Technical Appendix A

Toxicity Weights for TRI Chemicals and Chemical Categories

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1 Introduction

The RSEI model relies on chemical toxicity data from EPA and other published sources. All of the toxicity data used in the model can be found in the "Chemical" table in the model database and data dictionary, or in the "Chemical Modeling Data" selection in EasyRSEI. The toxicity weight for each chemical can be found in the spreadsheet installed in the toxicity weighting spreadsheet, available on the RSEI website. This appendix briefly describes the main parameters used, the sources from which the information is obtained, and decisions made regarding special cases.

2 Parameters

Four main parameters are used to determine toxicity weights: reference dose (RfD), reference concentration (RfC), oral slope factor (OSF) and inhalation unit risk (IUR). RSEI uses the weight-of-evidence (WOE) determination only to adjust certain toxicity weights for uncertainty. Each parameter is explained below.

2.1 Reference Dose (RfD) or Reference Concentration (RfC)

The RfD and RfC are defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure [or continuous inhalation exposure for the RfC] to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.[1] The RfD is generally expressed in units of milligram (mg) per kilogram (kg) of body weight per day (mg/kg-day), while the inhalation RfC is generally expressed in units of mg per cubic meter (m^3) of air (mg/m^3). A chemical's reference dose or reference concentration is typically based on a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL), combined with appropriate uncertainty factors to account for intraspecies variability in sensitivity, interspecies extrapolation, extrapolation from LOAELs to NOAELs, and extrapolation from subchronic to chronic data. In addition, a modifying factor can be applied to reflect EPA's best professional judgment on the quality of the entire toxicity database for the chemical. By definition, exposures below the RfD are unlikely to produce an adverse effect; above this value, an exposed individual may be at risk for the effect. Empirical evidence generally shows that as the dosage of a toxicant increases, the severity and/or incidence of effect increases (EPA, 1988), but for a given dose above the RfD, the specific probability of an effect is not known, nor is its severity. For purposes of the RSEI method, we assume that noncancer risk varies as the ratio of the estimated dose to the RfD.

As the RfC is typically expressed in units of exposure, that is, mg of chemical per m^3 of air, the RSEI method uses standard adult human exposure factors for inhalation rate (20 m^3/day) and body weight (70 kg) to convert the RfC to units of dose (mg/kg-day), as in the following example conversion:

$$1\frac{mg}{m^3} * \frac{1}{70kg} * \frac{20m^3}{day} = 3.5\frac{mg}{kg-day}$$

[1] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system

2.2 Oral Slope Factor (OSF)

The oral cancer slope factor is a measure of the incremental lifetime risk of cancer by oral intake of the chemical. It represents an upper-bound estimate of the slope of the dose-response curve in the low-dose region for carcinogens. The units of the OSF are usually expressed in units of proportion (of a population) affected per mg/kg-day. The oral slope factor is also referred to as the Q Star (Q*) value.

2.3 Inhalation Unit Risk (IUR)

The inhalation unit risk is the upper-bound excess cancer risk estimated to result from continuous exposure to a chemical at a concentration of 1 µg/m^3 in air for a lifetime. IUR values are expressed as risk per mg/m^3 in calculating RSEI toxicity weights. Similar to the RfC, the IUR is also expressed in terms of exposure and so is converted to units of dose (risk per mg/(kg-day)) when the toxicity weight is calculated, as in the following example:

$$1\frac{risk}{mg/m^3} * 70kg * \frac{1}{20m^3/day} = 3.5\frac{risk}{mg/(kg-day)}$$

Note that the formula for the RSEI inhalation toxicity weight for cancer is expressed as IUR (risk per mg/m^3) / 2.8 x 10^{-7}, where the denominator is simply the reciprocal of 3.5 (0.28) multiplied by the same arbitrary slope factor (1.0 x 10^{-6}) used in the calculation for the RSEI oral toxicity weight for cancer.

2.4 Weight of Evidence (WOE)

When evaluating the potential toxicity of a chemical to humans, toxicologists and risk assessors use a variety of data, including epidemiological data, *in vivo* acute and chronic animal studies, and *in vitro* and *in silico* toxicity testing methods. Together, these data form a body of evidence regarding the potential for toxic chemicals to cause particular health effect(s). Experts can judge qualitatively the strengths of this body of evidence when evaluating the probability of the occurrence of the effect(s) happening in humans. Based on this scientific judgment, the chemical is assigned a weight-of-evidence (WOE) classification. Weight-of-evidence schemes can be designed to indicate whether a chemical either causes specific health effect(s) in general, or specifically in humans.

For **cancer** effects, the WOE system used in the RSEI model relies on categorical definitions from the EPA Guidelines for Carcinogenic Risk Assessment (EPA, 1986a), which are related to the potential for a chemical to be carcinogenic to humans. The Cancer Guidelines define six WOE categories (A, B1, B2, C, D and E) based on the amount of evidence of carcinogenicity available from human epidemiology studies and animal data. In the RSEI model, weight-of-evidence categories A, B1, and B2 (known and probable carcinogens) are combined. Class C chemicals (possible carcinogens) are assigned weights by dividing the calculated toxicity weights by a factor of 10, because evidence that they cause cancer in humans is less certain. The choice of applying a factor of 10 is based on the advice of scientific peer review; an order of

magnitude is an arbitrary uncertainty factor. Categories D and E are not considered in this weighting scheme.

For **noncancer** effects, weight-of-evidence is considered qualitatively in the hazard identification step of determining an RfD or and RfC. The WOE evaluation for noncancer effects is different from that for carcinogenic effects. The WOE judgment for noncancer effects focuses on the dose where chemical exposure would be relevant to humans (Dourson, 1993). That is, the focus of the WOE evaluation and the expression of the level of confidence in the RfD is a judgment of the accuracy with which the dose relevant to humans has been estimated. The WOE evaluation is included qualitatively in the RfD, but does not affect its numerical calculation. Since weight of evidence has been considered in developing RfDs, the RSEI method does not consider WOE separately for noncancer effects.

3 Chemical Categories and Other Special Cases

EPA's annual Toxic Chemical Release Inventory Reporting Forms and Instructions[2] describes the reporting requirements for individually-listed toxic chemicals and for listed chemical categories. For most listed chemical categories, subject reporting facilities are not required to disclose the specific category member's identity in their Toxics Release Inventory (TRI) reporting forms. Because the identities and specific proportions of individual chemical waste management activity quantities within each reported chemical category are not known, professional judgment is used to assign surrogate values for the various toxicity parameters of each chemical category. In most cases, the most toxic chemical of each category, based on its calculated toxicity weight, is selected, and the toxicity data for that chemical is assigned to the entire chemical category. In these cases, the actual risk for the chemical category would be less than or equal to the modeled risk.

This section describes the surrogate toxicity data decisions made for certain chemical categories. In the case of most metal compound categories, TRI regulations define the category members to include any unique chemical substance that contains the named metal (e.g., lead, antimony, nickel, etc.) as part of that chemical's composition. To simplify toxicity weight calculations due to the identity uncertainties behind the metal compound category members that are reported to the TRI program, the RSEI model combines TRI-listed metal compound categories (e.g., nickel compounds) together with separately listed TRI elemental metals (e.g., nickel) into one RSEI chemical category (e.g., nickel and nickel compounds). Both nickel and nickel compounds are reported to TRI to reflect the quantities of the nickel parent metal that is ultimately released to the environment, where in some cases, reporting facilities may combine the two into a single report and report their release quantities to TRI as nickel compounds. For RSEI modeling purposes, the model combines the reported metal release quantities into one entry listed as "nickel and nickel compounds" and assumes that the elemental metal and metal compound category members have the same toxicity weight. It is also assumed that elemental metals and metal compounds are released in the valence or oxidation state associated with the highest chronic toxicity value, although in reality it may be that certain metal compounds may have differing associated chronic toxicity values due to environmental releases of less toxic valence or

[2] https://ordspub.epa.gov/ords/guideme_ext/f?p=guideme:rfi-home

oxidation states. Other "special case" chemicals, where surrogate information was used or anomalous characteristics were noted, are also described below.

3.1 Asbestos

Due to this chemical substance's fibrous structure, toxicity information is expressed in different units (i.e., risk per fibers/mL). A conversion factor of 5 ($\mu g/m^3$)/(f/mL) was used to convert to risk per $\mu g/m^3$.

3.2 Butoxyethyl ester, 2,4-D, 2-

For 2,4-D 2-butoxyethyl ester (Chemical Abstracts Service Registry Number (CASRN) 1929-73-3), toxicity information is based on 2,4-D (CASRN 94-75-7).

3.3 Butyl alcohol, tert- and sec-

For *sec*-butyl alcohol (CASRN 78-92-2) and *tert*-butyl alcohol (CASRN 75-65-0), toxicity information is based on *n*-butyl alcohol (CASRN 71-36-3).

3.4 Chlorophenols

For the chlorophenols chemical category (N084), toxicity information is based on pentachlorophenol (CASRN 87-86-5).

3.5 Chromium and Chromium Compounds

Toxicity data for chromium (CASRN 7440-47-3) and the chromium compounds chemical category (N090) is based on hexavalent chromium (Cr VI), the most toxic value in this category. It is assumed that facilities may release some combination of hexavalent chromium and trivalent chromium (Cr III). Facility- and North American Industry Classification System (NAICS)-code specific estimates from the National Emissions Inventory (NEI) are used to estimate the fraction of each type[3]. As trivalent chromium has a very low toxicity, only the hexavalent fraction is modeled, using a toxicity weight specifically for that valence state.

3.6 Cyanide Compounds

Because cyanide compounds in a gaseous state exhibit markedly different properties than compounds in solution, two surrogate compounds are used for toxicity weights. For the inhalation toxicity weight, hydrogen cyanide (CASRN 74-90-8) is used, as it is the most toxic gaseous compound. For the oral exposure pathway, toxicity data were collected for metal cyanide compounds, the most toxic group of non-gaseous cyanide compounds. Copper cyanide was found to be the most toxic of these compounds, so its toxicity weight is used for the cyanide compounds chemical category (N106).

[3] NEI data are available at https://www.epa.gov/air-emissions-inventories/national-emissions-inventory-nei

3.7 Diaminotoluene (mixed isomers)

For diaminotoluene (mixed isomers) (CASRN 25376-45-8), toxicity information is based on 2,4-diaminotoluene (CASRN 95-80-7).

3.8 Dioxin and Dioxin-like Compounds

EPA first required reporting for the dioxin and dioxin-like compounds chemical category (N150) in 2000. Facilities were required to report total dioxin and dioxin-like compounds releases/transfers (in units of grams) released/transferred to each medium, as well as the distribution of the 17 congeners that comprise the category released/transferred to all media combined (or just air/water/land releases, depending on the data available). EPA changed the reporting requirements beginning in reporting year 2008, when reporters were required to provide the amounts of each congener released or transferred to each medium. Toxicity information is only available for one congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), but EPA has determined a toxicity equivalence factor (TEF) for each congener, based on its toxicity relative to TCDD[4]. RSEI combines TRI's reported congener breakdowns with EPA's TEFs to calculate a weighted average TEF for each release/transfer. When multiplied by the toxicity weight for TCDD, this provides a toxicity weight for each category member release/transfer. For releases/transfers where the congener breakdown is blank or invalid, RSEI adopts the mean TEF for all of the dioxin releases to that medium in the reporting facility's 4-digit NAICS code. If a 4-digit NAICS code for the reporting facility is not available, the overall mean for the specific medium is used.

3.9 Ethylenebisdithiocarbamic acid, salts and esters

Chemicals reportable under the ethylenebisdithiocarbamic acid, salts and esters chemical category (N171) include ethylenebisdithiocarbamic acid (CASRN 111-54-6) and pesticides such as mancozeb (CASRN 8018-01-7). Toxicity information for this chemical category is based on related chemicals reportable to TRI. The RfD for this chemical category is based on metiram (CASRN 9006-42-2); the OSF is based on ethylene thiourea (CASRN 96-45-7).

3.10 Ethylhexyl ester, 2,4-D, 2-

For 2,4-D 2-ethylhexyl ester (CASRN 1928-43-4), toxicity information is based on 2,4-D (CASRN 94-75-7).

3.11 Certain glycol ethers

Of eight common glycol ethers, four had available toxicity data. 2-Methoxyethanol (ethylene glycol monomethyl ether, (CASRN 109-86-4)) has the highest toxicity weight, and therefore is used as a surrogate for the certain glycol ethers chemical category (N230).

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[4] TEFs are consensus estimates of compound-specific toxicity/potency relative to the toxicity/potency of an index chemical. TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data. For more detail on the dioxin TEFs, see https://www.epa.gov/risk/documents-recommended-toxicity-equivalency-factors-human-health-risk-assessments-dioxin-and.

3.12 Hydrazine sulfate

For hydrazine sulfate (1:1) (CASRN 10034-93-2), toxicity information is based on hydrazine (CASRN 302-01-2).

3.13 Lead and Lead Compounds

For both lead (CASRN 7439-92-1) and the lead compounds chemical category (N420), the RfD is derived from the CalEPA Public Health Goal. An IUR from CalEPA was excluded and the oral toxicity weight based on a non-cancer endpoint is used for the inhalation pathway because of the large body of evidence suggesting a low threshold for the non-cancer effects of lead.

3.14 Maneb

For maneb (CASRN 12427-38-2), the OSF is based on ethylene thiourea (CASRN 96-45-7).

3.15 Mercury and Mercury Compounds

Because mercury in various forms converts to methyl mercury in the environment,[5] toxicity information is based on elemental mercury (CASRN 7439-97-6) for the inhalation pathway, and methyl mercury (CASRN 22967-92-6) for the oral pathway.

3.16 Nitrate Compounds

For the nitrate compounds chemical category (N511), toxicity information is based on nitrate (CASRN 14797-55-8).

3.17 Polycyclic Aromatic Compounds

For the polycyclic aromatic compounds (PACs) chemical category (N590), the toxicity of this group is assumed to be 18% of the toxicity for benzo[a]pyrene (CASRN 50-32-8), its most toxic member. This approach follows that used in EPA's National-Scale Air Toxics Assessment (NATA) evaluation for polycyclic organic matter (POM).[6]

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[5]References that show that mercury converts to methyl mercury in the environment include: Beckert, W.F. et al., "Formation of Methylmercury in a Terrestrial Environment." Nature, 249, 674-75 (1974); Berdicevsky, I.H., et al. "Formation of Methylmercury in Marine Sediments," Environ. Res,, 20, 325-34 (1979); Hamdy, M.K. and O.R. Noyes, "Formation of Methyl Mercury by Bacteria," Appl. Microbiol., 30, 424-432 (1975); Jensen, S. and A. Jernelov, "Biological Methylation of Mercury in Aquatic Organisms," Nature, 223, 753-54 (1969); Wood, J.M. et al., "Synthesis of Methylmercury Compounds by Extracts of a Methanogenic Bacterium," Nature, 200, 173-74 (1968); and Wood, L.M., "Metabolic Cycles for Toxic Elements in the Environment", in Heavy Metals in the Aquatic Environment, P.A. Krenkel (ed.), Pergamon Press, Oxford, England, 105-12 (1975).

[6] Additional information is available in the NATA documentation. RSEI assumes that PAC emissions reported to TRI are most like NATA's "7-PAH" category.

3.18 Sodium dicamba

For sodium dicamba (CASRN 1982-69-0), toxicity information is based on dicamba (CASRN 1918-00-9).

3.19 Sodium nitrite

For sodium nitrite (CASRN 7632-00-0), toxicity information is based on nitrite (CASRN 14797-65-0).

3.20 Strychnine and salts

For the strychnine and salts chemical category (N746), toxicity information is based on strychnine (CASRN 57-24-9).

3.21 Thallium and Thallium Compounds

For thallium (CASRN 7440-28-0) and the thallium compounds chemical category (N760), toxicity information is based on thallic oxide (CASRN 1314-32-5).

3.22 Thorium dioxide

For thorium dioxide (CASRN 1314-20-1), the toxicity weights are based on derived values and a qualitative assessment of toxicity.

3.23 Warfarin and salts

For the warfarin and salts chemical category (N874), toxicity information is based on warfarin (CASRN 81-81-2).

4 Sources of Toxicity Data

Information regarding the toxicity data used for RSEI toxicity weights of TRI-listed chemicals and chemical categories is compiled from the sources listed below. Data from these sources are categorized in three-tiered, hierarchical fashion to give preference to EPA and consensus data sources, where possible. Toxicity values are gathered separately for chronic health effect endpoints (e.g., for cancer and noncancer effects); a chemical's RfD may be from EPA's Integrated Risk Information System (IRIS) Program, while its OSF may be from EPA's Health Effects Assessment Summary Tables (HEAST). However, if the source of information for any chronic health effect endpoint is IRIS and there are non-IRIS sources for other chronic health effect endpoints of comparable date, then the IRIS file must be evaluated to determine if that source(s) of toxicity data had been evaluated and if a rationale was provided explaining why no toxicity values were applied to that endpoint or exposure pathway. If a clearly stated rationale is provided for not using the available data, RSEI will leave that endpoint blank. For a full description of the hierarchy used in toxicity weighting, please refer to the Methodology Document.

4.1 IRIS

The primary (and most preferred) source of these data is EPA's Integrated Risk Information System (IRIS). IRIS is available on the internet, and includes information on EPA evaluations of chemical toxicity for both cancer and noncancer effects of chemicals. IRIS provides both background information on the studies used to develop the toxicity evaluations and the numerical toxicity values used by EPA to characterize risks from these chemicals. These values include upper-bound oral slope factors or inhalation unit risk values for chemicals with carcinogenic effects as well as reference doses or reference concentrations for chemicals with noncancer effects. Data contained in IRIS have been peer-reviewed and represent Agency-wide expert judgments. The peer-review process involves literature review and evaluation of a chemical by individual EPA program offices and intra-Agency workgroups before inclusion in IRIS.

4.2 AirToxScreen/NATA

EPA's Air Toxics Screening Assessment (AirToxScreen), formerly known as the National Air Toxics Assessment (NATA), generally obtains data from the other sources listed in this list, but in some cases uses values derived by EPA's Office of Air Quality Planning and Standards (OAQPS).

4.3 OPP

EPA's Office of Pesticide Programs (OPP) Reference Dose Tracking Reports list OPP's evaluations of the noncarcinogenic potential of chemicals that are of interest to OPP. OPP also publishes the List of Chemicals Evaluated for Carcinogenic Potential, which examines carcinogens. Both of these lists are updated periodically. Additionally, some data were taken directly from OPP's Pesticide Reregistration Eligibility Decision (RED) documents.

4.4 ATSDR

The Agency for Toxic Substances and Disease Registry (ATSDR) is an agency of the U.S. Department of Health and Human Services (HHS), which deals with the effect on public health of hazardous substances in the environment. ATSDR develops Minimal Risk Levels (MRLs) for chemicals on the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) National Priorities List (NPL). MRLs are an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. RSEI uses data from MRLs developed for chronic exposure only. MRLs are intended to serve as screening levels only, and are useful in identifying contaminants and potential health effects that may be of concern at hazardous waste sites. The ATSDR website has more information on MRLs and specific values.

4.5 CalEPA

The California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard and Assessment (OEHHA) is responsible for developing and distributing toxicological and medical information needed to protect public health. RSEI uses final toxicity values published by CalEPA in the Consolidated Table of OEHHA & California's Air Resources Board (ARB) Approved Risk Assessment Health Values. The table is periodically updated.

4.6 PPRTVs

EPA's Provisional Peer-Reviewed Toxicity Values (PPRTVs) include toxicity values developed by the Office of Research and Development (ORD), Center for Public Health and Environmental Assessment (CPHEA), formerly known as the National Center for Environmental Assessment (NCEA), Superfund Health Risk Technical Support Center (STSC).

4.7 HEAST

EPA's Health Effects Assessment Summary Tables (HEAST) are constructed for use in the CERCLA and RCRA programs but do not represent Agency-wide expert scientific judgments. These tables are publicly available from the CERCLA's Superfund program. The tables include OSFs, IURs, and WOE categorizations for chemicals with cancer effects, and RfDs and RfCs for noncancer effects.

4.8 Derived Values

For chemicals for which sufficient data was not found in the above sources, a group of EPA expert health scientists review other available data to derive appropriate toxicity values and toxicity weights. Although individual literature searches for toxicological and epidemiological data for each chemical are beyond the scope of this project, sources such as the Hazardous Substances Data Bank (HSDB), as well as various EPA and ATSDR summary documents, provide succinct summaries of toxic effects and quantitative data, toxicological and epidemiological studies, and, in some cases, regulatory status data. When the available data on chronic human toxicity are sufficient to derive values, a toxicity weighting summary can be developed summarizing the information used to develop each of the values. EPA scientists have used a technical approach analogous to the Agency's method for deriving RfD values, RfC values, cancer risk estimates, and WOE determinations. However, it must be emphasized that these derived values are not the equivalent of the more rigorous and resource-intensive IRIS process and are only useful for screening-level purposes.

5 References

Dourson, M. 1993. Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency. Personal communication, October 19.

U.S. Environmental Protection Agency (EPA). 1988. IRIS Background Document #1. *Reference Dose (RfD): Description and Use in Health Risk Assessments.* Integrated Risk Information System (IRIS). Online. Maintained by Environmental Criteria and Assessment Office, Cincinnati, OH.

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