REPORT ON REVIEW OF TOXICITY VALUES

GTAC Requisition 30-026

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Final December 29, 1999

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1.0 Introduction

The Pennsylvania Department of Environmental Protection (PADEP) maintains a database of toxicity factors for use in its Land Recycling Program, which is available as Table 5 (A and B) of Appendix A of the regulations at Pennsylvania Code Title 25, Chapter 250 (the Regulations). These factors are obtained from a number of toxicity databases. Data are supplemented by making route-to-route extrapolations (i.e., assuming inhalation and oral toxicity factors are equivalent, including the calculation of oral toxicity factors for Reference Concentrations and Cancer Unit Risk Values), and assuming that certain compounds may act as a surrogate in determining the toxicity of another (e.g., the toxicity of 2-methyl naphthalene is assumed to be equivalent to naphthalene). From time to time toxicity values change or superior values are found, requiring an update of this table.

In February of 1999 PADEP provided Ogden Environmental and Energy Services company, Inc. (Ogden) with a series of amendments to the toxicity factors, which Ogden reviewed and prepared a draft report on in April 1999. Review consisted of verifying the numerical value and checking its source and basis. The draft report was reviewed and discussed in a meeting of the Cleanup Standard Science Advisory Board (CSSAB) on June 18, 1999. A discussion at this meeting centered on certain practices used to optimize the number of values that can be applied to the database; in particular the extrapolation of toxicity factors derived from studies using one route of exposure[1] to another. In connection with this discussion was a consideration of how to balance the acquisition of data from the most reliable sources with the need to minimize uncertainty produced by route-to-route extrapolation. The result of this discussion was the creation of a decision tree by the CSSAB and PADEP, which is shown in Figure 1 of this report (Process for Evaluating New Toxicological Data).

The present report provides recommendations from Ogden on each of the toxicity changes delivered by PADEP. The recommendations are based on a review of each change in the context of the Process for Evaluating New Toxicological Data, as well as

[1] Exposure routes are the means by which a compound is introduced to an experimental animal or by which a human is exposed in an environmental situation. Routes of exposure may include ingestion, inhalation, dermal absorption, or injection (intramuscular, intravenous, or intraperitoneal).

verification of the numerical value and determination of whether the value was still current with the organization responsible for maintenance of the toxicity databases. The results of this evaluation, with recommendations and comments are provided in Table 1. Table 1 presents, in addition to the original and suggested toxicity values, answers to the "questions" asked by the process decision tree, which are discussed below, and presents a final recommendation from Ogden. Comments relate to professional judgements entering into the decision. Discussion of the review and recommendations is provided in the remainder of this report.

2.0 The Process for Evaluating New Toxicological Data

The decision Process for Evaluating New Toxicological Data (the Process) shown in Figure 1 requires selecting data from the most reliable source, unless route-to-route extrapolations can be avoided by selecting from a data source lower in the hierarchy. Where both data sources have route-to-route extrapolation problems, information from the higher data source is preferred. Evaluation of information using the Process require definition of the hierarchy of data sources and what constitutes a "problem" for route to route extrapolation.

Hierarchy of data sources: There is no specification of the hierarchy of data sources for the development of Statewide Standards in Act 2, but the hierarchy required for Site-Specific Standards, as noted at 250.605, is appropriate and identifies, by preference:

1. The Integrated Risk Information Service (IRIS)
2. The Health Effects Summary Tables (HEAST)
3. the National Center for Environmental Assessment (NCEA) of the U.S. Environmental Protection Agency (U.S. EPA)
4. The Agency for Toxic Substances and Disease Registry (ATSDR)
5. California EPA (for Cancer Potency Factors), and
6. Various Criteria Documents from the U.S. EPA

The hierarchy is similar to that in many other state programs and seems to represent the sources in order their level of review, frequency of update, and ready-availability of information on the basis of the toxicity values. With regard to the timeliness of the information, it may be of interest to follow developments on the maintenance of the HEAST database. During the course of the review provided in this report, Ogden had

occasion to discuss toxicity information with NCEA (specifically, the Superfund Technical Support Center of NCEA), who, in addition to developing provisional values, were responsible for the publication of HEAST. We were informed that HEAST is now the responsibility of the Oak Ridge National Laboratory, who plan to make the information available on-line. No specific date is known for this availability, but the initial offering will be comprised of data in the 1997 version of HEAST, which is the most recent. The upshot of this planning is that HEAST is currently seriously out of date, to the extent that several of the provisional values from NCEA are more up to date than HEAST information. It will be described later that for at least one toxicity factor (inhalation Reference Dose for chlorobenzene), Ogden has recommended use of a value from NCEA even though it is technically inconsistent with the Process (i.e. the old value was from a higher source, HEAST, and no route-to-route extrapolation problems exist).

Ogden is not necessarily suggesting that a change in the hierarchy of information should be considered at this time, as HEAST is still superior to NCEA in the transparency of information[2]. However, the schedule for release of a new HEAST bears watching.

Route-to-Route Extrapolation: Toxic response to a compound may vary with route of exposure due to differences in pharamcokinetics or because of toxic endpoints that are unique to the exposure route (e.g., portal of entry effects, such as lung irritation by the inhalation route). Pharmacokinetic differences may be complex and were beyond the scope of the present evaluation. For purposes of implementing the Process, a "problem" with route-to-route extrapolation simply means that the extrapolation was done for an endpoint that was likely unique to the studied exposure route. This means that extrapolation across exposure routes would not be considered a problem if the endpoint were a systemic effect that might be expected from any exposure type. It should be noted that Ogden applied a decision rule that a toxicity factor based on the correct exposure route was preferable to a route-to-route extrapolation, even if the latter were considered appropriate. PADEP may wish to consider whether this decision rule is appropriate where the correct exposure route comes from a data source of lower priority than one with an appropriate route-to-route extrapolation (see Table 1 on the inhalation reference dose for ethylene glycol).

[2] The basis for derivation of provisional values in many cases will not be released by NCEA to anyone outside of U.S. EPA.

3.0 Status of Toxicity Values Provided by PADEP

In reviewing the new toxicity values proposed by PADEP, Ogden determined if these values were still current according to the sources indicated in the list and whether the underlying toxicity data and derivation methods were consistent with past practices and the goals of the Land Recycling Program. Sources consulted were:

- IRIS on-line (http://www.epa.gov /ngispgm3/iris/);
- HEAST, 1997;
- telephone and fax communications with officials at the NCEA;
- EPA Drinking Water Regulations and Health Advisories (EPA, 1996);
- ATSDR website[3] (http://www.atsdr.cdc.gov/mrls.htm); and
- California Environmental Protection Agency (California EPA, 1996).

The status of the values provided to Ogden by PADEP in February, 1999 is listed in Table 1[4] and is summarized below.

3.1 Oral Reference Dose (RfD_o)

For the following chemicals, Ogden confirmed that the new RfD_o values are current with IRIS, NCEA, or the most recent Drinking Water Health Advisory list (EPA, 1996):

- Beryllium;
- chromium (III);
- chromium (VI);
- cumene;
- 1,2-dichloropropane;
- methyl methacrylate;
- methyl tert-butyl ether;
- naphthalene;
- 4-nitrophenol;
- 1,3,5-trichlorobenzene; and

[3] The ATSDR publishes Chronic Minimum Response Levels (MRL) which are treated as identical to an RfD per the Regulations.

[4] Where newer data have been found, Table 1 highlights the information as "new data" on a second row for the compound.

- vanadium.

Ogden obtained "new" data on five other RfD_o. One of these values, for chlordane, was a new IRIS citation. The remainder were in the form written documentation on the NCEA provisional values for aniline, 1,3-dichlorobenzene, 1,4-dichlorobenzene, and 1,1,1-trichloroethane, and are discussed in the following section.

3.1.1 NCEA RfD_o Values

A number of the RfD_o values supplied by PADEP are categorized as "provisional" values from NCEA. Provisional values have a finite life of 2 years, at which time they must be re-evaluated or "retired". In checking with this organization, it was reported that a number of the RfD_o values proposed by PADEP, have been retired, including:

- chloroethane;
- 4-nitrophenol (n.b., this value is still present in the 1996 Drinking Water Health Advisory); and,
- trichloroethene.

Thus, it is necessary for PADEP to consider whether they wish to employ a value that is no longer supported by NCEA. In this regard, it is important to recognize that these values are retired based solely on time passed since the derivation of the RfD_o. There is no connotation that anything is wrong with the underlying study or the protocol applied to derive the value. On the other hand, a retired value means NCEA has reviewed no data appearing since derivation was conducted.

NCEA provisional values are often not readily available. Ogden requested several documents supporting "current" provisional values, but was supplied with only one (1,1,1-trichloroethane) by NCEA. Ogden was referred to the Region 3 Toxics Integration Coordinator (RTIC), Dr. Dawn Ioven, who supplied several other NCEA documents (aniline, chlordane, 1,3-dichlorobenzene, 1,4-dichlorobenzene). These documents are reproduced in Appendix A to this Report and form the basis of our evaluation of these compounds. These documents are very informative and it is recommended that a request be made to RTIC to obtain documentation whenever toxicity values in the PADEP database are based on NCEA provisional values.

3.1.2 RfD_o Based on Route-to-Route Extrapolation

Two other RfD_o changes were confirmed based on verification of a Reference Concentration (RfC) in IRIS, which was subsequently used for extrapolation to an oral toxicity factor. These compounds include:

- acetaldehyde; and
- aniline.

As was discussed above, the extrapolation of toxicity factors across routes is an uncertain process that was undertaken in the original development of Table 5 of Appendix A of the Regulations to maximize the available data. Several of the changes provided by PADEP and confirmed in this report were aimed at replacing values derived by route-to route extrapolation with RfD_o values based on toxicity studies using oral dosing, which is an appropriate prioritization of the use of available data. However, certain compounds, such as those addressed here, have no readily available data from oral studies and require route-to-route extrapolation, if an RfD_o is to be had. The Process developed by PADEP and CSSAB are aimed at evaluating extrapolation problems. Ogden applied this Process to the evaluation of all compounds and made several decisions that should be reviewed by PADEP to they are appropriate:

Acetaldehyde: Both the original and the new RfD_o for acetaldehyde are based on extrapolation from the RfC. The RfC for acetaldehyde is based on studies using the toxic endpoint of degeneration of olfactory epithelium (i.e., effects on tissue in the nasal passages), an effect that is relevant only to the inhalation route of exposure. As such, Ogden has recommended that neither the original nor the new RfD_o for acetaldehyde be accepted, because it is questionable whether the route-to-route extrapolation for acetaldehyde is meaningful, verification of the RfC notwithstanding. This recommendation may not be consistent with the Process, in that there are no points on the decision tree that allow for elimination of a toxicity value (either the old values are retained or new values accepted).

Chloroethane: The RfD_o provided to Ogden by PADEP for chloroethane was calculated by NCEA based on a toxicology experiment using the inhalation exposure route (it is important to note that this value is among the "retired" NCEA values). In the derivation, NCEA added an additional uncertainty factor of ten to account for the uncertainty of

route-to-route extrapolation. This approach is not consistent with RfD_o values that have been converted from RfCs by PADEP, where the calculation is made based only exposure parameters (breathing rate and body weight) without an uncertainty adjustment. Therefore, Ogden has recommended that the old RfD_o be retained as more consistent with other calculations. There is no specific consideration of consistency in the Process (Ogden offers its opinion based on the "professional judgement" step in the Process) and PADEP may therefore wish to consider whether the present recommendation has merit.

1,1,1-Trichloroethane: NCEA provided documentation on a provisional RfD_o for 1,1,1-trichloroethane that is based on route-to-route extrapolation using a fairly sophisticated physiologically-based pharmacokinetic model (document provided in Appendix A). NCEA points out that different daily doses would be required to reach the steady-state internal dose level of interest, depending on how long the exposure was to last. Thus, RfD_o based on 7 and 70-year exposure periods were calculated. These values 3.0 and 0.3 mg/kg day are different and appear linear in dosing time. The value provided to Ogden by PADEP is the lower (lifetime) RfD_o from these calculations. This route-to-route extrapolation is perfectly appropriate within the context of the Process, but it should be recognized that in performing this type of extrapolation, NCEA has developed an RfDo that may not be compatible with the algorithms provided in Act 2 for calculating Media-Specific Concentrations (MSC). That is, the ingestion algorithms shown at 250.306 include an "averaging time" for non-carcinogens (AT_{nc}) that is equal to the exposure durations (ED) for the various exposure scenarios. In the case of 1,1,1-trichloroethane, AT_{nc} might more appropriately be a function of the duration assumed to derive the RfD_o by the pharmacokinetic method.

3.1.3 Other

PADEP provided changes to toxicity factors for 2-methyl naphthalene, mercury and thallium that were verified, but require some clarification.

2-Methylnaphthalene: There is no RfD_o published for 2-methylnaphthalene. Previous versions of Appendix A Table 5 include the RfD_o for naphthalene as a surrogate value. Continuing with this practice, the change in the RfD_o for 2-methylnaphthalene reflects the verified change in the RfD_o for naphthalene that was entered into IRIS in September, 1998.

Mercury: The change in the RfD_o for mercury alters the value from 8.57 x 10^{-5} mg/kg day (based on route-to-route extrapolation of an RfC) to 3 x 10^{-4} mg/kg day, based on an oral RfD cited in the Drinking Water Health Advisories (EPA, 1996). The latter value is verified and appropriate, but it must be noted that it is based on experiments with mercuric chloride and therefore relates specifically to ionic, specifically mercuric, forms of mercury. It is generally believed that the mercurous (trivalent) ion of mercury is less toxic than the mercuric forms (Goyer, 1996), so the suggested RfD_o might also be applied to these forms, but would be conservative. The original RfD_o was based on studies with mercury vapor (i.e., elemental mercury), whose toxicity may be both qualitatively and quantitatively different from ionic forms. As such, it may be of use to retain both RfD_o values and specify that one (8.57 x 10^{-5} mg/kg day) is to be applied to sites with elemental mercury and the other (3 x 10^{-4} mg/kg day) is applicable to ionic mercury. It should finally be noted that neither of these values can be used for assessment of organic mercury (particularly methylmercury), for which an appropriate derivation of the RfD_o is currently being debated.

Thallium: The change in the value for thallium represents an adjustment of the RfD_o for thallium carbonate to account for the mass of the thallium ion portion of the compound. This is appropriate, as analytical laboratories are typically report the mass of thallium in an environmental sample, regardless of the compound that may have existed. It further explains why this RfD_o is slightly different than the values presented in IRIS for several salts of thallium (e.g., thallium carbonate, thallium acetate, thallium sulfate). Thus, the RfD_o values in IRIS could also be used for risk assessment under Chapter 250, and indeed would be consistent with the value presented here, if the risk assessor was evaluating a specific salt of thallium (analytical results reporting the total mass of the salt).

3.2 Inhalation Reference Dose (RfD_i)

Ogden confirmed that the new RfD_i values provided by PADEP for the following chemicals are current by verifying in IRIS, HEAST (1997; with confirmation from NCEA), or the ATSDR website:

- acetaldehyde;
- barium and compounds;
- beryllium;

- chlorobenzene;
- chlordane;
- chloroform;
- chromium (VI);
- cumene;
- 1,1-dichloroethane;
- 1,2-dichlorobenzene;
- dichlorodifluoromethane;
- 1,2-dichloropropane;
- 2-ethoxyethanol;
- formaldehyde;
- furfural;
- methyl isobutyl ketone;
- methyl methacrylate;
- naphthalene;
- nickel;
- nitrobenzene;
- 1,1,1-trichloroethane; and
- xylenes (total).

Documentation was obtained from NCEA on chloroform (provided in Appendix A, which confirm the toxicity values supplied to Ogden by PADEP, but documentation on chlorobenzene, and 1,3-dichlorobenzene and tetrachloroethene were in conflict with the PADEP values, as noted in Section 3.2.1.

It should be noted that for a number of the compounds listed above (barium, 1,1-dichloroethane, 1,2-dichloropropane, furfural, methyl isobutyl ketone, nitrobenzene) the "changes" provided by PADEP actually represent a calculation of RfD_i from an RfC using either more or fewer significant figures than applied in the original calculation. For instance, the calculation of an RfD_i from the RfC for 1,1,-dichloroethane provided in HEAST (0.5 mg/m^3) is:

$$(0.5\ mg/m^3 \times 20\ m^3/day)/70\ kg = 0.001\ mg/kg\ day$$

whereas the previous value was calculated as:

$$(0.5 \text{ mg/m}^3 \text{ x } 20 \text{ m}^3\text{/day})/70 \text{ kg} = 0.0014 \text{ mg/kg day}$$

The first calculation (the "new" value) is more appropriate as it represents the correct number of significant figures equal to the number of figures in the RfC from which it was calculated. Ogden recommends that all calculated RfD_i be reported to one significant figure, as this appears to be the number of significant figures reported for the current RfCs underlying the RfD_i. The significant figure correction is noted in Table 1 of this report.

3.2.1 Other

Certain differences between values supplied by PADEP and those ultimately confirmed are noted below:

Acetonitrile: An RfD_i value for acetonitrile different than that provided by PADEP was found in the IRIS database. This newer value is shown in Table 1.

Chlorobenzene: A slightly different value for RfD_i for chlorobenzene than that provided by PADEP was found in the new documentation of the provisional values by NCEA. This newer value is shown in Table 1.

1,3-Dichlorbenzene: There is no RfD_i for 1,3-dichlorobenzene. A value is listed in the EPA, Region III Risk-Based Concentration (RBC) Tables and attributed to NCEA, but in personal communication with this organization Ogden was told that no such value existed. NCEA has written a Risk Assessment Issues Paper on this substance (provided in Appendix A), which concludes that data are inadequate for deriving an RfD. Ogden recommends that the RfD_i for 1,3-dichlorobenzene be eliminated based on lack of supporting information, but recognizes that PADEP may find this to be inconsistent with the Process.

Ethylene Glycol: The RfD_i (actually, an MRL from the ATSDR) for ethylene glycol provided by PADEP was confirmed. However, it should be pointed out that ATSDR considers this an acute value. No chronic inhalation MRL is given. However, ATSDR does provide both acute and chronic MRLs for the oral exposure route and the values are identical. By analogy then, the acute inhalation MRL might be extended to the chronic inhalation exposure situation.

Tetrachloroethene: A slightly different RfD_I than that provided by PADEP was found in NCEA documentation, and has been added to Table 1.

3.3 Oral Cancer Slope Factor (CSF_o)

Ogden reviewed IRIS and CalEPA files and confirmed that the new CSF_o values provided by PADEP for the following chemicals are current:

- BHC, gamma (lindane);
- Beryllium;
- 1,1,2,2-tetrachloroethane;
- chlordane; and
- o-toluidine.

However, it is of note that the change in the beryllium CSF_o occurred because EPA withdrew a value from IRIS, leaving only the CalEPA CSF_o as a still-published value. EPA reports withdrawing the CSF_o due to the fact that tumors in beryllium-exposed animals in the study underlying the toxicity factor were not significantly different from controls. The CalEPA value is based on the same data[5], resulting in the same uncertainty as to whether the CSF_o relates to a meaningful endpoint.

3.4 Inhalation Cancer Slope Factors (CSF_i)

Ogden reviewed IRIS, the CalEPA database, HEAST and NCEA and confirmed that the new CSF_i values proposed by PADEP for the following chemicals are current:

- 2-acetylaminofluorene;
- benzene;
- benzo(a)pyrene;
- bis-(2-ethylhexyl) phthalate
- chlordane;
- 1,4-dichlorobenzene;
- 1,2-dichloropropane; and
- pentachlorophenol;

[5] The difference in the CalEPA CSF_o derives solely from their application of a species scaling factor based on body weight rather than surface area.

Ogden obtained documentation for NCEA provisional values for benzo[a]pyrene, bis-(2-ethylhexyl) phthalate, and 1,4-dichlorobenzene (provided in Appendix A), which form the basis of our review of those compounds.

Finally, it should be noted that the "new" value for TCDD attributed to NCEA also is cited in HEAST (1997). This is noted only because HEAST represents a higher priority data source per the Process.

4.0 Conclusions

Table 1 provides recommendations for modification of the toxicity factors in Appendix A Table 5 of the Land Recycling Program. For the most part, the recommendations are to accept the value provided by PADEP, as it represents a factor from one of the accepted toxicity databases utilized under the Land Recycling Program and represents a change in the value since the creation of Appendix A Table 5 or an alternative, superior value, to those used previously. In the latter category are a number of factors based on experiments where the exposure route was similar to the anticipated exposure scenarios for which the toxicity factor will be used. Thus, the uncertain practice of route-to-route extrapolation is minimized.

During the course of this review, a number of issues were discovered that PADEP may wish to consider as policy decisions. PADEP and CSSAB have developed a process for evaluating toxicity values based on hierarchical data sources and minimizing route-to-route extrapolations. Certain subtleties related to the Process may deserve further clarification. These include:

1. Should be a provision for eliminating a toxicity value altogether (if, for instance, values were withdrawn or could not be documented), as opposed to the current limitation to either choose a new value or retain the former value?

2. If two data sources provide toxicity values, one of which is based on an <u>appropriate</u> route-to-route extrapolation and the other requiring no extrapolation, but the former is from a higher data source, which should take precedent?

Other policy issues deserving consideration include the use of significant figures and whether PADEP wishes to use toxicity factors that are "retired" by the NCEA, given that the documentation for their review may not be available. Ogden recommends that, unless specifically noted in the source databases, a single significant figure for non-cancer (i.e., Reference Dose) values be used, as this seems to be the level at which they are reported. With regard to provisional values, it should be recognized that such toxicity values expire at a specific time by policy, and should not necessarily be regarded as obsolete. However, some consideration to the data becoming available after the derivation of provisional standards may be in order. Ogden recommends requesting documentation on NCEA values whenever the provisional toxicity values are selected for use in the PADEP database. These can be kept on file and periodically reviewed for appropriateness, even after they have been retired by NCEA.

5.0 References

California EPA, 1996. Report of the Risk Assessment Advisory Committee, Appendix B. Tabulated Cancer Potency Values Used by Cal/EPA and U.S. EPA.

EPA, 1996. Drinking Water Regulations and Health Advisories. EPA 822/B-96/002. October.

EPA, 1997. Health Effects Summary Tables FY 1997 Update. EPA 540/R-97/036. July.

Goyer, R.A. 1996. Toxic effects of metals. In Casarett and Doull's Toxicology, The Basic Science of Poisons. 5th Edition. C.D. Klaassen, editor. Pages 709-712.

Figure 1
Process for Evaluating New Toxicological Data