Case Study Summary:

Practical Guidance on the Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with Trichloroethylene and Other Chemicals.

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1. Provide a few sentences summarizing the method illustrated by the case study. Within the process of chemical risk assessment, risk characterization of non-cancer endpoints lacks an established method to account for the uncertainties associated with a point value estimate of the non-cancer hazard. The lack of an established method to provide quantitative bounds on the uncertainty associated with non-cancer hazard estimates has been a considerable limitation upon effective risk management and decision-making at waste cleanup sites since the implementation of environmental assessment and remediation programs (e.g., CERCLA, RCRA and state cleanup programs) over the past thirty-five years. The National Academy of Sciences (2009; p. 128) discusses the value of presenting hazard ranges for characterizing non-cancer hazards:

"For noncancer end points, it is assumed that homeostatic and defense mechanisms lead to a dose threshold (that is, there is low-dose nonlinearity), below which effects do not occur or are extremely unlikely. For these agents, risk assessments have focused on defining the reference dose (RfD) or reference concentration (RfC), a putative quantity that is "likely to be without an appreciable risk of deleterious effects" (EPA 2002a, p. 4-4). The "hazard quotient" (the ratio of the environmental exposure to the RfD or RfC) and the "hazard index" (HI, the sum of hazard quotients of chemicals to which a person is exposed that affect the same target organ or operate by the same mechanism of action)

(EPA 2000b) are sometimes used as indicators of the likelihood of harm. An HI less than unity is generally understood as being indicative of lack of appreciable risk, and a value over unity indicates some increased risk. The larger the HI, the greater the risk, but the index is not related to the likelihood of adverse effect except in qualitative terms: “the HI cannot be translated to a probability that adverse effects will occur, and is not likely to be proportional to risk” (EPA 2006a). Thus, current RfD-based risk characterizations do not provide information on the fraction of the population adversely affected by a given dose or on any other direct measure of risk (EPA 2000a). That deficiency is present whether the dose is above the RfD (in which case the risk may be treated as nonzero but is not quantified) or below the RfD (in which case the risk can be treated as “unappreciable” or zero even though with some unquantified probability it is not zero). “

The estimate of non-cancer hazard (sometimes referred to as non-cancer risk), is based upon the hazard quotient (for exposures to a single chemical by a single route of exposure) or the hazard index (for aggregate exposures by multiple routes of exposure, or cumulative exposures to multiple

chemicals with the same mode of action or same target organ). The acceptable hazard quotient (HQ) and the acceptable hazard index (HI) are each generally represented as a point value of one (1), at or below which it may be assumed that human receptors (including sensitive subpopulations) are likely to be without appreciable risk of deleterious effects within a lifetime. The HQ is based upon the ratio of an environmental exposure to a toxicological criterion, i.e., the comparison of a concentration in air to a Reference Concentration (RfC), or the comparison of an average daily intake to a Reference Dose (RfD). The RfC and RfD have each been represented as a point estimate; uncertainty and variability are accounted for in the calculation of the point value, but are not numerically expressed as a range of values. Thus, even though the implicit uncertainty in each

noncancer toxicological criterion (i.e., the RfC or RfD) has been defined in the Integrated Risk Information System (IRIS) and elsewhere as having "uncertainty spanning perhaps an order of magnitude", the numerical expression of each criterion remains a point value. Therefore, neither the estimates of non-cancer hazard (i.e., the HQ or HI) nor the toxicological criterion (i.e., the RfC or the RfD) from which it is calculated, have an explicit range of values to account for the uncertainties implicit in their respective derivations.

In contrast, risk management decision-making with respect to the cancer endpoint generally employs a one hundredfold range of acceptable cancer risks (i.e., 10-4 to 10-6), thereby providing risk managers flexibility so that efforts to balance acceptable exposure levels with toxicity study uncertainty, technical feasibility, economic, cultural or other concerns that may affect the selection and implementation of a remedial action are appropriately bounded. The methods presented in this case study were used to develop a range of non-cancer hazards, similar to the range used for the evaluation of the cancer endpoint, when managing waste site cleanups. This range would enable risk managers to have acceptable bounds to quantitatively evaluate non-cancer hazards, based on the implicit uncertainties in the derivation of the RfC or RfD, and the uncertainties associated with the estimation of the exposure concentration or the average daily intake.

The method discussed here established a hazard range by defining floor and ceiling values that define the range and, in addition, a midpoint value within the range. The floor of the hazard range was identified as the RfC/RfD; in the case of an RfC/RfD based on two or more candidate RfC/RfD values, the floor has been identified as the candidate RfC/RfD with the higher(est) confidence. The RfC/RfD is developed using uncertainty factors that are protective based on the observed behaviors of a typical toxicant (Dourson and Stara, 1983; Dourson, et al., 1996), thereby ensuring that the RfC/RfD is an underestimate of the expected value. Therefore, the floor of the hazard range may be denoted as a point below which risk managers are unlikely to recommend remedial action or exposure control.

The ceiling value of the hazard range is defined as the adjusted point of departure (POD) for the determination of the RfC/RfD after appropriate adjustments. The POD is based on the critical concentration/dose (a value directly obtained from the toxicological study), with appropriate adjustments (as appropriate) for the dosing regime in the critical study and toxicokinetic differences between the test organism and the human population in order to determine the human equivalent concentration or dose (HEC or HED). In addition, the ceiling value incorporates the following adjustments to the POD (if not already accounted for in the development of the POD):

 Database quality, dose descriptor and study duration: a factor of three was used as the default correction for each. This was predicated on the average value (based on the research for the underlying database for these factors in general) of any uncertainty factors for database, the Lowest Observed Adverse Effect Level to the No Observed Adverse Effects Level (i.e., LOAEL to NOAEL), and/or duration extrapolation otherwise needed to estimate the RfC/RfD; note that if an average uncertainty factor cannot be obtained from the data, a value of 3-fold (or ½ logarithmic 10) is used as a default (Felter and Dourson, 1998); and Intraspecies variability (sensitive human subpopulations): a factor of 10 is used for human variability.

This adjusted POD is typically based on a value from the critical study, e.g., the NOAEL, LOAEL or a Benchmark Dose (BMD) value extrapolated to a response level below the level of observed response in the study (e.g., BMD05) that is presumed to fall near or below a threshold dose. The adjusted POD may be associated with either potential health effects in sensitive human subpopulations and/or idiosyncratic human responses that are otherwise due to a larger than expected remaining variability for toxicodynamic differences between the test organism and humans, and or human variability in response to toxic insult. The adjusted

POD therefore represents an exposure concentration above which a risk manager would likely be compelled to take measures to reduce exposure.

The midpoint value is a value within the hazard range that is unlikely to be associated with adverse effects in a human population, even though it is higher than the RfC/RfD. Since the RfC/RfD value is derived to systematically and quantitatively account for each source of uncertainty in a generally independent and protective manner, the collective result of applying two or more such adjustments may result in a substantial underestimate of the safe concentration or safe dose. The midpoint value of the RfC/RfD then, is a more plausible estimate of the concentration/dose above the RfC/RfD that is likely to be protective of the general population, including sensitive subpopulations (although it may be associated with idiosyncratic responses in some humans). The determination of the midpoint of the hazard range is based on judgment that considers four aspects of the RfC/RfD: The collective magnitude of the uncertainty factor(s); The steepness of the hazard slope describing the estimated population responses at exposures above the RfC/RfD, or barring this, an estimate of low, medium or high slope based on comparison of the observed NOAEL and LOAEL after consideration of the severity and intensity of the effects observed at the LOAEL; The confidence in the selection of the critical effect; and The confidence in the POD.

Midpoint values associated with a smaller uncertainty factor, a steeper hazard slope, a higher confidence in the critical effect and a higher confidence in the POD are quantitatively closer to the value of their respective RfC/RfD. Conversely, midpoint values associated with a larger uncertainty factor, a shallower hazard slope, a lower confidence in the critical effect and a lower confidence in the POD are quantitatively further from their respective RfC/RfD.

One method, drawn from the ARA's "Beyond Science and Decisions: From Problem Formulation to Dose Response" project, was considered to evaluate the dose-response data for the assessment of three separate non-cancer effects of trichloroethylene (TCE), as presented in EPA's toxicological assessment report (USEPA, 2011a). The method has also been contemplated for three other chemicals (see Appendix); however, the TCE case study is discussed in some additional detail because it presents additional opportunities (in being very data rich and having a detailed analysis). Specifically, the method that was applied was modeling risk above the RfC/RfD using the benchmark dose method; the benchmark dose was the basis of the derivation by EPA of two of the three "candidate RfC" values. For TCE, the process of establishing the non-cancer hazard range was especially challenging, since the numerical value of the RfC was developed from the results of three separate studies (NTP, 1988; Johnson et al., 2003; and Keil et al., 2009), each with its own critical effect (nephropathy in female rats; fetal heart malformations in rats; and decreased thymus weight in female mice, respectively) and "candidate" RfC (3 µg/m3; 2 µg/m3; and 2 µg/m3, respectively). Therefore, a hazard range for the RfC was elucidated in a stepwise manner. First, a hazard range for each of the three studies (i.e., each of the three endpoints) was defined (i.e., endpoint-specific floor, midpoint and ceiling values were established for each of the three studies). Secondly, a hazard range for the RfC was then constructed based upon the independent selection of the most appropriate endpoint-specific floor value, the most appropriate endpoint-specific midpoint value, and the most appropriate endpointspecific ceiling value.

An endpoint-specific floor, midpoint, and ceiling values were identified for each endpoint. For each study, the candidate RfC as proposed by USEPA was selected as the endpoint-specific floor value. The candidate RfC was considered a floor value since each candidate RfC quantitatively incorporated the sum total of adjustments for uncertainty (including HEC, uncertainty factors (UFs) and modifying factors (MFs)). The endpoint-specific ceiling value was the POD from each study (the critical dose [i.e., BMDL01, LOAEL] adjusted for dosing regime and human equivalency [i.e., HEC99]), and other uncertainties as appropriate. The intent is to use this ceiling value as an estimate, without conservatism, of the upper bound to the likely range of the RfC/D. Each endpoint-specific midpoint

value was adjudged from within the endpoint-specific uncertainty range, based on the four factors described above (i.e., magnitude of the uncertainty factors, the steepness of the hazard slope, the confidence in the critical effect and the confidence in the POD).

Based on an evaluation of the endpoint-specific floor, midpoint and ceiling values from each of the three studies (i.e., a matrix of nine values), the TCE non-cancer hazard range was judged to be 3 µg/m3 to 20 µg/m3. The NTP study was used to determine the floor and midpoint values of this hazard range. The controversial results from the Johnson et al. study, while associated with low confidence by many erudite developmental toxicologists, were nevertheless determined to be the most sensitive and used to determine the ceiling level of this hazard range, based on the HEC99 derived from the BMDL01, as performed by EPA from the authors' reported data. This is because the BMDL01 (i.e., the POD from the Johnson et al. study) represents a conservative characterization of any of the PODs for TCE identified on IRIS. The actual NOAEL (if additional dose levels were included in the study) would be expected to be higher than the BMDL01. The hazard range for TCE (3 µg/m3

to 20 µg/m3) was entirely within the wider endpoint-specific uncertainty range associated with the Keil et al. study; therefore, this latter study was considered to be confirmatory.

2. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

Non-cancer hazard is the principal determinant (i.e., "driver") of many risk management decisions, including those chemicals that have been evaluated on the basis of non-cancer endpoints only, and some chemicals that are evaluated on the basis of both the cancer and non-cancer endpoints. This case study

developed from a prior evaluation of TCE, and has since been applied to tetrachloroethylene (perchloroethylene, or PCE), chromium (VI) and arsenic, chemicals for which the non-cancer endpoint is the basis of establishing, or an important consideration in establishing acceptable exposure levels. It is hoped that the methodology may be usefully applied to the evaluation of other chemicals as well.

Previous to the establishment of the RfC for TCE on IRIS by EPA in 2011, most environmental exposures to chemicals evaluated with respect to both cancer and non-cancer endpoints were commonly regulated with cancer risk levels, since non-cancer hazards were negligible compared to cancer risks. With the cancer endpoint as the principal focus, risk managers were able to use an acceptable excess lifetime cancer risk range (i.e., 1 x 10-6 to 1 x 10-4) to determine the appropriate remedial actions (if any) needed at a given site. The RfC for TCE established in 2011 substantially affected risk management of TCE, since both short-term and long-term risk-based clean-up levels are now based on the non-cancer endpoint, particularly when the acceptable cancer risk is appreciably greater than 1 x 10-6 (e.g., an acceptable cancer risk level of 1 x 10-5 has been established in several states, including Indiana, Michigan, Texas and Ohio). Thus, the non-cancer endpoint often becomes the driver when any chemical is evaluated with respect to both non-cancer and cancer endpoints. Similar issues apply to other chemicals, which have not been determined to be carcinogenic or potentially carcinogenic, and are therefore evaluated on the basis of the non-cancer endpoint only.

In the implementation of environmental assessment and remediation programs over the past 35 years, the focus has largely been on the characterization of excess lifetime cancer risks. Historically, when a chemical has been evaluated with respect to both the cancer and non-cancer endpoints, cancer risk has generally been the driver and thus has been the primary concern of most risk managers. Consequently, risk managers have had more experience in estimating, balancing and communicating the uncertainties associated with cancer risk than they have had with the uncertainties associated with non-cancer hazard. Some

risk managers may not be aware that they have any flexibility at all when implementing risk management decisions based on point estimates of non-cancer hazard.

Consequently, in those circumstances where non-cancer is the driving endpoint, risk managers generally have limited resources (in terms of experience, precedent or guidance) in the interpretation and communication of the hazards posed at environmental exposures above the

RfC/RfD, or hazard quotient values above a hazard quotient of one. The challenges of interpreting and communicating hazards at exposures above the RfC/RfD and/or a HQ of one have become even more daunting, given that USEPA now supports a number of RfC or RfD determinations based on multiple critical studies. Consequently, many factors (i.e., multiple critical effects, methods of dose adjustment and human equivalency, levels of confidence and points of departure) are incorporated into a single RfC/RfD point value. The subject of this case study (i.e., the RfC for TCE) is one such example.

Thus, the problem formulated here is to address the need for a methodology so that risk management decisions based on the non-cancer endpoint may be predicated upon a range of acceptable exposure levels. To date, relatively few hazard ranges have been developed for characterizing non-cancer effects primarily because the evaluation of non-cancer hazards has been predicated upon the determination of a “safe dose” below which no toxic effect is expected, rather than upon an acceptable (if non-zero) probability that a non-cancer-causing event may occur. The NAS (2009) report has discussed the value of presenting hazard ranges for characterizing non-cancer hazards (see Section 1, above) .

3. Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.

The development of the hazard range is a generalizable approach, as shown in Table 1 of the appendix to this case study summary, for the RfC or RfD value of each of three additional chemicals from IRIS. In general:

 The individual RfC/RfD (or candidate RfC/RfD, in the event an RfC/RfD value is based upon two or more candidate values) is used as the floor of the hazard range. This is considered reasonable from a practical point of view, because risk managers are unlikely to take action below these values due to the protective nature implicit in the RfC/RfD. A midpoint is uniquely developed for each RfC/RfD balancing four considerations: 1) the magnitude of the uncertainty factor(s) applied to calculate the candidate RfC; 2) the steepness of the slope of the concentration-response relationship at concentrations above the candidate RfC; 3) the confidence in the choice of the critical effect; and 4) the confidence in the POD. The ceiling value was defined as the POD for each candidate RfC/RfD, a value based upon critical concentration/dose from the critical study (e.g., experimental study, epidemiological study) with suitable adjustments (as appropriate) for toxicokinetic differences between experimental animals and humans (if the critical dose is from an experimental study) and other remaining uncertainties associated with the underlying database. The NAS (2009) report suggested that methods for assessing non-cancer toxicity have the capability of determining hazard ranges. Work previously presented in an Alliance for Risk Assessment (ARA) “Beyond Science and Decisions: from Problem Formulation to Dose Response” workshop identified several case studies which attempt to do this. Of those

methods, one was used in the TCE case study and for three additional chemicals, i.e., modeling risk above the RfC/RfD using the benchmark dose method (Gentry et al., 2011).

Modeling risk above the RfC/RfD using the benchmark dose. This method supports development of the hazard range informed by the steepness of the slope of the response above the RfC, and providing the basis for the POD used as the ceiling of the hazard range. The method is generally applicable for chemicals with data sets that can be used with the BMD methodology, and where information is available to relate internal doses to external concentrations. The originally-published method relied on dose-response information in humans, though the authors note that physiologically-based pharmacokinetic (PBPK) models are available to estimate external concentrations associated with internal biomarkers (Gentry et al., 2011). In the TCE case study, USEPA's determination of benchmark dose (BMD) and the lower 95% confidence interval on the benchmark dose (BMDL) were the basis for two critical endpoints (i.e., fetal cardiac malformations and nephrotoxicity). In each of these two cases, the BMD/BMDL values were considered to correspond to the median human equivalent concentration or the HEC50 (USEPA, 2011a). In each case, the POD was the HEC99, i.e., the value for which the HEC will not be smaller for 99% of the modeled human population (thus conservatively accounting for human variability).

4. Discuss the overall strengths and weaknesses of the method.

The strength in the proposed methodology is that it provides essential information risk managers need in order to understand the risk associated with exposures above the RfC/RfD, to communicate the meaning of a risk-based screening level, and to provide flexibility for some level of "balancing" in exposure level risk management decisions. It also provides risk managers with technical support to convey the unlikelihood of risk of health effects at a range of background concentrations that may be encountered, given Appendix C

summarized in USEPA (2011b). The methodology will provide risk managers with a defined, numerical hazard range, based on the uncertainties associated with the derivation of the RfC or RfD for each of the supporting studies.

The range as defined by floor, midpoint and ceiling values is selected based on relevant descriptors, including type and magnitude of the uncertainty factors, steepness of the dose-response curve, confidence in the critical effect, and confidence in the POD. The hazard range and its component values are valuable decision tools and enable the risk manager to make more informed decisions regarding exposures above the RfC or RfD, and to effectively communicate the hazards associated with those exposures.

An RfC/RfD based upon a clearly-defined adverse effect from a high confidence study is likely to be associated with a narrow hazard range. Conversely, an RfC/RfD derived on the basis of multiple studies, with varying degrees of confidence and methods of dose adjustment, may be expected to have a relatively broad hazard range. The hazard range may be evaluated in conjunction with the uncertainty associated with site-specific exposure assessments (i.e., determination of the exposure concentration/dose that is compared to the RfC/RfD) and other site considerations to make informed and reasoned risk management decisions.

A weakness of the proposed methodology is that estimation of the midpoint of the range is based on an overall scientific judgment of the four factors (i.e., magnitude of the uncertainty factor(s); the steepness of the hazard slope describing the estimated population responses at exposures above the RfC/RfD; the confidence in the selection of the critical effect; and the confidence in the

POD). Because peer-reviewed criteria have not yet been developed to consistently judge those factors, considerable professional judgment is needed, with the potential for substantial variability across assessments. The Panel's help in refining and standardizing the criteria is sought. 5. Outline the minimum data requirements and describe the types of data sets that are needed.

The development of the proposed hazard range methodology relies upon the information provided in the derivation of the RfC/RfD itself. This information includes the identified critical study(ies), the identified critical effect(s), the selected point(s) of departure, the calculation of human equivalent concentration, the magnitude and type of uncertainty factors, and the identified levels of confidence in the critical study, the supporting database and the derivation of the RfC/RfD. This methodology may also require a critical review of each critical study, particularly with respect to assigning confidence levels to the selection of the critical effect and the POD.

Does your case study: A. Describe the dose-response relationship in the dose range relevant to human exposure? The RfC for TCE as developed by USEPA (i.e., 2 μg/m3), as well as the range of concentrations associated with the proposed hazard range (i.e., 3 μg/m3 to 20 μg/m3), are within the ranges of concentrations that have been encountered in ambient air and in indoor air at contaminated sites (see Appendix C of USEPA, 2011b). The overlap between the ambient concentrations and the RfC was an impetus to the development of the proposed hazard range for TCE in this case study. B. Address human variability and sensitive populations? The proposed method relies on the existing EPA guidance for RfC/RfD to address sensitive populations. In the case of TCE, human variability and sensitive populations were addressed during development of the candidate RfC/RfDs by the use of the following: 1) a POD based on human equivalent concentration-99 (HEC99, a value that the HEC is not expected to exceed in 99% of the population) from each of two studies, i.e., the NTP (1988) and Johnson et al. (2003) studies; 2) the selection of the BMDL05 (the 95% lower confidence limit on the predicted response in 5% of the population) as the critical dose from the NTP (1988) study, and the selection of the BMDL01 (the 95% lower confidence

limit on the predicted response in 1% of the population) as the critical dose in the Johnson et al. (2003) study; 3) the application of uncertainty factor for the toxicodynamics of sensitive human subpopulations (UF = 3) separately applied to the POD for each of the three studies. Therefore, human sensitivity and sensitive subpopulations have been quantitatively considered in the derivation of the RfC for TCE and the hazard range developed from it. C. Address background exposures or responses?

While background exposures are not specifically addressed in this method,this method is useful in cases to clarify the exposure risk whenever where background levels are close to, or inside the range. For example, for TCE, given that background (at 95th%) exposures of TCE may range from 0.56–3.3 µg/m3 (EPA, 2011b), having risk managers explain that in recent decades, household background ranges (95th%) of up to 3.3 µg/m3 (for 1995-2004; see Appendix C of EPA 2011b) do not constitute exceedances of the reference concentration such that health effects were likely. Higher background exposures (ranging from 2.8-15 µg/m3 at 95th% for 1981-1994; see Appendix C of EPA 2011b) in past decades are also unlikely to have resulted in health effects.

D. Address incorporation of existing biological understanding of the likely mode of action? Existing biological information is considered in assessing confidence in the critical endpoint for a candidate RfD or RfC and in the proposed hazard range methodology. In the case study for TCE, this was a significant consideration in evaluating the fetal cardiac malformation endpoint for TCE, as assessed using the study data in Johnson et al. (2003).

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation? The proposed method relies on the existing EPA guidance for RfD/C to address other extrapolations. Specifically, the

application of an uncertainty factor for toxicodynamic differences between rodents and humans (UF = 3) was applied to the POD for all three studies (NTP, 1988; Johnson et al., 2003; and Keil et al., 2009). An additional uncertainty factor was applied to account for the POD based on a LOAEL from the Keil et al. (2009) study (UF = 3 to extrapolate the LOAEL to a NOAEL; note here the use of an intermediate value of 3 rather than the default value of 10 to more appropriately estimate the upper limit of the RfC). The use of other uncertainty factors and equivalent dose/concentration modeling by PBPK was discussed in the response to Question B, above. F. Address uncertainty? The strength in this methodology is that it provides risk managers with an understanding of the uncertainty range within which toxicologists are unable to distinguish the absence of health risk. This allows the risk manager to make risk management decisions with respect to the non-cancer endpoint for inhalation/oral exposures by considering not only the RfC/RfD value, but the hazard range adapted from it. Thus, the method provides risk managers with a practical method to account for the implicit uncertainty in each RfC/RfD value, thereby acknowledging the IRIS Glossary definition that the RfC/RfD value includes “uncertainty spanning perhaps an order of magnitude”.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population? The proposed hazard range methodology is consistent with the established convention for the estimation of non-cancer hazard. Therefore, as stated by NAS (2009) in the excerpt quoted in Section 1 above, “the current RfD-based risk characterizations do not provide information on

the fraction of the population adversely affected by a given dose or on any other direct measure of risk.” The RfC/RfD, therefore, is the conservative estimate of the threshold dose below which human exposures may be associated with the absence of risk, and above which a risk may considered to be plausible. The proposed methodology provides a means for quantifying the range of values that

may represent the threshold dose or threshold concentration in the human population, given the uncertainty implicit in the derivation of the RfC/RfD. It may be assumed that an exposure above the ceiling value (i.e., the adjusted POD) of a chemical represents a greater likelihood of an adverse effect in a population than an exposure above its respective floor value (i.e., the RfC/RfD). However, a dose-response curve indicating the probability of an adverse effect should not be inferred within the hazard range as defined by the floor and ceiling values.

H. Work practically? If the method still requires development, how close is it to practical implementation? The proposed methodology for development of a hazard range may be implemented practically for various chemicals provided that information regarding derivation of the RfC/RfD needed to implement the methodology (e.g., adequate information regarding critical studies, critical effects, confidence levels, selection of the POD, and quantitative methods used to account for variability and uncertainty) are available. Additional methods development would be valuable to better define criteria for the four factors and how they weigh into the ultimate determination of the mid-point value. The choice of average values for the UFs is another area that may benefit from additional development.

The proposed method is practicable. However, successful implementation of this methodology requires that regulatory agencies and risk managers understand the proposed methodology, determine that it is compatible with existing regulations and policies, and initiate changes to customary practices. Thus, a lack of regulatory acceptance would impose a substantial impediment to the effective implementation of this methodology.

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