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# Managing risks of noncancer health effects at hazardous waste sites: A case study using the Reference Concentration (RfC) of trichloroethylene (TCE)

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ABSTRACT

A method for determining a safety range for non-cancer risks is proposed, similar in concept to the range used for cancer in the management of waste sites. This safety range brings transparency to the chemical specific Reference Dose or Concentration by replacing their "order of magnitude" definitions with a scientifically-based range. EPA's multiple RfCs for trichloroethylene (TCE) were evaluated as a case study. For TCE, a multi-endpoint safety range was judged to be 3 μg/m$^3$ to 30 μg/m,$^3$ based on a review of kidney effects found in NTP (1988), thymus effects found in Keil et al. (2009) and cardiac effects found in the Johnson et al. (2003) study. This multi-endpoint safety range is derived from studies for which the appropriate averaging time corresponds to different exposure durations, and, therefore, can be applied to both long- and short-term exposures with appropriate consideration of exposure averaging times. For shorter-term exposures, averaging time should be based on the time of cardiac development in humans during fetal growth, an average of approximately 20–25 days.


## 1. Introduction

Risk managers responsible for making choices about acceptable oral and inhalation chemical exposures at hazardous waste sites[1] have typically focused first on concerns about cancer. As risk managers became increasingly familiar with how to effectively manage these cancer risks, it became routine to make screening and closure decisions using the widely accepted 100-fold upper-bound, excess, lifetime, cancer risk range of $10^{-4}$ to $10^{-6}$ (U.S. Environmental Protection Agency (EPA), 1991a). This range allowed managers the flexibility needed to address the risk at waste sites that differed with respect to environmental setting, history, and current and future uses, based on the needs of the community.

Risk managers have also always considered non-cancer health effects in this process, but such effects often did not drive management decisions, or when they did, the evaluation lacked a corresponding non-cancer risk range. For example, risk managers generally applied a Hazard Quotient (HQ) of 1 as the criterion for a

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[1] Waste sites throughout the United States are often managed using risk assessment information and methods from the U.S. Environmental Protection Agency (EPA). Risk-based, medium-specific concentrations such as Regional Screening Levels (RSLs) (formerly known as risk-based concentrations (RBCs) or preliminary remediation goals (PRGs)) have been derived using these EPA methods (EPA, 1989, 1991b, 2004, 2009, 2012a) and have been widely used in the assessment and management of site-related risks from environmental sources.

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non-cancer effect, rather than applying a range of acceptable HQ values.[2] The HQ concept is used by various agencies, each using its allowable health protective level as the denominator in the equation (for examples of these levels please see: http://toxnet.nlm.nih.gov/newtoxnet/iter.htm). Although EPA (Barnes and Dourson, 1988; EPA, 1994, 2002) and others such as Felter and Dourson (1998) have shown that the information underlying the HQ, that is, the Reference Dose (RfD) or Reference Concentration (RfC) [collectively referred to here as the RfD(C)], possesses "uncertainty spanning perhaps an order of magnitude," risk managers have generally not implemented decisions based upon this stated uncertainty. Consequently, non-cancer hazards have frequently been evaluated and regulated as if a bright line existed when exposures were at, or very near, the RfD or RfC, *i.e.*, where the hazard quotient of one (1) or less was interpreted as without risk, and values greater than 1 were associated with some unspecified, unacceptable risk.

It can be easily argued that the phrase in the definition of an RfD(C) "with uncertainty spanning perhaps an order of magnitude" is precautionary. This is because the RfD(C) derivation process contains several uncertainties, and the application of a factor for each of these uncertainties provides a margin of safety based on the behavior of the "average" chemical (Dourson and Stara, 1983; Dourson et al., 1996). Since most determinations of the RfD(C) have more than one source of uncertainty, and consequently exhibit multiple successive precautionary adjustments (*i.e.*, the application of multiple uncertainty factors), this implicit margin of safety increases as the overall uncertainty factor gets larger, as does the implicit protectiveness of the resulting RfD(C), as demonstrated theoretically by Swartout et al. (1998).

Since their origin by Barnes and Dourson (1988) and EPA (1994), RfDs and RfCs have increasingly been based upon more sophisticated data, algorithms and models (*e.g.*, Renwick, 1991, 1993; Renwick and Walker, 1993; Jarabek, 1995a, 1995b; Dourson et al., 1996; Guth et al., 1997; Kalberlah and Schneider, 1998; Meek et al., 2001; Haber et al., 2001, 2002; Dourson and Younes, 2002; EPA, 2002; Dourson and Patterson, 2003; IPCS, 2005; Seed et al., 2005; Dourson and Parker, 2007; Gentry et al., 2003; EPA, 2012b; Meek et al., 2014; Dourson et al., 2013). This increased sophistication has defined internal concentrations from exposure dosing, accounted for toxicokinetic differences between the test animal and human populations, characterized route-to-route internal dose extrapolations, and interpolated effects levels between the LOAEL and NOAEL in the experimental study, among others. These probability-based elements fundamentally change the RfD(C) development process and necessitate a clearer understanding of risk in practical application. These changes require the user to go beyond the bright line decision process currently employed. Expert bodies are also urging such movement (NAS, 2009, 2014; EPA, 2014). For example,

> "EPA should clearly present two dose-response estimates: a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived. The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value." And further on: "EPA should develop IRIS-specific guidelines to frame uncertainty analysis and uncertainty communication. Moreover, uncertainty analysis should become an integral component of the IRIS process" (NAS, 2014; page 130).

In addition, risk managers must now contend with situations where risk management decisions at sites may be driven by non-cancer endpoints, even when the cancer endpoint has also been quantitatively defined for a given chemical. For example, the RfD and RfC values for trichloroethylene (TCE) have been revised to lower levels, suggesting greater toxicity than before (EPA, 2011), whereas the available cancer risk-specific doses have increased slightly, suggesting less cancer risk. Therefore, in any given exposure setting, the resulting HQ for the non-cancer endpoints for TCE is correspondingly increased (*i.e.*, indicative of greater toxicity). As a result, these lower RfD and RfC values are now within the $10^{-4}$ to $10^{-6}$ range of risk-specific doses or risk-specific concentrations associated with the cancer endpoint. Consequently, risk managers may encounter unfamiliar challenges in making effective risk management decisions at sites with TCE contamination, in part because the non-cancer endpoint does not have an associated risk range.

These challenges to effective risk management are not simply academic. For example, TCE exhibits significant toxicity from both oral and inhalation exposures, and is frequently encountered at contaminated sites (ATSDR, 2015). Moreover, TCE has been reported as part of "background" conditions in about half the residential structures in the United States (Dawson and McAlary, 2009), with higher background concentrations approaching the range of EPA's RfCs. For TCE specifically, risk managers are thus confronted with twin challenges: (1) the discernment of TCE concentrations that are attributable to environmental (subsurface) contamination from TCE concentrations from those that are associated with confounding, background sources and (2) determining a remedial objective resulting in acceptable indoor air concentrations of TCE. The multiple variables affecting potential and actual human exposures to TCE are relevant and important to risk managers, and these variables amplify the need for a clearer understanding of the non-cancer hazards associated with environmental concentrations above the RfD or RfC, represented by HQ values greater than 1.

In part because of these concerns, the Alliance for Risk Assessment (*ARA*) was petitioned to form a coalition to develop guidance to facilitate effective risk management decisions at TCE-contaminated sites. Several open meetings and deliberations were held in 2012 and 2013; these efforts culminated in a guidance document posted at http://allianceforrisk.org/guidance-for-contaminated-sites/. The analysis presented herein is based in part on this work. Specifically, this paper proposes a process to determine a range that is consistent with the uncertainty in the RfD or RfC, and that is similar in concept to the acceptable risk range of $10^{-6}$ to $10^{-4}$ for upper-bound, excess, lifetime, cancer effects. This "safety range" would allow managers to have comparable flexibility in the management and/or regulatory closure of waste sites, particularly where the evaluation of non-cancer effects drives the risk assessment. The evaluation of the non-cancer effects associated with TCE is used as an example to illustrate the determination of this safety range and its subsequent application in risk management due its prevalence at waste sites. The choice of TCE is particularly relevant because of its overlapping exposure concentrations associated with its cancer and non-cancer effects, and the uncertainties associated with its confounding background sources resulting in exposure concentrations near the RfC.

## 2. Methods

The information used to evaluate the TCE risk assessment values

[2] For ingestion exposures, the hazard quotient (HQ) is the ratio of an average daily dose to the Reference Dose (RfD). For inhalation exposures, the HQ is the ratio of the exposure concentration of a substance (EC) to its Reference Concentration (RfC). The HQ associated with acceptable exposures is generally one (1), with a precision of one significant figure (*i.e.*, an implicit HQ range of 0.95–1.5).

were taken directly from EPA's Integrated Risk Information System (IRIS) report (2011). EPA identified three candidate RfC values for non-cancer inhalation toxicity. These three candidates are described briefly as:

- a candidate RfC of 3 μg/m$^3$, based on toxic nephropathy in female rats (NTP, 1988);
- a candidate RfC of 2 μg/m$^3$ based on decreased thymus weight in female mice (Keil et al., 2009);
- a candidate RfC of 2 μg/m$^3$ based on fetal heart malformations in rats (Johnson et al., 2003); however, at least one letter to the editor and 2 errata have been published clarifying errors in the original report (Anonymous, 2005; Hardin et al., 2004; Johnson et al., 2004); findings from five studies conducted from 1989 to 1995 (US EPA, 2011) using a novel dissection method, and have not been confirmed using guideline compliant, GLP methods.

Each of the candidate RfC values may be evaluated with respect to its underlying uncertainty, including the precision and the safety inherent in its derivation.

The safety range for each candidate RfC was built from the actual definition of the RfD(C) as having "uncertainty spanning perhaps an order of magnitude." We evaluated each of the candidate RfC values with respect to its underlying uncertainty, including the precision and the safety inherent in its development by focusing on the word "perhaps" by Barnes and Dourson (1988). This word was used in the definition because of the variation in the underlying toxicity databases of different chemicals (as per author Dourson). For example, a chemical database may have sufficient information in humans and experimental animals so that the resulting RfD(C) can be developed with a one-fold or three-fold uncertainty factor. Uncertainty in such an RfD(C) is smaller, that is, perhaps *less than* an order of magnitude. In other cases, fewer data are available so that the resulting RfD(C) is developed with an aggregate uncertainty factor of 1000 or more. Uncertainty in these RfD(C) values is greater, that is, perhaps *more than* an order of magnitude.

The uncertainty in each RfD(C) value includes its inherent precision and safety. Precision refers to the repeatability of the overall process. What this means for a RfD(C) is how close a second RfD(C), estimated for the same chemical given the same information, would be if developed by a different expert or expert group. In such cases, the precision might be best characterized as perhaps threefold on either side of the RfD(C) (Felter and Dourson, 1998; EPA, 2002), although this could be less than or greater than a threefold margin, as described above.

Within the uncertainty of each RfD(C), the concept of safety refers to the determination of its degree of protectiveness. This degree of protectiveness is expected to vary, because a RfD(C) is developed using one or more uncertainty factors, each of which is protective based on the observed behavior of the "average" chemical (Dourson and Stara, 1983; Dourson et al., 1996). This protectiveness provides assurance that any RfD(C) is an underestimate of the expected value of the actual safe dose, *i.e.*, the No Observed Adverse Effect Level (NOAEL) for a sensitive human subpopulation.[3] Furthermore, the use of multiple uncertainty factors results in even more protective RfD(C) values as theoretically demonstrated by Swartout et al. (1998). Because of this, the portion of the uncertainty in an RfD(C) associated with safety is best characterized as a range *above* the RfD(C), where the latter is considered as the floor to this safety range, *i.e.,* the RfD(C) is the lowest value within the range (Dourson and Stara, 1983; Felter and Dourson, 1998).[4]

Based on this understanding of precision and safety within an "order of magnitude," we then developed a range associated with each of the candidate RfCs for TCE. This range was developed with a floor, a ceiling and an intermediate value, and because each of these RfCs was based on different data, the ranges were anticipated to be somewhat different. As further described in ARA (2013), criteria chosen to reflect the judgment of this range included:

- overall confidence in the RfC as demonstrated by the size of the overall uncertainty factor;
- determination of the steepness of the dose response slope for the specified effect (Summary from ARA. 2013);
- confidence in the determination of the critical effect; and
- confidence in the determination of the point of departure (POD).

Furthermore, since risk managers might wish to see an overall safety range based on all three RfCs, we determined a "Multiple-endpoint range of safety" through an integration of the above four criteria for each of the three RfCs using professional judgment. Finally, the overall safety range was compared to three hypothetical TCE exposure scenarios to show how such a range might be used at a waste site.

## 3. Results

### 3.1. Defining the uncertainty range in the TCE RfCs

As described in Methods, the precision of each of the candidate RfCs may be considered as a uniform or equal distribution around the RfC (*i.e.*, the RfC is the central value of the distribution). This precision would be expected to vary among the RfD or RfC values for different chemical substances, and among the three different candidate RfC values. This is because the individual and aggregate uncertainty factors are unique to each risk value, and because the judgment of the critical effect for a chemical substance is not always straightforward. Thus, a second expert group might develop a different value given the same information.

TCE itself exemplifies this variation in precision. Depending on the choice of critical effect and uncertainty factor, EPA (2011) judged RfCs to be either 2 μg/m$^3$ for the two candidate RfCs based on either Keil et al. (2009) and Johnson et al. (2003),[5] or to be 3 μg/m$^3$ for the candidate RfC based on NTP (1988). The precision of any one of these candidate RfC values can be determined by comparison to any second one. Depending on which TCE RfC is developed first, this precision is either 30% lower or 50% higher.

[3] This follows directly from the definition of the RfD or RfC, and is reflected in several examples on EPA's Integrated Risk Information System (IRIS) where NOAEL values for a sensitive human subpopulation have been used as the basis of an RfD with an aggregate uncertainty factor of 1.

[4] For example, see Dourson and Stara (1983), which states, "A possible modification to the standard approach would be to present a range for the ADI rather than one value. The range could be based at the high end on the average reductions in dose needed to estimate the ADI (from Figs. I and 3) and the body-surface area ratio (Fig. 2), and at the low end on the standard 10-fold reductions." (p. 234). The ADI is the acceptable daily intake, a parameter that is similar or equivalent to the RfD, both of which are usually represented in units of milligram per kilogram body weight per day (mg/kg-d). This recommendation is similar to that suggested by NAS (2014, *vide supra*).

[5] Please note that the use of the Johnson et al. (2003) study is for demonstration purposes only. During the course of this study, it became apparent that EPA's use of cardiac anomalies for developing an RfC is highly controversial and not universally shared among government agencies and expert bodies (see supplemental materials, ARA, 2013, section 2). It may be that an analysis of this specific effect is warranted by appropriate experts, but at the very least risk managers need to understand that this endpoint cannot, by itself, be used with confidence to form the basis of any quantitative hazard estimate.

**Table 1**
Different safety ranges for candidate TCE RfCs. All values are in μg/m$^3$. Shaded areas indicate best overall safety range for risk management purposes. See ARA (2013) for additional discussion as described in supplemental materials.

| Study | IRIS UF[a] | Steep Slope[b] | Confidence | | Safety ranges | | |
|---|---|---|---|---|---|---|---|
| | | | Critical Effect[c] | Point of Departure[d] | Floor | Intermediate | Ceiling |
| Johnson et al. (2003) | 10 | Lower | Low | Low | 2 | 10 | 20 |
| NTP (1988) | 10 | Higher | Medium | Medium to Low | 3 | 9 | 30 |
| Keil et al., 2009 | 100 | NA | Medium | Medium to Low | 2 | 20 | 63 |

NA=Not available.
[a] Size of the uncertainty factor as on IRIS.
[b] Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per ARA (2013)
[c] Confidence in the choice of critical effect as per ARA (2013) and text.
[d] Confidence in the point of departure as per ARA (2013) and text.

In contrast to precision, the safety in each of the three candidate RfC values for TCE is associated with a unique range of values that is expected to lie above each candidate RfC, because choices made at each step in the process of its derivation incorporate a margin of safety. These choices include judgments of critical effects of differing severity, the use of an effect that may not relate to humans, the use of a lower limit on the benchmark dose (BMD), and/or the use of a 10-fold default uncertainty factor *in lieu* of data suggesting that a smaller uncertainty factor may be more appropriate. The range of safety may not be the same among these candidate RfC values because each was developed using a different critical effect, POD and aggregate uncertainty factor.

For risk management decisions, the range of safety associated with each RfD or RfC is generally more important than the respective range of precision. This is because risk managers are interested in making decisions that are protective of public health and it is an understanding of the range of safety in each RfD or RfC that is generally more informative. With this risk management mindset, we determined a unique safety range associated with each candidate RfC for TCE as follows.

For each candidate RfC, the safety range is defined by a floor value based upon the actual candidate RfC point value, as described on IRIS. This choice of the individual candidate RfC as the floor of the range for each non-cancer endpoint is reasonable from a practical point of view, because managers are unlikely to take regulatory action at or below these values, due to the protective nature implicit in the derivation of each candidate RfC, as described above. However, using the RfD or RfC as the floor to a range in its value also has theoretical support where it is shown that uncertainty factors are protective based on the behavior of the average chemical (see Methods). These floor values for each endpoint-specific safety range are shown in Table 1.

For each candidate RfC, the safety range is also defined by a ceiling value based upon the POD for each candidate RfC, as described on IRIS. This ceiling value is then further adjusted downward, if needed, to reflect the known toxicokinetic differences between the test organism and the human population in order to determine the human equivalent concentration, and/or known uncertainties in the overall database, such as the lack of NOAEL, a study of insufficient duration, or the lack of a study investigating important endpoints. These reductions are based on available data, or a default factor of three as per EPA (2002). The intent of these reductions, if needed, is to estimate the likely human equivalent NOAEL from a chronic experimental animal study (or other study duration, if appropriate for the endpoint).

Specifically, the unadjusted ceiling value for each candidate RfC's safety range is the POD of 20 μg/m$^3$ for cardiac effects from the controversial Johnson et al. (2003) study, of 30 μg/m$^3$ for kidney effects from NTP (1988), and of 190 μg/m$^3$ for immune effects from the Keil et al. (2009). No adjustments were needed to the first two PODs because both of them represent the human equivalent NOAEL for the duration of interest; however, an adjustment to the final POD from Keil et al. (2009) was considered necessary because it was based on a LOAEL, rather than a NOAEL. The adjusted POD was 63 μg/m$^3$ found by reducing the LOAEL of 190 μg/m$^3$ by an uncertainty factor of three. The use of three-fold uncertainty factor represents the midpoint of the uncertainty factor of 10 for use of a LOAEL. Each of these ceiling values is reasonable from a practical point of view, because risk managers are likely to take regulatory action at or above these values due to the fact that specific toxic effects can sometimes be associated, or be anticipated, with them. These ceiling values for each endpoint-specific safety range are also shown in Table 1.

Because the range between the floor and ceiling varies for each RfC, we also developed an intermediate value within each safety range. This intermediate value might enable risk managers to gauge whether to take regulatory action when exposures fall within the range. The determination of the intermediate value of the safety range for each RfD or RfC may encompass many attributes. As a start, we mesh four considerations:

- size of the total uncertainty factor on EPA's IRIS as a crude measure of the overall uncertainty in the database;
- steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC, see supplemental materials, ARA, 2013, section 3);
- confidence[6] in the choices of critical effect; and
- confidence in the POD.

The intermediate values of those safety ranges that are closer to their respective candidate RfC (*i.e.,* floor value) are generally associated with a smaller aggregate uncertainty factor, a steeper hazard slope, a higher confidence in the critical effect, and a higher confidence in the POD. The intermediate values of those safety ranges that are further from their respective RfC (*i.e.*, floor value) are generally associated with a larger aggregate uncertainty factor, a shallower hazard slope, a lower confidence in the critical effect, and a lower confidence in the POD.

For the controversial fetal malformation endpoint based on Johnson et al. (2003), we judged the intermediate value of the endpoint-specific uncertainty range to be 10 μg/m$^3$, or five-fold above its respective candidate RfC. This is due to its small aggregate uncertainty factor of 10 (which argues for a value closer to the candidate RfC), shallower hazard slope (which argues for a value

[6] Our judgment of confidence follows the EPA practice of defining low confidence as the likelihood of new data changing the critical effect, point of departure, and/or uncertainty factor (greater likelihood = lower confidence) (Dourson, personal experience as RfD(C) Work Group Co-Chair 1986 to 1994).

farther from the candidate RfC), low confidence[7] in the critical effect (which argues for a value farther from the candidate RfC), and low confidence in the choice of a benchmark response of 1% (which argues for a value farther from the candidate RfC). See also supplemental materials.

For the toxic nephropathy endpoint based on the NTP (1988) study, we judged the intermediate value of the endpoint-specific uncertainty range to be 9 μg/m$^3$, or three-fold above its respective candidate RfC. This is due to its small aggregate uncertainty factor of 10 (which argues for a value closer to the candidate RfC), steeper hazard slope (which argues for a value closer to the candidate RfC), medium confidence in the critical effect (which argues for a value neither closer to nor farther from the candidate RfC), and medium to low confidence in the choice of a benchmark response of 5% (which argues for a value farther from the candidate RfC). See also supplemental materials.

For the decreased thymus weight endpoint based on the Keil et al. (2009) study, we judged the intermediate value of the endpoint-specific uncertainty range to be 20 μg/m$^3$, or 10-fold above its respective candidate RfC due to its larger uncertainty factor of 100 (which argues for a value farther from the candidate RfC), medium confidence in the critical effect (which argues for a value neither closer to nor farther from the candidate RfC), and medium to low confidence in its choice of a lowest observed adverse effect level (LOAEL) as the POD (which argues for a value farther from the candidate RfC). The effect shown by Keil et al. (2009) does not lend itself to dose response modeling, so a judgment of steepness of hazard slope is not possible (see supplemental materials.

The safety range for each candidate RfC is shown in Table 1.

### 3.2. Defining the multi-endpoint range of safety

Since EPA developed three candidate RfCs for non-cancer effects, the endpoint-specific safety range of each of the candidate RfCs may be considered individually, or collectively, in risk management decisions. From the collective evaluation of the endpoint-specific safety ranges of all three candidate RfCs, a "total safety range" of 2 μg/m$^3$ to 63 μg/m$^3$ may be inferred. However, extraction of a "multi-endpoint safety range" from the broader total safety range may be more useful for risk management decision-making. The multi-endpoint safety range may be defined here as an estimate of "a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." This is based upon the definition of the RfD(C) (Barnes and Dourson, 1988; EPA, 1994, 2002), but where the phrase "with uncertainty spanning perhaps an order of magnitude" is absent, because the range is now specified for each RfD(C) value.

The POD for the RfD(C) is typically (although not always) based upon a NOAEL from a single study for a single critical effect. The assessment of confidence levels in the study design, critical effect and POD of a single study and critical effect enables the assignation of uncertainty factors in a relatively straightforward manner. The use of the definition of the RfD(C) to also define the multi-endpoint safety range is a recognition of the complexity associated with the prediction of a "safe dose" or "safe concentration" associated with multiple effects, observed in multiple studies and species, and multiple PODs, each variously based on a $BMDL_{01}$, $BMDL_{05}$ or LOAEL value, appropriately averaged over two different exposure periods, as relevant for developmental or chronic effects. Therefore, the concept of a "safe dose" for the non-cancer effects of TCE has been applied here to a range of values (*i.e.*, the multi-endpoint safety range) which represents a "safe concentration" for multiple endpoints and multiple studies, with various degrees of confidence in study design, critical effect and POD, as illustrated by the shaded cells in Table 1.

Specifically, the multi-endpoint safety range of the RfC for TCE was determined by careful discernment of the confidence, precision and safety associated with each endpoint-specific floor, intermediate and ceiling value. The floor of the multi-endpoint uncertainty range of the RfC for TCE was determined by comparing the candidate RfC values from each of the three studies (*i.e.*, 2 μg/m$^3$ for both the decreased thymus weight and controversial fetal cardiac malformation endpoints, and 3 μg/m$^3$ for the toxic nephropathy endpoint). These three floor values are so closely clustered that, based on the inherent precision, the values are toxicologically indistinguishable. The endpoint-specific floor value of 3 μg/m$^3$ based on toxic nephropathy represents the endpoint-specific floor value of the highest overall confidence from among the three endpoint-specific floor values (see Table 1). Therefore, the value of 3 μg/m$^3$ was selected to represent the floor value of the multi-endpoint uncertainty range.

Similarly, the intermediate value of the multi-endpoint uncertainty range of the RfC for TCE is determined by comparing the endpoint-specific intermediate values from each of the three studies (*i.e.*, 20 μg/m$^3$ for the decreased thymus weight endpoint, 10 μg/m$^3$ for the controversial fetal cardiac malformation endpoint, and 9 μg/m$^3$ for the toxic nephropathy endpoint). The intermediate values for the fetal cardiac malformation and toxic nephropathy endpoints are so closely clustered that the values are toxicologically indistinguishable. The endpoint-specific intermediate value of 9 μg/m$^3$ based on toxic nephropathy not only represents the endpoint-specific intermediate value of the highest overall confidence from among the three endpoint-specific intermediate values (see Table 1), but is lower than or equivalent to the other two endpoint-specific intermediate values. Therefore, the endpoint-specific intermediate value of 9 μg/m$^3$ was selected to represent the intermediate value of the multi-endpoint uncertainty range.

The ceiling of the multi-endpoint uncertainty range of the RfC for TCE is determined by comparing the endpoint-specific ceiling values from each of the three studies (*i.e.*, 63 μg/m$^3$ for the decreased thymus weight endpoint, 20 μg/m$^3$ for the controversial fetal cardiac malformation endpoint, and 30 μg/m$^3$ for the toxic nephropathy endpoint). The endpoint-specific ceiling values for the fetal cardiac malformation and toxic nephropathy endpoints are closely clustered, and the mathematical precision ranges of the two values overlap[8]; the endpoint-specific ceiling value for decreased thymus weight is substantially higher. Therefore, the endpoint-specific ceiling value for toxic nephropathy (30 μg/m$^3$) has been selected here as the ceiling value for the multi-endpoint uncertainty range, because it is the endpoint with higher degree of confidence than the controversial fetal cardiac malformations endpoint.

In summary, the confidence in each of the endpoint-specific safety range was subsequently considered in the determination of the multi-endpoint safety range for risk management purposes (*i.e.*, 3 μg/m$^3$ to 30 μg/m$^3$). The higher-confidence results of the NTP

[7] Low confidence argues for an intermediate value that is farther from the RfC because choices of critical effect and POD in such situations are generally more protective.

[8] The mathematical precision (at HQ = 1) associated with the endpoint-specific ceiling value of 20 μg/m$^3$ corresponds to a range of 19 μg/m$^3$ to 30 μg/m$^3$; the mathematical precision (at HQ = 1) of the endpoint-specific ceiling value of 30 μg/m$^3$ corresponds to a range of 28 μg/m$^3$ to 45 μg/m$^3$. Thus, the HQ ranges associated with the implicit precision of each endpoint-specific ceiling value overlap.

study were used to determine the floor, intermediate and ceiling of this safety range. The highly controversial results from the Johnson et al. (2003) study, while associated with low confidence (see Supplemental materials, section 2), were nevertheless used to support this safety range. This multi-endpoint safety range is embedded within the individual safety range from Keil et al. (2009); therefore, this study was also considered to be confirmatory.

### 3.3. Risk management use of "uncertainty spanning perhaps an order of magnitude"

Toxicologists are not able to distinguish the absence of health risk between any two or more values within the uncertainty range determined for any RfD(C) by its inherent precision and safety. For TCE specifically, toxicologists cannot differentiate the "safety" of any value within a range of 3 μg/m$^3$ to 30 μg/m$^3$, nor can they differentiate among hazard quotients (HQs) developed from any value within this range. Because of this, managers may use different values within the multi-endpoint safety range, along with site-specific exposure assessments, and other site risk management considerations to make different decisions on a case-by-case basis.

Fig. 1 shows three hypothetical exposure scenarios overlaid on the TCE safety range of 3 μg/m$^3$ to 30 μg/m$^3$. For example, when a site-specific exposure assessment defines a range of exposures that is primarily below the multi-endpoint safety range of 3 μg/m$^3$ to 30 μg/m$^3$, then the probability of inducing any non-cancer effects in the exposure population is lower and the priority for any risk management action is reduced (see Fig. 1a). In this case, a risk manager may decide to take no action, or to delay action pending further information. Such action would be readily seen as the current practice at waste sites throughout the country.

In contrast, when the exposure assessment defines a range in exposures that also exceeds the multi-endpoint safety range of 3 μg/m$^3$ to 30 μg/m$^3$, then the probability of inducing non-cancer effects in the exposure population is higher and the priority for risk management action is increased (see Fig. 1c). In this case, a risk manager may decide to take action, or to ask for specific information that would refine the estimates of health risk and/or exposure. Likewise, such action would be readily seen as the current practice at waste sites throughout the country.

When the exposure assessment defines a range in exposures that is primarily in the multi-endpoint safety range of 3 μg/m$^3$ to 30 μg/m$^3$, then risk managers can use the intermediate value in this safety range, that is 9 μg/m$^3$ and other site considerations, to gauge whether a management action is needed or if further information should be sought (see Fig. 1b).

## 4. Discussion

In this paper, a "safety range" is proposed for each RfD(C). This safety range provides further clarification to the phrase "with uncertainty spanning perhaps an order of magnitude" in the definition of the RfD(C). This safety range can also be used with exposure measurements at waste sites to develop a "hazard range"[9] to facilitate risk management decisions for non-cancer health effects. This hazard range is similar in concept to the upper bound, excess, lifetime, cancer risk range of $10^{-6}$ to $10^{-4}$.

The lower end of this safety range is the value of the RfD(C); the lower end for the corresponding hazard range is a HQ value of 1. These lower bounds are not only consistent with the definition and intent of any RfD(C) value, but also reflect typical risk management decisions about HQs at waste sites. The upper end of either of these ranges can vary depending in part on the basis of choice of and confidence in the critical effect, the relevant POD and any of its necessary adjustments, the aggregate uncertainty factor, and, for the hazard range, the uncertainty inherent in the estimates of exposure. For the safety ranges derived specifically for the three TCE RfCs, the upper end varies from 10 to ~30 times above the RfD(C). Fortunately, the information needed to determine the lower and upper ends of these safety ranges are readily available for any chemical on EPA's IRIS or the International Toxicity Estimates for Risk (*ITER*) on the National Library of Medicine's Toxnet. The resulting hazard ranges, expressed as the range of the HQ, can then be determined from these safety ranges and available information related to site-specific exposures.

Risk management decisions about exposure levels wholly below the lower end of a safety range may be straightforward. For example, when a site-specific exposure assessment defines TCE exposures that are primarily below the multi-endpoint safety range of 3 μg/m$^3$ to 30 μg/m$^3$, the risk manager may decide to take no action, or to delay action pending further information. Risk management decisions may also be likewise straightforward when the exposure levels are wholly above the upper end of this safety range of 3 μg/m$^3$ to 30 μg/; in such cases, a risk manager may decide to take action, or to ask for specific information that would refine the estimates of health risk and/or exposure. Risk management decisions about exposure levels wholly or partially within the range are more complex; therefore, it may be helpful to have an intermediate value within the safety range to aid in these decisions. The intermediate values we develop are based on information that is often available and reflects our best collective judgment. Other criteria and judgments might also be reasonable. For example, a recent publication notes five different ways to characterize the uncertainty inherent in risk assessment values such as RfCs, with the suggestion to develop a range being one of them (Beck et al., 2016). In addition, the science panel of the *ARA* project "Beyond Science and Decisions: From Problem Formulation to Dose Response" recommended changes incorporating some of the findings of Beck et al. (2016) into our proposed method.[10] Some of these suggestions have been adopted here.

Additional discussion is warranted with respect to establishing the floor of our multi-endpoint safety range for TCE. The mathematical precision of the cardiac or immune endpoint-specific floor value of 2 μg/m$^3$ corresponds to a range of 1.5 μg/m$^3$ to 2.5 μg/m$^3$; the mathematical precision of the nephropathy endpoint-specific floor value of 3 μg/m$^3$ corresponds to a range of 2.5 μg/m$^3$ to 3.5 μg/m$^3$. Thus, the ranges associated with the implicit precision of the three endpoint-specific floors coincide at a precision of one significant figure. Since the endpoint-specific value of 3 μg/m$^3$ based on toxic nephropathy has the highest overall confidence from among the three endpoint-specific floor values (see Table 1), and since its precision coincides with the other two endpoint-specific values, its choice of the floor of the multi-endpoint range seems most reasonable.

Some discussion is also warranted with respect to establishing the ceiling value for this multi-endpoint safety range for TCE. For example, the toxic nephropathy endpoint (30 μg/m$^3$) is a preferred representation of the ceiling value based on its overall confidence, whereas an alternative value of 20 μg/m$^3$ based on cardiac effects is a less plausible representation of the ceiling value, based on the high uncertainty regarding the frankness and severity of the observed effect and the quantification of the response, and the ongoing

[9] The term "hazard range" is introduced here since this incorporates the safety range of the RfD(C) and also exposure measurements.

[10] See http://allianceforrisk.org/wp-content/uploads/2015/07/DR8_Meeting_Report_and_Appendices.pdf).

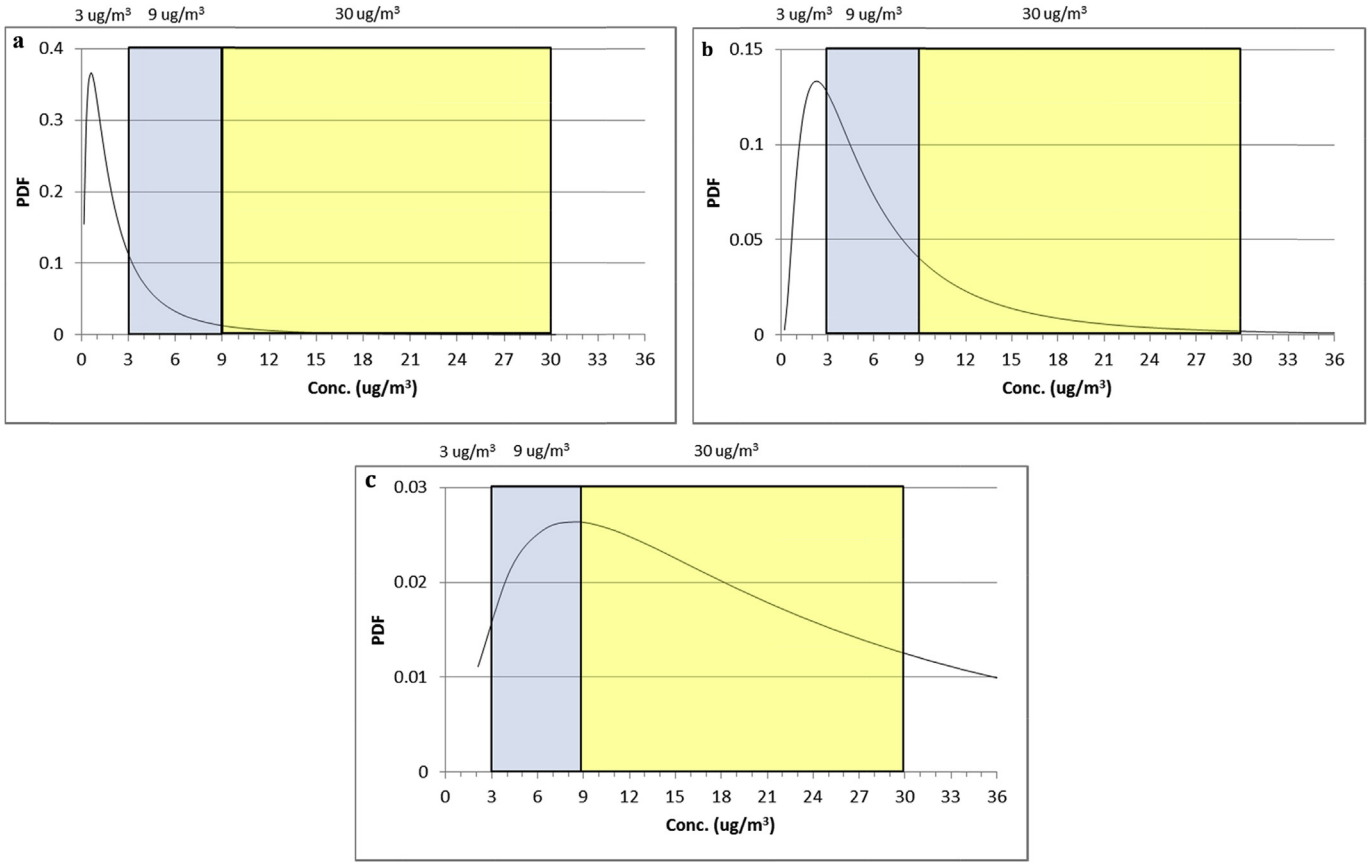


**Fig. 1.** Three Hypothetical Exposure Scenarios Overlaid on the TCE Safety Range. **a. Hypothetical probability density function of e**xposures of TCE in indoor air lies primarily below the 3 μg/m$^3$ to 30 μg/m$^3$ safety range. A relatively small proportion of exposures is higher than 3 μg/m$^3$. Nominal actions or no further action may be warranted for risk management. **b. Hypothetical probability density function of e**xposures of TCE in indoor air falling within the 3 μg/m$^3$ to 30 μg/m$^3$ safety range. A relatively small proportion of exposures is higher than 9 μg/m$^3$. Limited action may be warranted for risk management. **c. Hypothetical probability density function of e**xposure of TCE in indoor air falling within the 3 μg/m$^3$ to 30 μg/m$^3$ safety range. A relatively small proportion of exposures is higher than 30 μg/m$^3$. Actions to reduce exposures may be warranted for risk management.

controversy regarding the use of this study in dose-response assessment. Specifically, we favor the endpoint-specific ceiling value for toxic nephropathy over the endpoint-specific ceiling value for fetal cardiac malformation on the basis of higher confidence not only in the critical effect (high *versus* low) but also in the POD (medium *versus* low); the latter comparison is of particular relevance since the POD serves as the endpoint-specific ceiling value for each endpoint. Nevertheless, the mathematical precision ranges of the HQs based on either of the endpoint-specific ceiling values also coincide. In this case, the values may be considered to be approximately equivalent, enabling risk manager to conservatively account for potential developmental endpoints when the multi-endpoint safety range is used as the basis for risk management decisions.[11]

For TCE, the multi-endpoint safety range is based on floor, intermediate and ceiling values for effects of different exposure durations (*i.e.*, developmental or chronic exposure periods) with expected different averaging times. Therefore, this range for TCE can be applied to both long-term and short-term exposures, with the associated differences in exposure averaging times. For shorter-term exposures, the results from the Johnson et al. (2003) might also be used to describe the best exposure averaging time, but if so, this exposure averaging time should be based on the average time of cardiac development in human fetal growth, approximately 20–25 days (based on Marcela et al., 2012; Hood, 2011; Dhanantwari et al., 2009; Martin et al., 2002; Schleich, 2002), rather than a specific window of time. This is because the use of only a narrow window of exposure during the cardiac development in humans would be inconsistent with the results of the Johnson et al. (2003).[12]

It should be recognized that risk management decisions at

[11] Significant science controversy surrounds the use of the Johnson et al. (2003) study in regulating TCE exposures, and if the science community had a higher level of confidence in the Johnson et al. (2003) study, we would have used it to set the ceiling of the range at 20 μg/m$^3$, as opposed to 30 μg/m$^3$. However, it is important to recognize that the regulatory community, USEPA and States, are likely to continue to support the use of this study, at least in the interim. Thus, risk managers should consider whether to use 20 μg/m$^3$ as the ceiling of the range because it represents a POD, which can be, and has been (ATSDR, 2013a; 2103b), interpreted as an "effects level", or a level at which expression of the toxic effect is often measurable or "real". The risk of a toxic effect below these levels, especially in acute or subchronic exposure, is minimal. Because of continued regulatory support for the Johnson et al. study, at least over the interim, this may be an important guidance issue for anyone making day to day risk based decisions for immediate action.

[12] Based on the available information, the human heart starts developing between days 21 and 23 after gestation or later and may be completely formed by 43–46 days into gestation or later (Hood, 2011), indicating the length of cardiac development in humans during fetal growth to be in the approximate range of 20–25 days. Since EPA's RfC is based on all effects that occurred during the whole time of cardiac development in the rat by Johnson et al. (2003), it is reasonable to use the whole time of cardiac development in humans, 20–25 days, as the averaging time for risk management decisions. This range falls within the previously stated range of 21–30 days (see supplemental materials), and for similar reasons.

different waste sites may differ, even for the same set of chemicals with the same underlying hazard information, because other aspects of the site problem formulation differ. In fact, differences in risk management decisions, and in the products of the individual components of hazard characterization, dose–response assessment, exposure assessment, and risk characterizations, should be expected based on different problem formulations (Dourson et al., 2013; Ethridge et al., 2015). Such differences in risk management outcomes do not mean that the science behind the decision has been tampered, but rather that these situations should be addressed on a case-by-case basis.

As risk managers struggle with waste site decisions that integrate various aspects of hazard identification, dose response assessment, exposure assessment and risk characterization, understanding the uncertainties underlying each component will increasingly be important. Our approach is an attempt to put uncertainties in perspective and advance transparency in the chemical risk assessment process. Such perspective and transparency should promote more confident use of allowable levels, such as RfDs and HQs, and their associated safety and hazard ranges, in waste site management decision-making.

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## Transparency document

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## Appendix A. Supplementary data

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