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.

Appendix:

Evaluation of Hazard Range for Three Additional Chemicals: Tetrachloroethylene, Chromium (VI) and Arsenic

6 May 2014

The Case Study Report (*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*) provides a general overview for a proposed methodology for developing a hazard range for the evaluation of the non-cancer endpoints of chemicals, based upon the Reference Concentration (RfC) or Reference Dose (RfD) values developed through the U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). The proposed methodology was first developed with respect to the RfC for trichloroethylene (TCE) (http://www.allianceforrisk.org/Projects/ARA TCE Risk Assessment Guidance for Contaminated Sites 2013.pdf); the application of the methodology to the RfC for TCE is presented briefly in the Case Study Summary, and in more detail in the Case Study Report. This appendix provides three additional examples (*i.e.*, tetrachloroethylene (perchloroethylene, PCE), chromium (VI) and arsenic) in which the hazard range methodology is applied to a RfD value, based on the information currently available on IRIS.

Table 1 provides a summary of the key information available on IRIS for each chemical (*i.e.*, the RfD, point of departure [POD] and uncertainty factors). In addition, the table synopsizes the relevant information based upon the specific application of the proposed methodology to each chemical (*i.e.*, steepness of the dose-response slope, confidence in the critical effect, confidence in the POD, and the floor, midpoint [intermediate] and ceiling values which define the hazard range). A discussion of the specific application of the methodology for each chemical follows below.

Table 1. Summary of data for the Development of the Hazard Range for the Arsenic, Tetrachloroethylene and Chromium (VI) RfDs on IRIS (2014)

(All values for these ranges are in mg/kg-day).

Chemical	**IRIS RfD**	**IRIS POD**	**IRIS UF[a]**	**Steep Slope[b]**	**Confidence**		**Hazard Ranges (mg/kg-day)**		
	(mg/kg-day)				**Critical Effect[c]**	**Point of Departure[d]**	**Floor**	**Midpoint (Inter-mediate)**	**Ceiling**
Tetrachloro-ethylene	6E-3	6E-0	1000	Low	High	Low	6E-3	6E-2	6E-1
Chromium (VI)	3E-3	2.5	300 x 3	Low	Low	Low	3E-3	3E-2	3E-1
Arsenic*	3E-4	8E-4	3	Low	High	Medium	1E-4*	3E-4	8E-4*

*The floor to ceiling range as found on IRIS

a. Size of the uncertainty factor, as per IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of a hypothetical line describing population responses at concentrations above the RfD), as per Section 3 of the Case Study Summary.
c. Confidence in the choices of critical effect, as per Section 4 of the Case Study Summary.
d. Confidence in the point of departure, as per Section 4 of the Case Study Summary

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

Tetrachloroethylene

IRIS excerpts

Oral RfD Summary (after IRIS)

Principal Study/Critical Effect	POD (mg/kg-day)*	UF	Candidate RfDs (mg/kg-day)	RfD (mg/kg-day)**
Echeverria et al. (1995): neurotoxicity (reaction time, cognitive effects) in occupationally-exposed adults	LOAEL = 9.7	1,000	0.0097	0.006
Cavalleri et al. (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 2.6	1,000	0.0026	

*Derived by route-to-route extrapolation from inhalation exposure using PBPK model of Chiu and Ginsberg (2011).
**The RfD is supported by the two principal studies, as a midpoint of the range of available values (then rounded to one significant figure).

"The database of human and animal studies of tetrachloroethylene is adequate to support derivation of an oral reference value. To derive an RfD, the application of pharmacokinetic models for a route-to-route extrapolation of the inhalation studies was utilized because the available oral studies were less well suited for dose-response analysis… A number of targets of toxicity from chronic exposure to tetrachloroethylene have been identified in published animal and human studies. These targets include the central nervous system, kidney, liver, immune and hematologic system, and development and reproduction. In general, neurological effects were found to be associated with lower tetrachloroethylene inhalation exposures.

The nervous system is an expected target with oral tetrachloroethylene exposures because tetrachloroethylene and metabolites produced from inhalation exposures will also reach the target tissue via oral exposure. In addition, other organ systems such as the liver and kidney are common targets associated with both inhalation and oral routes of exposure which supports the use of route extrapolation to compare PODs for oral and inhalation exposure. In addition, differences in first-pass metabolism between oral and inhalation exposures can be adequately accounted for by the PBPK model (Chiu and Ginsberg, 2011).

For these reasons, the inhalation neurotoxicity studies used to derive the RfC (see I.B.2) are chosen as principal studies for the RfD: Echeverria et al. (1995) and Cavalleri et al. (1994). Candidate RfDs for tetrachloroethylene were derived by dividing the route-to-route extrapolated points of departures (PODs) of 2.6 mg/kg-day (Cavalleri et al., 1994) and 9.7 mg/kg-day (Echeverria et al., 1995) by a total UF of 1,000, comprised of 10 for interindividual variability, 10 for extrapolation from a LOAEL to a NOAEL, and 10 for database uncertainty."

"Candidate RfDs for tetrachloroethylene were derived by dividing the route-to-route extrapolated points of departures (PODs) of 2.6 mg/kg-day (Cavalleri et al., 1994) and 9.7 mg/kg-day (Echeverria et al., 1995) by a total UF of 1,000, comprised of 10 for interindividual variability, 10 for extrapolation from a LOAEL to a NOAEL, and 10 for database uncertainty."

"…The overall confidence in the RfD is medium. Although the confidence in the evidence of neurotoxicological hazard is high, the estimates from studies for which candidate RfDs were calculated are of medium confidence. These studies were considered to be methodologically sound based on study quality attributes, including study population selection, exposure measurement methods, and endpoint measurement methods. Other strengths are that they are human studies of chronic duration, obviating the need for extrapolation across species and exposure duration. However, high confidence was not attained for the studies for which candidate RfDs were calculated because they identified a LOAEL rather than a NOAEL, and dose-response modeling could not be used for POD derivation due to lack of sufficient data [e.g., no control group (Echeverria et al., 1995) or lack of an important covariate (age) (Cavalleri et al., 1994)]. Additionally, the studies for which candidate RfDs were calculated are of occupationally exposed subjects; no data concerning potential susceptibility or variability among subjects were available. Because of the adequacy of the PBPK model (Chiu and Ginsberg, 2011) for extrapolating from inhalation to oral exposures, the use of inhalation studies for deriving the RfD did not decrease confidence.

Medium confidence in the database is based on a number of limitations of both the human and animal literature. Regarding neurotoxicity, there is a need for high quality epidemiologic studies of residential exposures and chronic-duration animal studies (including in developing animals). A fuller characterization is also needed of the noncancer effects other than the critical effect of neurotoxicity, particularly immunological and hematological effects."

Evaluation

Using the approach developed in this case study, the floor of the hazard range is 6 µg/kg-day, which is the stated value of the RfD on IRIS.

The ceiling of the hazard range is 600 µg/kg-day, which is the POD after appropriate adjustment; specifically, dividing the POD by a composite UF of 10, which is comprised of a UF of 3 for extrapolation from a LOAEL to a NOAEL, and a UF of 3 for database uncertainty. Note that these three-fold values are median estimates of the 10-fold default uncertainty factors in *lieu* of specific data, and are used to estimate, without conservatism, the upper bound to the likely range of the RfD.

The midpoint would likely be 60 µg/kg-day based on the:

- Overall IRIS UF of 1000;
- Low steepness of the hazard slope, since a NOAEL has not been defined, and therefore, a sense of the slope of the dose response curve for the critical effect was not determinable;
- **High to medium confidence** of the critical effect since it is defined in a group of humans, albeit, sensitive humans were likely not monitored; and
- Low confidence in the point of departure, because the LOAEL was based on a route-to-route conversion and a NOAEL was not established.

Chromium (VI)

IRIS excerpts

Oral RfD Summary (after IRIS)

Critical Effect	Experimental Doses	UF	MF	RfD
None Reported Rat, 1-year drinking water study MacKenzie et al., 1958	NOAEL: 25 mg/L of chromium as K_2CrO_4 2.5 mg/kg-day (adj.)	300	3	3E-3 mg/kg-day

"Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0.45-11.2 ppm (0.45-11.2 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group (10/sex) received distilled water. A second experiment involved three groups of 12 male and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (as K_2CrO_4), a second received 25 ppm chromium in the form of chromic chloride, and the controls again received distilled water. No significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K_2CrO_4) showed an approximate 20% reduction in water consumption. Based on the body weight of the rat (0.35 kg) and the average daily drinking water consumption for the rat (0.035 l/day), this dose can be converted to give an adjusted NOAEL of 2.5 mg/kg-day chromium(VI). For rats treated with 0-11 ppm (in drinking water), blood was examined monthly, and tissues (livers, kidneys, and femurs) were examined at 6 mo and 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except that no animals were killed at 6 mo. An abrupt rise in tissue chromium concentrations was noted in rats treated with more than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group. Similar no-effect levels have been observed in dogs. Anwar et al. (1961) observed no significant effects in female dogs (2/dose group) given up to 11.2 ppm chromium(VI) (as K_2CrO_4) in drinking water for 4 years. The calculated doses were 0.012-0.30 mg/kg of chromium(VI)."

"The uncertainty factor of 300 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu

of specific data, and an additional factor of 3 to compensate for the less-than-lifetime exposure duration of the principal study… The modifying factor of 3 is to account for concerns raised by the study of Zhang and Li (1987)."

"The overall confidence in this RfD assessment is low. Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured, and the lack of toxic effect at the highest dose tested.

Confidence in the database is low because the supporting studies are of equally low quality and the developmental toxicity endpoints are not well studied."

Evaluation

Using the approach developed in this case study, the floor of the hazard range is 3 µg/kg-day, which is the stated value of the RfD on IRIS.

The ceiling of the hazard range is 300 µg/kg-day, which is the POD after appropriate adjustment; specifically, dividing the POD by a composite UF of 10, which is comprised of a UF of 3 for interspecies variability, and a UF of 3 for both the duration adjustment and modifying factor. Note that the first three-fold value is a median estimate of the 10-fold default factor for experimental animal to human extrapolation in *lieu* of specific data; the second 3-fold factor is a median estimate of the conflation of the duration uncertainty factor and modifying factor. These 3-fold factors are used to estimate, without conservatism, the upper bound to the likely range of the RfD.

The midpoint would likely be 30 µg/kg-day based on the:

- Overall IRIS UF-MF of 1000 (*i.e.,* UF of 300 x MF of 3);Low steepness of the hazard slope, since a LOAEL has not been defined, and therefore, a sense of the slope of the dose response curve for the critical effect was not determinable;
- **Low confidence** of the critical effect since an adverse effect is not defined in the chosen study described on IRIS; and
- Low confidence in the point of departure, because the NOAEL because the NOAEL occurred in the highest dose tested.

Arsenic

IRIS excerpts

Oral RfD Summary (after IRIS)

Critical Effect	Experimental Doses	UF	MF	RfD
Hyperpigmentation, keratosis and possible vascular complications Human Chronic oral exposure Tseng, 1977; Tseng *et al.*, 1968	NOAEL: 0.009 mg/L, converted to 0.0008 mg/kg-day LOAEL: 0.17 mg/L, converted to 0.014 mg/kg-day	3	1	3E-4 mg/kg-day

"There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account."

"The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a recent report indicates that it may not be strictly due to arsenic exposure (Lu, 1990). The data in Tseng et al. (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng et al. (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This group is considered a NOAEL.

The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 ug/L (range: 1-17 ug/L) (Abernathy et al., 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 ug/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy et al. (1989), the NOAEL and LOAEL doses for both food and water are as follows: LOAEL - [170 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 14 ug/kg/day; NOAEL - [9 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 0.8 ug/kg/day."

"The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals."

"Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (> 40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity database is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. Similar criticisms can be made of other studies, although the database does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows."

Evaluation

Please note that IRIS specified that the range of uncertainty associated with the RfD is 0.1 to 0.8 µg/kg-day (*i.e.*, 1E-4 to 8E-4 mg/kg-day), a range that is different than what might otherwise be developed using the methods described in this case study.

For example, using the approach developed in this case study, the floor of the hazard range would be 0.3 µg/kg-day, which is the stated value of the RfD on IRIS.

The ceiling of the hazard range would be 0.8 µg/kg-day, which is the stated POD and which does not need further adjustment since it is based on humans for the appropriate duration of exposure.

The midpoint would lie likely halfway between these two values based on the:

- Overall IRIS UF of 3;
- Low steepness of the hazard slope, since the distance between the NOAEL and

LOAEL are larger than usual;

- High confidence of the critical effect, since the effect is from a large population of humans, likely including sensitive individuals; and
- Medium confidence in the point of departure, because although the NOAEL is an average of different wells, the range in well concentrations span 17-fold.

Note that instead of applying the standard approach, the range for the RfD provided by IRIS is used, reflecting that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day" (IRIS). Also, the 8E-4 mg/kg-day ceiling (Table 1) is consistent with the proposed method, while the 1E-4 mg/kg-day for the floor is more conservative than the approach specified by the method - using the IRIS RfD - and is used in lieu of the value obtained by strict application of the method.