's constant and k a positive number that will determine the shape of the dose-response curve. Extra risk is defined as $R_D = [P_D - P_0]/[1 - P_0]$ where P_0 is the risk at zero exposure (background). Using this adjustment, the extra risk is given by

$$R_D = 1 - e^{-\alpha D^k} \quad [3]$$

In a log-linear relationship the value of k is equal to 1.

In the risk calculation for cancer, EPA uses a virtually safe dose (VSD) of 1 extra cancer per 1 million people exposed (EPA 2005), whereas California uses 1 extra cancer per 100,000 people exposed(OEHHA 2010).. If we assume that the acceptable risk level at the MRL is known, usually in the range of 10^{-6} to 10^{-4}, we can calculate k. Let

$$R_{BMD}=1-e^{-\alpha BMD^k} \quad [4]$$

where R_{BMD} is the response (BMR). Using this same equation, the response at the MRL will follow the equation:

$$R_{MRL}=\varepsilon=1-e^{-\alpha MRL^k} \quad [5]$$

where ε is the acceptable risk at the MRL. Since the value of α is the same for equation [4] and [5], it follows that:

$$\frac{-\ln(1-R_{BMD})}{BMD^k}=\alpha=\frac{-\ln(1-\varepsilon)}{MRL^k} \quad [6]$$

Solving for k we will have:

$$\frac{\ln(1-R_{BMD})}{\ln(1-\varepsilon)}=\left(\frac{BMD}{MRL}\right)^k \quad [7]$$

then

$$k=\frac{\ln\left(\frac{\ln(1-R_{BMD})}{\ln(1-\varepsilon)}\right)}{\ln\left(\frac{BMD}{MRL}\right)}. \quad [8]$$

Once we have this estimate of k, equation [6] can be used to derive an estimate of a.

If we assume that k is fixed and that the model must hold throughout the range of the possible exposures between the BMD and 0, then we can calculate a pseudo upper bound on the risk at the MRL. If the BMDL is the lower limit of the 95% confidence interval at the BMD, applying the formula [3] results in

$$\alpha_{UB}=\frac{-\ln(1-R_{BMD})}{BMDL^k} \quad [9]$$

where a_{UB} is the upper bound on the slope a. From this, we can calculate the upper bound risk at the MRL as:

$$R_{UBMRL}=1-e^{-\alpha_{UB}\,MRL^{k}} \quad [10]$$

Thus, using the information from the benchmark modeling and the MRL value, and assuming a negligible risk at the MRL, we can calculate k and the corresponding upper risk at the MRL value for that compound. From this, for any dose D near the MRL, a risk (equation [3]) and an upper bound risk (equation [10]) can be calculated.

When the point of departure to derive the MRL is the LOAEL, the extra risk response at the LOAEL (R_{LOAEL}) can be derived as follows:

$$R_{LOAEL}=\frac{P(LOAEL)-P(0)}{1-P(0)} \quad [11]$$

where *P(LOAEL)* is the probability of affected individuals at the *LOAEL*, *P(0)* is the probability in the control group. If 95% confidence intervals for the NOAEL are available or can be calculated directly using the provided data, these should be applied to get confidence bounds. If not, the estimate of variance and the 95% CI response at the LOAEL can be derived using any of several methods (Newman 2001). For quantal response data, we used the unconditional maximum likelihood formulae:

$$var(R_{LOAEL})=\sqrt{\frac{\mathrm{p(loael)q(loael)}}{\mathrm{n(loael)}}+\frac{\mathrm{p0q0}}{\mathrm{n0}}} \quad [12]$$

where n(loael) is the number of individuals in the LOAEL group, and n0 is the number of individuals in the control group.

The 95% confidence interval will be then calculated as following:

$$(R_{LBL},R_{UBL})=R_{LOAEL}\pm Z_{\alpha/2}\sqrt{\mathrm{var}(R_{LOAEL})} \quad [13]$$

The appropriate changes using the LOAEL and its risks and bounds can be substituted into equations [3] through [10] to derive the estimates.

With equation [9] modified as

$$\alpha_{UB}=\frac{-\ln(1-R_{UBLLOAEL})}{LOAEL^{k}}$$

The same approach can be applied to NOAELs as long as upper confidence bounds can be developed.

Derivation of the model using the log-logistic approach—Using the loglogistic model, the extra risk P(d) is given by the formula

$$P(d)=\frac{1}{1+e^{-[i+ln(d)s]}} \quad [14]$$

If we assume that the acceptable risk level at the MRL is known, usually in the range of 10^{-6} to 10^{-4}, we can calculate *s*, a positive number that will determine the shape of the dose-response curve. Let

$$R_{BMD}=\frac{1}{1+e^{-(i+ln(BMD)s)}} \quad [15]$$

where R_{BMD} is the response (BMR). Using this same equation, the response at the MRL will follow the equation:

$$R_{MRL}=\varepsilon=\frac{1}{1+e^{-(i+ln(MRL)s)}} \quad [16]$$

where ε is the acceptable risk at the MRL. Since the value of *s* is the same for equation [15] and [16], it follows that:

$$s=\frac{\ln\left(\frac{1}{R_{BMD}}-1\right)-\ln\left(\frac{1}{\varepsilon}-1\right)}{\ln(MRL)-\ln(BMD)} \quad [17]$$

which leads to

$$i=-\ln\left(\frac{1}{R_{BMD}}-1\right)-ln(BMD)s \quad [18]$$

and the i_{UB} Pseudo-Upper bound

$$i^{UB}=-\ln\left(\frac{1}{R_{BMD}}-1\right)-ln(BMDL)s \quad [19]$$

From this, we can calculate the upper bound risk at the MRL as:

$$R_{UBMRL}=\varepsilon=\frac{1}{1+e^{-[iub+ln(MRL)s]}} \quad [20]$$

When the point of departure to derive the MRL is the LOAEL, the extra risk response at the LOAEL (R_{LOAEL}) can be derived as follows:

$$s=\frac{\ln\left(\frac{1}{R_{LOAEL}}-1\right)-\ln\left(\frac{1}{\varepsilon}-1\right)}{\ln(MRL)-\ln(LOAEL)} \quad [21]$$

Which leads to:

$$i=-\ln\left(\frac{1}{R_{LOAEL}}-1\right)-ln(LOAEL)s \quad [22]$$

and for the Pseudo-Upper bound

$$iub=-\ln\left(\frac{1}{R_{UBLOAEL}}-1\right)-ln(LOAEL)s \quad [23]$$

where $R_{UBLOAEL}$ is the Upper bound Risk at LOAEL

Calculation of risk for a chemical mixture

If the risk of a negative health outcome given exposure to chemical i is defined as;

$$\mathrm{R_{Ei}=Pr[Disease|E_i]} \quad [24]$$

then the risk of no health outcome given exposure to a chemical is defined as

$$\mathrm{1-R_{Ei}=Pr[No\ Disease|E_i]} \quad [25]$$

Under a simple independence assumption, the risk of no health outcome given exposure to n chemicals (i=1, 2, … n) is

$$\mathrm{Pr[No\ Disease|E_1\ and\ E_2\ and\ \ldots\ E_n]=Pr[No\ Disease|E_1]\ and Pr[No\ Disease|E_2]\ and\ \ldots\ Pr[No\ Disease|E_n]}$$

[26]

It then follows that the combined risk of no health outcome ($1-R_{\Sigma}$) for exposure to n chemicals is

$$1-R_{\sum}=\prod_{i=1}^{n}(1-R_{Ei})=\prod_{i=1}^{n}\left(1-(1-e^{-\alpha_i E_i^{k_i}})\right)=\prod_{i=1}^{n}e^{-\alpha_i E_i^{k_i}}=e^{-\sum_{i=1}^{n}\alpha_i E_i^{k_i}} \quad [27]$$

where α_i and k_i are the derived parameter estimates for chemical i. It then follows that:

$$R_{\sum}=1-e^{-\sum_{i=1}^{n}\alpha_i E_i^{k_i}} \quad [28]$$

This method is inappropriate if the chemicals in the mixture interact to induce a synergy or antagomism in the response. In these cases, if this relationship is known, a different model must be developed and applied appropriately. One specific case is worth noting. When chemicals act through a common mechanistic target in the body, the use of a dose-additive model is more appropriate than a model of simple independent action. In this case, the doses of the various chemicals in the mixture are added together, adjusting for differences in potency, to estimate the risk. For example, in human risk assessment, the risk for a mixture of dioxin-like compounds is based upon the combined potency of dioxin-like effects of individual chemicals. To assess the risk associated with exposure to mixtures of dioxin-like compounds, EPA (EPA 1989a) developed toxicity equivalency factors (TEFs) that compare the relative toxicity of individual chemicals or a mixture of chemicals to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) assuming a common mechanism of action involving binding of the compound(s) to the aryl hydrocarbon receptor (AhR). The dose response for the mixture could be predicted based upon the potency-adjusted dose-additive effect of the individual compounds present within the defined mixture. These factors have been evaluated for cancer and non-cancer endpoints (DeVito et al. 1997; Hamm et al. 2003; Toyoshiba et al. 2004; Walker et al. 2005). Toxicity of dioxin-like chemicals is expressed in toxicity equivalents (TEQs) which is defined as the product of the concentration of an individual dioxin-like compound in a complex environmental mixture and the corresponding TCDD TEF for that compound. In 2005 the World Health Organization (WHO) re-evaluated the TEFs system (Van den Berg et al. 2006). A value of 1 was assigned to TCDD but also to 1,2,3,7,8-penta-chloro-dibenzo-p-dioxin. Currently, TEFs are available for 7 chlorinated dibenzo-p-dioxins, 10 chlorinated dibenzofurans (CDFs) and 12 PCBs congeners (4 non-ortho and 8 mono-ortho substituted PCBs).

To calculate the adjusted risk-specific doses for exposure to other compounds in an additive mixture, the equation [28] will be replaced by

$$R_{\sum}=1-e^{-\alpha_1\left(\sum_{i=1}^{n}\frac{\alpha_i}{\alpha_1}E_i\right)^{k_1}} \quad [29]$$

where chemical 1 is considered the index compound, a_1 and k_1 are derived as above but k_i is set to the same value as k_1 and a_i is derived using equation [6] and this value of k. This would work identically to the use of TEFs for dioxin-like compounds.

Pseudo Risk Ratios

Rather than using the method described here to provide direct estimates of risk which would have very little accuracy, it would be better to provide risk ratios and use these to guide decisions. In the context of this report, the risk ration is given by:

$$RR_E = \frac{R_E}{R_{MRL}} \quad [30]$$

Using equation [3] we have:

$$e^{-aD^k} = 1 - R_D \quad [31]$$

which, after some minor algebra leads to:

$$D = \sqrt[k]{\frac{LN(1-R_D)}{-a}} \quad [32]$$

Therefore

$$\frac{E}{MRL} = \sqrt[k]{\frac{LN(1-R_E)}{-a}} \times \sqrt[k]{\frac{-a}{LN(1-R_{MRL})}} = \sqrt[k]{\frac{LN(1-R_E)}{LN(1-R_{MRL})}} \quad [33]$$

Since both R_E and R_{MRL} are generally assumed to be in the range of de minimis risk, they will be small which means $LN(1-R_E)$ is approximately $-R_E$ and $LN(1-R_{MRL})$ is approximately R_{MRL}. Thus:

$$\frac{R_E}{R_{MRL}} \cong \left(\frac{E}{MRL}\right)^k \quad [34]$$

Similar results hold for the upper bound on the risk ratio. Under the assumption of independent action, where

$$1 - R_{\sum} = \prod_{i=1}^{n} (1 - R_{E_i}) \quad [35]$$

it then follows that

$$-LN(1-R_{\sum})=\sum_{i=1}^{n}\alpha_i E_i^{k_i} \quad [36]$$

Again, assuming the risk at the combined exposures is small, the risk ratio becomes

$$\frac{R_{\sum}}{R_{\mathrm{MRL}}}=\frac{\sum_{i=1}^{n}\alpha_i E_i^{k_i}}{\varepsilon} \quad [37]$$

Note that the risk at each of the MRLs is the same, ε. The denominator of equation [37] can also be replaced with an approximation that would be given by the average of the weighted MRLs as follows:

$$\frac{R_{\sum}}{R_{\mathrm{MRL}}}=\frac{\sum_{i=1}^{n}\alpha_i E_i^{k_i}}{\frac{1}{n}\sum_{i=1}^{n}\alpha_i MRL_i^{k_i}} \quad [38]$$

Results

Derivation of Parameters for Single Chemicals

We searched the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL) database (ATSDR 2012) to identify chemicals for which current MRL values relied on BMD modeling. We identified 18 chemicals where the MRLs were derived from oral exposure and one chemical derived from inhalation exposure. Of these 19 chemicals, four of the phosphate ester flame retardants (tributyl phosphate, tris(2-butoxyethyl) phosphate, tris(2-chloroethyl) phosphate, tris(1,3-dichloro-2-propyl) phosphate) had MRLs for different durations of exposure. In addition, from the Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) database (EPA 2012), we obtained information on benzene and 1,3 butadiene. Thus, a total of 25 entries from the MRL database could be analyzed (Table 1).

For each chemical, we determined whether the principal study identified for each chemical's BMD assessment was derived from quantal (dichotomous) or continuous critical effect data (Table 1). For substances with BMD values based on quantal data, the BMR is expressed in terms of a percent increase in risk of adverse outcome compared with background, which is typically set at the lower end of the range of responses that can be detected experimentally. Generally, the BMR is set at: a) 10% for an animal study with any endpoint other than a change in reproductive ability or outcome; b) 5% for extrapolation from animal studies with reproductive changes, and; c) 1% for extrapolation from a human epidemiological study (EPA 2000). For BMD/BMC values derived from continuous critical effect data, a change in response of 1 standard deviation from control is considered approximately equivalent to a 10% increase in risk of adverse response from exposure. Therefore, the dose that resulted in a 1-standard-deviation change from control was considered as equivalent to the BMD_{10} and

is equal to a BMR of 10% derived from quantal data (EPA 2000). Table 1 shows the values of k, α, and α_{ub} and the upper bound risk at the MRL for each compound analyzed when the de minimis risk at the MRL was $\varepsilon = 10^{-5}$.

We identified nine MRLs that were derived using the LOAEL as the point of departure. These MRLs came from 7 chemicals; the calculated risk and the upper bound risk at the MRL are reported on Table 2.

Figure 2 shows the values of k from MRL/RfCs derived from BMDs or LOAELs when the acceptable risk at the MRL is $\varepsilon = 10^{-5}$. Figure 3 shows the relative risk ratio at exposure twice the MRL/RfC. The relative risk ratio was calculated as the ratio between the risk at the dose and the risk at MRL, and it is a useful tool to compare the risk of developing an adverse health effect at a given exposure in people compared to exposure at the MRL. With the exception of Vanadium, the risk ratios do not change dramatically for the three different choices of ε making the risk ratio a useful tool in decision making semi-independent of ε. Vanadium had the largest value of k (2.42) which drives the higher ratios seen here. Supplemental Table 2 provides the actual risk ratios from Figure 3 and Supplemental Table 3 provides the risk ratios for the case where the exposure is 5 times the MRL/RfC. For the case of 5-fold over the MRL, there are greater differences in the risk ratios but never more than an order of magnitude and in all cases, even the smallest risk ratio would suggest concern.

Calculation of Pseudo Risk Ratios for Chemical Mixtures

As a simple example, we assumed a population has been exposed for several months (but less than 1 year and therefore we use the MRL from intermediate duration) to the following chemicals: 1) 0.001 mg/kg/day of cadmium (twice the MRL); 2) 0.018 mg/kg/day of tributyl phosphate (TnBP) (slightly below the MRL); and 3) 0.1 mg/kg/day of Barium Salts (half the MRL). Assuming that the acceptable risk at the MRL is $\varepsilon = 10^{-5}$, the risk of an adverse health outcome for cadmium R_{Cd} is $3*10^{-5}$ (upper bound risk = $1*10^{-4}$), the risk for tributyl phosphate R_{TnBP} is $8*10^{-6}$ (upper bound risk = $2*10^{-5}$), and the risk for barium R_B is $3*10^{-6}$ (upper bound risk = $5.5*10^{-6}$). Applying formula [28], the combined risk R_Σ is equal to $4.5*10^{-5}$ with an upper bound of $1.5*10^{-4}$. The relative risk ratio in this case is 4.5 and the upper bound is 15. Table 3 shows the combined risk and upper bound risk for the mixture assuming an acceptable risk at the MRL is $\varepsilon = 10^{-4}$, $\varepsilon = 10^{-5}$, or 10^{-6}. There is almost no difference in the risk ratios regardless of the choice of the risk at the MRL.

As example of a real scenario, yearly canister data were available from four areas (Areas 1,2,3,4) in Corpus Christi, Texas. Area 1 mean air concentrations for benzene and 1,3-butadiene were 0.295 ppb and 0.034 ppb, respectively. Area 2 mean air concentrations were 0.536 ppb and 0.045 ppb for benzene and 1,3-butadiene, respectively. Regardless of the chosen risk at the MRLs, the relative risk ratios are significantly less than 1 indicating no risk to the communities (Table 3). In Areas 3 and 4, benzene, toluene, ethylbenzene, and xylenes (BTEX) were detected. Mean air concentrations in Area 3 were 0.000403 ppm of benzene, 0.000326 ppm of toluene, 0.000058 ppm of ethylbenzene, and 0.000195 ppm of xylenes. Mean air concentrations in Area 4 were 0.00154 ppm of benzene, 0.00098 ppm of toluene, 0.00013 ppm of ethylbenzene, and 0.00111 ppm of xylenes. As with Areas 1 and 2,

the risk ratios in Areas 3 and 4 are below 1, but not to as great a magnitude. Indeed, for Area 4 and all risks at the MRL, the upper bound on the relative risk is almost 1 (Table 3). If, instead of estimating k based upon a risk at the MRL, we fixed k to be 1 (as is done for genotoxic carcinogens in EPA's risk assessment approach), the risks at the MRLs for all four Areas would be above 10^{-5}, close to 10^{-4}.

To address model sensitivity, the analyses of the Corpus Christie samples were also done using the log-logistic model (see Table 3). The results are virtually identical indicating very little sensitivity of the method to the use of either of these two models.

Discussion

A recent report by the National Academy of Sciences (NRC 2009) made recommendations for an approach to be developed by the USEPA that redefines the RfD or RfC as a risk-specific dose. The convenience of the risk-specific dose is that it "will provide information on the percentage of the population that can be expected to be above or below a defined acceptable risk with a specific degree of confidence" (NRC 2009). By definition, EPA's RfDs and RfCs, as well as ATSDR's MRLs are chemical-specific exposure values thought "likely to be without an appreciable risk of adverse, non-cancer effects over a specified duration of exposure". The present study outlines the advantages of such an approach when considering mixtures.

In the present study, we describe a method to calculate the risk-specific dose for exposure to chemical mixtures. The main assumption needed for this approach is to assign a risk level at the MRL, RfD and/or RfC. The assigned risk enables the estimation of parameters in an exponential model, providing a complete dose-response curve for each compound from the chosen point of departure (BMD or LOAEL) to zero as shown in Figure 1. For risk management of Superfund sites, EPA policy uses acceptable risk for environmental carcinogens of 10^{-4} to 10^{-6} as the target risk range (EPA 1991). The advantages of using a pre-defined acceptable risk at the MRL are the ability to estimate risk for any exposure below the BMD or other point of departure and the ability to combine risks for mixtures. The estimated risk for the mixture represents the probability of harm from the exposures even though for different chemicals, the types of harm may be different. The combination of the risks simply allows one to see whether the overall health of the community is likely to be compromised by the exposures or not.

We estimated parameters for 27 chemicals from the ATSDR toxicological profiles and from the EPA IRIS database. The value of k, which determines the shape of the dose-response curve, was moderately insensitive to the choice of the risk at the MRL. The values of k over the 27 chemicals ranged from 1.00 to 1.82 when the risk is set to 10^{-4}, whereas the value of k ranged from 1.32 to 2.43 when $\varepsilon = 10^{-5}$ and between 1.65 to 3.03 when $\varepsilon = 10^{-6}$ (Tables 1 and 2). If the estimate of k was very sensitive to the choice of the risk at the MRL, then for different choices of ε, you could have widely different choices of k. This in turn would make risk ratios vary greatly as well. Since k is insensitive to the choice of ε, then risk ratios don't change dramatically and the assumption of which ε to use is not critical to the risk ratios.

The pseudo-upper 95% confidence interval risk at the MRL is then derived from the 95% lower bound on the BMD (BMDL) or the upper 95% confidence interval response at the LOAEL. Since the MRL has already built in uncertainty factors to account for human variability and sensitive populations, this pseudo-upper bound risk represents only one type of statistical confidence bound on the estimated risk and does not reflect the broader range of uncertainty linked to a procedure like this one.

One of the reasons a log-linear model is used for cancer risk assessment is that it is believed to be conservative (EPA 2005). For the analysis proposed in this paper, it is possible to compare our upper bound risks to those that would be derived from a linear model. Using a log-linear approach (k=1) and assuming the true risk at the MRL is 10^{-5}, the estimated relative risk due to using a linear model for the sample mixture we used and for the mixtures from Corpus Christi ranged from 3.8 times to 160 times higher than expected (Table 3). The linear model was significantly more conservative than the approach suggested here and could potentially over estimate risks. For the 4 samples from Corpus Christi, our procedure suggested the mixtures posed no risk to the population whereas the linear model suggests the risk might be unacceptable.

The approach presented here allows for the calculation of a combined risk from multiple chemical exposures in a community. In the examples used, the cumulative risks are assumed to be independent. However, in the case of Areas 3 and 4, the chemicals share many of the same metabolic pathways and thus we could have treated them as dose-additive and used equation [29]. However, although the compounds compete for the same substrate enzyme, a physiologically-based pharmacokinetic model of the mixtures in Areas 3 and 4 indicates that the type of interaction is approximately independent when each chemical is under 20 ppm (ATSDR 2004). Thus, in this case, even though dose additivity might have been a better approach, the practical approach outlined for simple independence should work. This may be true of other chemical combinations as well.

The method proposed here is not very sensitive to the choice of the risk at the MRL. When looking at the examples in Table 3, you can see that the increase in risk ratios of the mixtures for the Corpus Christi examples is fairly stable regardless of the risk at the MRL. The relative difference between using 10^{-5} and 10^{-6} for the four areas ranges from about 1.5 to as high as 3.

The approximation to the risk ratio given in Equation [34] leads to a simple method for addressing mixtures that is similar to methods used by several groups, the use of hazard quotients (EPA 1986, 1989b; Mumtaz et al. 1994, 1997; NRC 1989). The hazard quotient is defined as the exposure divided by the MRL, RFC, or RFD (whichever is being used). Thus, for the MRL, this would be HQ=*E/MRL*. Equation [34] is then $(HQ)^k$, the hazard quotient raised to the k^{th} power. In essence, we have derived a revision to the Hazard Quotient that has a bit more generality. The formula we use for the mixture, given as equation [37] is similar to the Hazard Index (the sum of the Hazard Quotients for a mixture), but with the approximate risks in the numerator and the assumed risk at the MRL in the denominator. To put this in context, if k=1 were used for all of the chemicals (as is done by US EPA for genotoxic carcinogens), this would be the sum of the exposures for each component of the

chemical times it's slope value divided by the target risk. The method proposed is generalizing methods already in existence and creating a logical linkage between cancer and non-cancer risk assessment, especially for mixtures.

Different models may give different answers or could potentially be more accurate. We investigated this issue using both the Weibull model and the log-logistic model and assessed the impact of model choice (see Supplemental Table 4). There was virtually no difference in the calculated results between the two models for multiple scenarios. Indeed, it is unlikely that other models would have a dramatic effect in this area of the dose response curve. The procedure uses three points to anchor the model (doses of 0, MRL and BMD and the associated risks). Any smooth functional form that can fit these points exactly will likely yield almost identical results in the range of exposures we are interested in. If the true exposure more than 10-fold above the MRL, then other models might predict different values, but the practical impact of this would not be serious since under all models, the risk would likely be unacceptable.

Finally, because this method actually assigns a risk to an exposure in a community, it would be possible to compare this chemical-derived risk to other risks the community faces. Social, societal and other risk factors, if extant in the community, could confer a far greater risk than a chemical exposure and it may be more effective, from a public health perspective, to address the highest risks first if limited resources are available.

In conclusion, we have modified the HI concept to include nonlinearity. As with using the HI approach, this method is for early tier evaluation of mixtures and should not replace methods that can be supported by mechanistic data on chemicals in the mixture. The approach can be used to calculate risk at or near the MRL derived from a BMD or LOAEL. It can also be applied when the point of departure is the NOAEL, but with some restrictions. The method allows for estimating the probability of an adverse response at any multiple chemical exposure level and, for management purpose, can also provide estimates of the percentage of the population above and below a specified risk level. The concept of "acceptable risk" arises from the awareness that the absolute absence of risk, or absolute safety, is usually an unachievable goal since even very low exposure to toxic substances may confer some risk level. From a risk management viewpoint, the MRL represents the reduction level where exposure could not be completely or cost-effectively eliminated. For risk management decisions, the choice of the risk at the MRL may be based on the site specific conditions, including any remaining uncertainties on the nature and extent of the contamination and associated risks. The procedure can be used to derive risk ratios which are somewhat independent of the risk choice for the MRL. The proposed method unifies cancer and non-cancer risk assessments by expanding upon the linear extrapolation used for cancer risk assessment without the conservative assumption of a linear model. The proposed risk ratios could be a practical tool for risk management of cancer and non-cancer endpoints and could be useful for cost–benefit analyses of pollution control strategies, particularly when there are multiple chemicals involved with exposure doses at or above the MRL or the EPA reference dose/concentration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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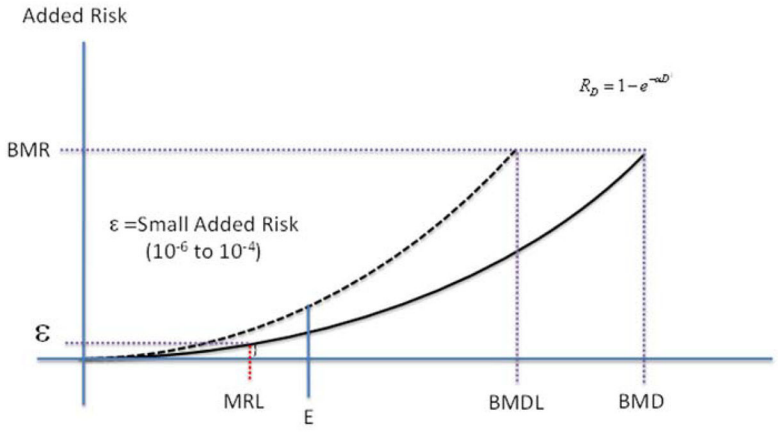

Figure 1.
Graphical representation of the use of a dose-response model to estimate risks between the benchmark dose and the MRL.

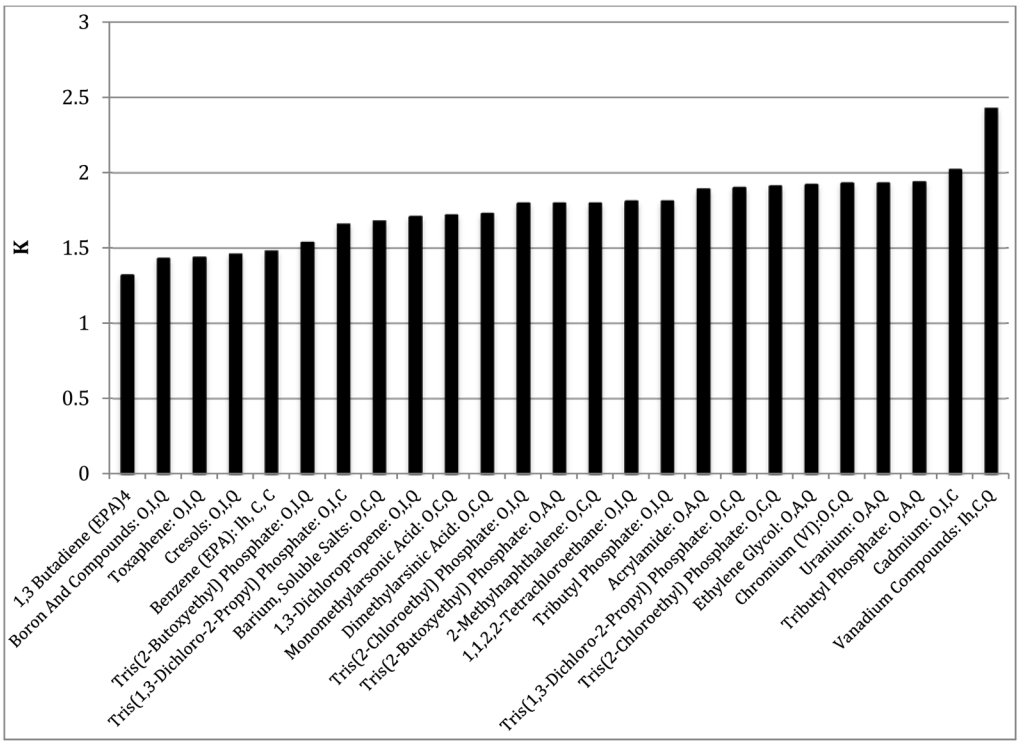

Figure 2.

The values for k from MRLs/RFCs derived from BMDs or LOAELs when the acceptable risk at the MRL is $\varepsilon=10^{-5}$

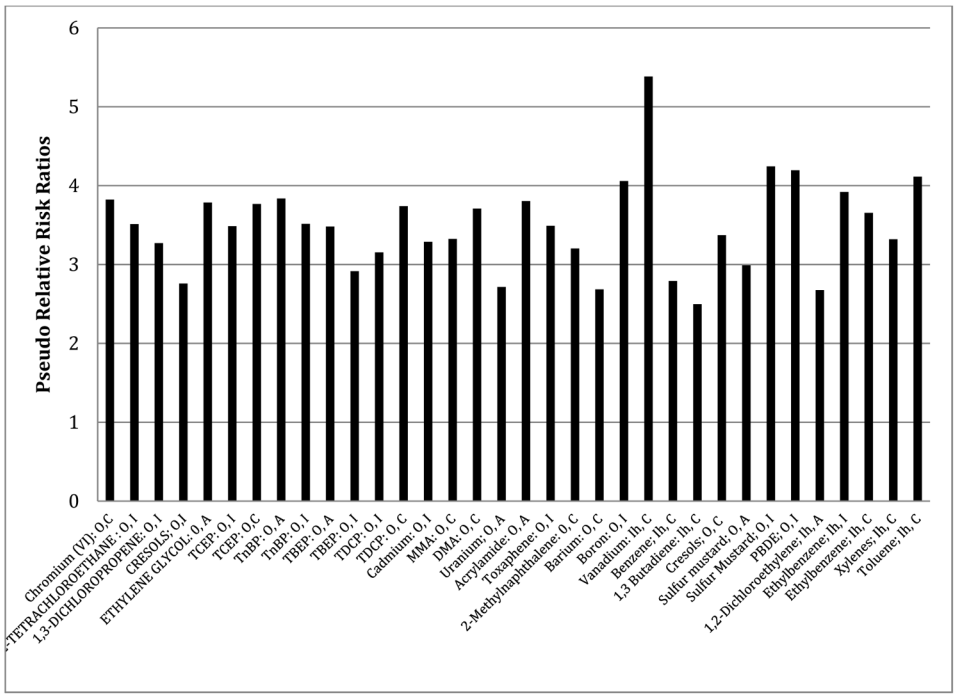

Figure 3.

Risk ratio when exposure is twice MRL using acceptable risk at the MRL equal to $\varepsilon=10^{-5}$.

Table 1

Derived model estimates for chemicals with the MRL derived from benchmark doses when the risk at the MRL is $\epsilon=10^{-5}$

Substance	Type[1]	MRL[2]	BMD[2]	BMDL[2]	UF	BMR	K	Upper Bound Risk $\epsilon=10^{-5}$	α	α_{ub}	α_{ub}/α
Chromium (VI)	O,C,Q	0.001	0.12	0.09	100	0.1	1.93	1.74E−05	6.37E+00	1.11E+01	1.74
1,1,2,2-Tetrachloroethane	O,I,Q	0.5	82.89	53.88	100	0.1	1.81	2.18E−05	3.51E−05	7.67E−05	2.18
1,3-Dichloropropene	O,I,Q	0.04	9.00	3.57	100	0.1	1.71	4.86E−05	2.46E−03	1.19E−02	4.86
Cresols	O,I,Q	0.1	55.89	13.94	100	0.1	1.46	7.64E−05	2.91E−04	2.22E−03	7.64
Ethylene Glycol	O,A,Q	0.8	99.35	75.56	100	0.1	1.92	1.69E−05	1.54E−05	2.60E−05	1.69
Tris(2-Chloroethyl) Phosphate	O,I,Q	0.6	102.44	60.76	100	0.1	1.80	2.56E−05	2.51E−05	6.43E−05	2.56
	O,C,Q	0.3	37.92	25.78	100	0.1	1.91	2.09E−05	1.00E−04	2.10E−04	2.09
Tributyl Phosphate	O,A,Q	1.1	130.32	111.47	100	0.1	1.94	1.35E−05	8.31E−06	1.13E−05	1.35
	O,I,Q	0.02	3.30	1.96	100	0.1	1.81	2.57E−05	1.21E−02	3.11E−02	2.57
Tris(2-Butoxyethyl) Phosphate	O,A,Q	4.8	824.97	477.25	100	0.1	1.70	2.68E−05	5.94E−07	1.59E−06	2.68
	O,I,Q	0.2	80.62	21.92	100	0.1	1.54	7.47E−05	1.20E−04	8.96E−04	7.47
Tris(1,3-Dichloro-2-Propyl) Phosphate	O,I,C	0.05	13.36	4.49	100	0.1	1.66	6.09E−05	1.43E−03	8.74E−03	6.09
	O,C,Q	0.02	2.60	1.94	100	0.1	1.90	1.75E−05	1.71E−02	2.99E−02	1.75
Monomethylarsonic Acid	O,C,Q	0.01	2.09	1.09	100	0.1	1.73	3.09E−05	2.93E−02	9.07E−02	3.09
Dimethylarsinic Acid	O,C,Q	0.02	2.68	1.80	100	0.1	1.89	2.12E−05	1.63E−02	3.47E−02	2.12
Acrylamide	O,A,Q	0.02	2.44	1.78	100	0.1	1.93	1.84E−05	1.89E−02	3.47E−02	1.84
Toxaphene	O,I,Q	0.002	0.34	0.22	100	0.1	1.80	2.19E−05	7.37E−01	1.62E+00	2.19
Uranium	O,A,Q	0.002	0.75	0.20	100	0.05	1.44	6.72E−05	7.76E−02	5.22E−01	6.72
2-Methylnaphthalene	O,C,Q	0.04	6.47	4.30	100	0.05	1.68	1.99E−05	2.23E−03	4.43E−03	1.99
Barium, Soluble Salts	O,C,Q	0.2	80.06	61.13	300	0.05	1.43	1.47E−05	9.92E−05	1.46E−04	1.47
Boron And Compounds	O,I,Q	0.2	13.70	10.30	66	0.05	2.02	1.78E−05	2.59E−04	4.60E−04	1.78
Vanadium Compounds[3]	Ih,C,Q	0.0001	0.0045	0.003	30	0.1	2.43	2.72E−05	5.19E+04	1.41E+05	2.72
Cadmium	O,I,C	0.0005	0.11	0.05	100	0.1	1.72	3.87E−05	3.29E+05	1.27E+04	3.87
Benzene (EPA)	Ih, C, C	0.03	15.6	8.2	300	0.1	1.48	2.59E−05	1.80E−03	4.67E−03	2.58
1,3 Butadiene (EPA) [4]	Ih, C, C	0.0009	1.0	0.88	10	0.0023	1.32	1.18E−05	1.15E−05	1.36E−05	1.18

[1] Entries are route, length of exposure, data where route is oral (O), inhalation (Ih); length is acute (A), intermediate (I), chronic (C); data is quantal (Q), continuous (C).

[2] mg/kg/day.

[3] Exposure entries here are mg/cubic meter.

[4] Exposure entries here are part-per-million (ppm)

Table 2

Derived model estimates for chemicals with the MRL derived from LOAELs when the risk at the MRL is $\varepsilon=10^{-5}$.

Substance	Type[1]	MRL[2]	LOAEL[2]	UF	BMR	Upper Bound BMR	K	Upper Bound Risk @MRL $\varepsilon=10^{-5}$	α	α_{ub}	α_{ub}/α
Cresols	O,C,	0.1	100	1000	0.84	0.94	1.75	1.55E−05	5.68E−04	8.80E−04	1.55
Polybrominated Diphenyl Ethers (PBDEs)	O,I	0.007	2	300	0.70	0.98	2.07	3.44E−05	2.87E−01	9.86E−01	3.44
Sulfur mustard	O,A	$5*10^{-4}$	0.5	1000	0.42	0.61	1.58	1.73E−05	2.99E−05	5.16E−05	1.73
	O,I	$7*10^{-5}$	0.02	300	0.73	0.82	2.09	1.31E−05	2.56E−03	3.35E−03	1.31
1,2-Dichloroethylene[3]	Ih, I	0.2	200	1000	0.17	0.47	1.42	3.43E−05	9.83E−05	3.37E−04	3.43
Ethylbenzene[3]	Ih, I	0.7	200	300	0.50	0.85	1.97	2.70E−05	2.02E−05	5.46E−05	2.70
	Ih, C	0.06	17.45	300	0.33	0.49	1.87	1.66E−05	1.93E−03	3.20E−03	1.66
Toluene[3]	Ih,C	0.08	8.33	100	0.12	0.30	2.04	2.71E−05	1.73E−03	4.69E−03	2.71
Xylenes[3]	Ih,C	0.05	14	300	0.16	0.24	1.73	1.63E−05	1.79E−03	2.91E−03	1.63

[1] Entries are route, length of exposure, data where route is oral (O), inhalation (Ih); length is acute (A), intermediate (I), chronic (C); data is quantal (Q), continuous (C)

[2] Exposures are in mg/kg/day except where otherwise noted in the name of the chemical

[3] Exposures are in parts per million (ppm)

Table 3

Risk ratios (RR) for Weibull model and log-logistic model for a mixture at MRL assuming values of $\epsilon=10^{-4} - 10^{-6}$

Substances[1]	MRL $\epsilon = 10^{-4}$		MRL $\epsilon = 10^{-5}$		MRL $\epsilon = 10^{-6}$		Log-linear risk (k=1)	
	RR (Upper Bound RR)		RR(Upper Bound RR)		RR(Upper Bound RR)		RR (Upper Bound RR) [2]	
	Weibull	Log-Logistic	Weibull	Log-Logistic	Weibull	Log-Logistic	Weibull K=1	Log-Logistic S=1
Mixture Cd, B, TnBP	3.8 (9.2)	3.8 (9.3)	4.5 (15.4)	4.5 (15.6)	5.5 (27.0)	5.5 (27.4)	160 (316)	168 (332)
Area 1	0.06 (0.04)	0.06 (0.09)	0.02 (0.03)	0.02 (0.03)	0.01 (0.01)	0.01 (0.01)	1.0 (1.6)	1.0 (1.7)
Area 2	0.09 (0.08)	0.09 (0.14)	0.03 (0.06)	0.03 (0.06)	0.01 (0.03)	0.01 (0.02)	1.6 (2.7)	1.7 (2.9)
Area 3	0.03 (0.06)	0.03 (0.06)	0.01 (0.02)	0.01 (0.02)	0.003 (0.010)	0.003 (0.010)	1.8 (3.7)	1.9 (4.2)
Area 4	0.14 (0.29)	0.14 (0.28)	0.07 (0.18)	0.07 (0.18)	0.04 (0.12)	0.04 (0.12)	6.5 (13.2)	7.0 (15.0)

[1] Areas 1, 2, 3, and 4 represent four different monitoring stations in Corpus Christi, Texas

[2] relative to a nominal risk at the MRL of 10^{-5}