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, or the "Chemical Data" form in EasyRSEI. The toxicity weight for each chemical, as well as its calculation, can be found in the spreadsheet installed in the toxicity weighting spreadsheet, available on the RSEI website (http://www.epa.gov/rsei). 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: RfD, RfC, Oral Slope Factor and Inhalation Unit Risk. RSEI uses the weight-of-evidence 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 the RfC] to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious [noncancer] effects during a lifetime" (EPA, 1988). The units of RfD are mg/kg-day, while the units of the Inhalation Reference Concentration are mg/m^3. A chemical's Reference Dose or Reference Concentration is based on a No Observable Adverse Effect Level (NOAEL) or Lowest Observable 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:

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

2.2 Oral Slope Factor (Q*)

The oral cancer slope factor is a measure of the incremental lifetime risk of cancer by oral intake of the chemical. It represents the upper-bound estimate of the slope of the dose-response curve in

the low-dose region for carcinogens. The units of the slope factor are usually expressed as risk per mg/kg-day. The oral slope factor is also referred to as the Q Star value.

2.3 Inhalation Unit Risk

The unit inhalation risk is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 mg/m^3 in air. In RSEI, the Inhalation Unit Risk has units of risk per. In some sources, the IUR is given in units of risk per µg/m^3; if so, the value is first multiplied by 1,000 to convert to units of risk per mg/m^3.

Similar to the RfC, the IUR is also expressed in terms of exposure (risk per mg/m^3), 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 cancer/inhalation toxicity weight is expressed as Inhalation Unit Risk (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 cancer/oral toxicity weight.

2.4 Weight of Evidence (WOE)

Weight of evidence categories indicate how likely a chemical is to be a human carcinogen, based on considerations of the quality and adequacy of data and type of responses induced by the suspected carcinogen.

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 Indicators 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 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 Risk-Screening Environmental Indicators method does not consider WOE separately for noncancer effects.

3 Chemical Categories and Other Special Cases

EPA's annual 'Reporting Form R and Instructions' describes the reporting requirements for several categories that combine similar chemicals into one release report. For these categories, facilities are not required to report the pounds released of each individual chemical in the category, but only the total pounds released for the entire category. Because the proportions of individual chemicals released within each category are not known, professional judgment was used to assign surrogate values for the various toxicity parameters to each category. In most cases, the most toxic chemical of each category, based on the calculated toxicity weight, was selected, and the toxicity data for the chemical were 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 each chemical category. 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'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

Toxicity information is based on 2,4-D.

3.3 Butyl alcohol, tert- and sec-

Toxicity information is based on n-butyl alcohol.

3.4 Chlorophenols

Pentachlorophenol had the highest toxicity value, so that chemical was used as a surrogate for toxicity data.

3.5 Chromium and Chromium Compounds

Toxicity data for chromium and chromium compounds was based on chromium(VI), the most toxic value in this category. It is assumed that facilities may release some combination of hexavalent chromium and trivalent chromium. SIC-code specific estimates from the 2002 National Emissions Inventory are used to estimate the fraction of each type (available from http://www.epa.gov/ttn/chief/net/2002inventory.html). 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 were used for toxicity scares. For the inhalation toxicity score, hydrogen cyanide was 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 nongaseous cyanide compounds. Copper cyanide was found to be the most toxic of these compounds, so its toxicity score was used.

3.7 Diaminotoluene (mixed isomers)

Toxicity information is based on 2,4-Diaminotoluene.

3.8 Dioxin and Dioxin-like Compounds

EPA first required reporting of releases and transfers for this category in 2000. Facilities were required to report total dioxin releases/transfers (in 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 RY 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[1]. 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 dioxin 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 (EBDC) acid, salts and esters

Chemicals regulated in this category include the pesticides maneb, mancozeb, metiram, nabam, zineb, and amobam. Toxicity data were available for four compounds (mancozeb, maneb, metiram, and zineb); of these, metiram had the highest toxicity weight and so was selected as a surrogate for toxicity data for this category.

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

Toxicity information is based on 2,4-D.

3.11 Glycol ethers

Of the eight common glycol ethers, four had available toxicity data. Ethylene glycol monomethyl ether had the highest toxicity weight of these four, and therefore was used as a surrogate for the category.

[1] 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 http://www2.epa.gov/sites/production/files/2013-09/documents/tefs-for-dioxin-epa-00-r-10-005-final.pdf.

3.12 Hydrazine sulfate

Toxicity information is based on hydrazine.

3.13 Lead and Lead Compounds

The reference dose (RfD) that was used was derived from CalEPA Public Health Goal. An inhalation unit risk (IUR) from CalEPA was excluded and the oral toxicity weight based on a non-cancer endpoint was 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

The slope factor used for maneb is based on ethylene thiourea, as designated in the OPP 8/2000 Report.

3.15 Mercury and Mercury Compounds

Because mercury in various forms converts to methyl mercury in the environment,[2] toxicity information is based on elemental mercury for the inhalation pathway, and methyl mercury for the oral pathway.

3.16 Nitrate Compounds

Toxicity information is based on nitrate.

3.17 Polycyclic Aromatic Compounds

The toxicity of this group is assumed to be 18% of the toxicity for benzo(a)pyrene, its most toxic member. This approach follows that used in EPA's National-Scale Air Toxics Assessment (NATA) evaluation for polycyclic organic matter (POM).[3]

3.18 Sodium dicamba

Toxicity information is based on dicamba.

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[2]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).

[3] Additional information is available in the NATA documentation (http://www3.epa.gov/nata2005/methods.html). RSEI assumes that PAC emissions reported to TRI are most like NATA's "7-PAH" category.

3.19 Sodium nitrite

Toxicity information is based on nitrite.

3.20 Strychnine and salts

This category includes any unique chemical substance that contains strychnine or a strychnine salt as part of its infrastructure. Toxicity information for this category was based on strychnine.

3.21 Thallium and Thallium Compounds

Toxicity information was based on thallic oxide.

3.22 Thorium dioxide

Oral toxicity weight was based on a qualitative assessment of toxicity.

3.23 Warfarin and salts

This category includes any unique chemical substance that contains warfarin or a warfarin salt as part of its infrastructure. Toxicity information for this category was based on warfarin.

4 Sources of Data

Information regarding the human health effects data on the TRI chemicals 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. Data is gathered separately for individual endpoints; a chemical's RfD may be from IRIS, while its Oral Slope Factor may be from HEAST. However, if the source of information for any of the four chronic endpoints is IRIS and there are non-IRIS sources for any of the other 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 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 (at http://www.epa.gov/iris/), 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 RfDs or RfCs 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 work groups before inclusion in IRIS.

4.2 NATA

EPA's National-Scale Air Toxics Assessment (NATA), generally obtains data from the other sources listed in this list, but in some cases uses values derived by the 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 was taken directly from OPP's Pesticide Reregistration Eligibility Documents (REDs).

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, which deals with the effect on public health of hazardous substances in the environment. ATSDR develops Minimum Risk Levels (MRLs) for chemicals on the CERCLA National Priorities List. An MRL is 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 MRLs 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. See http://www.atsdr.cdc.gov/mrls.html for 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 continuously updated and can be found on the internet at http://www.arb.ca.gov/toxics/healthval/healthval.htm.

4.6 PPRTVs

PPRTVs. EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs) include toxicity values developed by the Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center (STSC).

4.7 HEAST

EPA's Health Effects Assessment Tables (HEAST) are constructed for use in the Superfund and RCRA programs but do not represent Agency-wide expert judgments. These tables are publicly available from the Superfund program. The tables include Slope Factors, Unit Risks, 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 reviewed other available data to derive appropriate toxicity weights. Although individual literature searches for toxicological and epidemiological data for each chemical were beyond the scope of this project, sources such as the Hazardous Substances Data Base (HSDB), as well as various EPA and ATSDR summary documents, provided 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 were sufficient to derive values, a toxicity weighting summary was developed summarizing the information used to develop each of these values. The summaries can be found below. The EPA scientists use a technical approach analogous to the Agency's method for deriving RfD values, RfC values, cancer risk estimates, and Weight of Evidence (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.