IDENTIFICATION AND SELECTION OF TOXICITY VALUES/CRITERIA FOR CERCLA AND HAZARDOUS WASTE SITE RISK ASSESSMENTS IN THE ABSENCE OF IRIS VALUES

Introduction

The ECOS-DoD Sustainability Work Group's Emerging Contaminants Task Group prepared this paper based on discussions held at the February 2006 Work Group meeting that identified the selection of toxicity values/criteria for Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and hazardous waste sites in the absence of an Integrated Risk Information System (IRIS) value as a specific Risk Assessment issue to be addressed by the Task Group. Risk Assessment was prioritized as an item to be addressed by the Task Group at the November 2005 Forging Partnerships on Emerging Contaminants Forum.

Issue:

Toxicity value/criteria identification is a crucial step in conducting risk assessments. EPA's Office of Superfund Remediation and Technology Innovation (OSRTI) has developed a hierarchy of sources of toxicity information for use in Superfund risk assessments. However, other environmental programs and health and environmental agencies may have developed their own hierarchies for selecting toxicity values and may have different criteria for implementing peer review processes and addressing scientific uncertainties with toxicity values/criteria used in conducting health risk assessments. For example, some States have developed their own specific toxicity values and risk assessment criteria within their States regulatory framework, which may supplement or supersede US EPA guidance for that State's uses. This document is not intended to supersede such State values or regulations but rather to provide guidance and a suggested framework for identification and selection of toxicity criteria/values as the need arises.

The purpose of this paper is to provide recommendations on the identification and selection of toxicity values for those chemicals for which an IRIS toxicity value is not available.

Background:

The EPA Risk Assessment Guidance for Superfund (RAGS), Volume I Human Health Evaluation Manual (Part A) of December 1989 recommended a hierarchy for selecting toxicity factors and justified it by indicating that toxicity information may change rapidly; therefore, the most recent, high quality data should be used. EPA's IRIS was the first step in the hierarchy. At that time, EPA's Health Effects Assessment Summary Tables (HEAST) was the second most current choice. The third tier in the hierarchy was other

EPA documents although it was specifically stated that other document values may not necessarily have been verified by the RfD (Reference Dose) or CRAVE (Cancer Risk Assessment Verification Effort) Work Groups[1]. RAGS specifically stated, "The use of up to date verified information is preferred to the use of interim information and, therefore, toxicity information should be obtained from other EPA references only if information could not be found in IRIS and HEAST. Before using references other than those cited in IRIS and HEAST, check with ECAO [Environmental Criteria and Assessment Office]."

On December 5, 2003, EPA's Office of Superfund Remediation and Technology Innovation (OSRTI) issued guidance as Directive 9285.7-53. This Directive provided a new hierarchy for selecting human health toxicity values to reflect that HEAST values were not being updated and may not have been through an adequate peer review. A tiered approach was developed to prioritize the selection of chemical toxicity data; this hierarchy is directly based on the quality of the underlying toxicity database and the extent of peer review. The tiered approach hierarchy is:

- Tier 1 – EPA's IRIS. The toxicity values listed in IRIS are considered to be validated and have undergone rigorous peer review. The completion of IRIS assessments is a multi-step process including internal peer review, EPA program and regional office review, federal interagency review, and external peer review with a public notice and comment period. The various steps are described in IRIS Track, if one opens and reviews the status of any assessment currently presented http://cfpub.epa.gov/iristrac/index.cfm. The assessment methodologies used for both IRIS and PPRTV assessments are available on this webpage: http://www.epa.gov/iris/backgr-d.htm

- Tier 2 – EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs) – The Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center develops PPRTVs on a chemical-specific basis when requested by the EPA's Superfund program for use in site specific risk assessments. However, the PPRTVs are developed in a shorter period of time and although these assessments undergo external peer review, their development does not include Agency and interagency review as is done with the IRIS assessments. Furthermore, their development typically includes a limited evaluation of information on mode of action, other toxicological end points, and other information that provides a better understanding of the toxicology of these chemicals. Often, the amount of relevant information on the toxicity of these chemicals is less because fewer studies have been conducted and reported. However, the PPRTVs are generally the best quantification of the dose-response scientific data that is available at the time they are developed because the PPRTVs utilize current information and methodologies.

[1] The CRAVE and RfD workgroups no longer exist.

- Tier 3 – Other Toxicity Values – Tier 3 includes additional EPA/non-EPA sources of toxicity information. Priority should be given to sources of information that are most current, peer reviewed, transparent and publicly available. Example sources for Tier 3 include the California Environmental Protection Agency (Cal EPA) toxicity values, the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level and HEAST Table values.

OSRTI Directive 9285.7-53 specifically states "In general, draft toxicity assessments are not appropriate for use until they have been through peer review, the peer review comments have been addressed in a revised draft, and the revised draft is publicly available". However, there are some agencies applying and requiring that the draft toxicity assessments be used in health risk assessments.

Numerous chemicals are now undergoing scientific review and others will be in the future. Sometimes a difference of opinion over chemical-specific toxicity values results in a conflict when performing a site-specific risk assessment for a given chemical (e.g., TCE, perchlorate). Scientific debate regarding proposed toxicity values and adoption by some agencies of these values has in some instances resulted in conflicts over site-specific risk assessments for certain chemicals among various responsible parties, and state health and environmental agencies.

There is a need for a consistent approach to identify toxicity values. It should be noted that EPA/OSRTI did not attempt to identify all Tier 3 sources when it developed the 2003 hierarchy. EPA/OSRTI expects to identify other Tier 3 sources, and is open to other potential Tier 3 sources that States, DoD (or other parties) may propose. Nothing in this paper should be construed as an attempt to limit such flexibility on the part of the States or other parties.

It is also important that flexibility in the selection of the best toxicity value at a point in time be retained. This is described in the OSRTI directive. The OSRTI directive "provides guidance for the sources of toxicity information that should generally be used in performing human health risk assessments at …Superfund sites." It acknowledges that "..in some cases more recent, credible and relevant data may come to the Agency's attention.", and states that "EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties." This discussion in the OSRTI directive is in the context of all sources of toxicity values, including IRIS.

Development of PPRTVs, Tier 2 sources, is described below. Discussion of Tier 3 sources and recommendations for identifying Tier 3 toxicity values follows.

Development of PPRTVs

Many chemicals found at hazardous waste sites have not yet been evaluated by the IRIS program. In order to quantitatively evaluate the risk of these chemicals before they have

been evaluated by the IRIS program, EPA has developed the Provisional Peer-Reviewed Toxicity Values (PPRTVs), which represent the second tier of human health toxicity values for the EPA Superfund and Resource Conservation and Recovery Act (RCRA) hazardous waste programs. The PPRTVs are developed specifically for use in site-specific risk assessment for the EPA Superfund Program, although the RCRA program has also found them useful for their risk assessments. The development of these values provides a useful paradigm for how to address chemicals without IRIS values and what characteristics these toxicity values should ideally possess. These characteristics can also be used to evaluate Tier 3 sources to help select from among divergent toxicity values produced by different public health agencies.

Because the PPRTVs have been developed specifically for EPA's Superfund program, they have not undergone the Agency and interagency review required for toxicity values to be placed in IRIS. For this reason, they can be developed more expeditiously, but they have not been promoted for use in other EPA or non-EPA programs. However, because they are developed using the same type of data sources analyzed with the same level of scrutiny and were developed specifically for use at hazardous waste sites they may be useful to other programs. We encourage EPA to make the PPRTVs publicly available for others to use in hazardous waste site risk assessment and encourage their use where appropriate. Although they appear in the Superfund program hierarchy ahead of toxicity values produced by organizations other than EPA, typically PPRTVs will not be developed if toxicity values of similar quality have already been produced by other organizations such as ATSDR or California EPA. PPRTVs are typically developed at the request of regional EPA risk assessors or as part of the process to replace HEAST.

Characteristics of PPRTVs

A PPRTV is more than a simple toxicity value and includes a support document that describes the general toxicity characteristics of a chemical and basis for development of the PPRTV. As the “provisional” designation for toxicity values connotes less detail in the write-up than for values developed for IRIS, the primary focus for provisional value development will be on the following critical elements:

1. Selection of critical study (or studies),
2. Selection of appropriate dose-response model in deriving toxicity values,
3. Uncertainty factor selection,
4. p-RfD/p-RfC calculation,
5. Carcinogenicity weight-of-evidence classification,
6. Slope factor/unit risk calculation, and
7. Confidence evaluation.

The PPRTV development is consistent with Agency methodologies and practices for the development of toxicity values [including oral reference doses (RfDs) and inhalation reference concentrations (RfCs) for noncancer toxicity and slope factors and inhalation unit risks for cancer risk]. PPRTVs are derived after a review of the relevant scientific literature using the methods, sources of data, and guidance for value derivation used by

the EPA IRIS Program. All provisional peer-reviewed toxicity values receive internal review by two EPA scientists and external peer review by at least three, and typically five, scientific experts. PPRTVs differ in part from IRIS values in that PPRTVs do not receive the Agency and interagency review provided for IRIS values. EPA's ORD and OSRTI jointly developed standard operating procedures for deriving PPRTVs.

Peer review is an important part of the development of PPRTVs. In general, there is a preference for risk assessments that have been externally and independently peer reviewed. The charge questions that are the focus of the external peer review for the PPRTV support documents include the following:

- Is sufficient and appropriate detail available to substantiate the quality and accuracy of the PPRTV manuscript?
- Have all studies been correctly selected, interpreted, and adequately described for the purpose of this document? Comment on the representation of the most important studies, those that define or directly support (or contradict) the quantitative assessment (including uncertainty factors), or support the classification of carcinogenicity.
- Discuss the extent to which the assessment is consistent with EPA's Risk Assessment Methodologies, especially the cancer guidelines or noncancer guidance and whether any departures are reasonable and adequately discussed. Considerations include selection of critical studies, endpoints, relevant toxicokinetic/toxicodynamic data, classification of carcinogenicity, and support for uncertainty factors. This particular charge is meant to address the more general qualitative issues of the guidance.
- Discuss the extent to which the assessment for the derived provisional RfD, RfC, SFO (oral slope factor), and/or IUR (inhalation unit risk) is valid. Comment on the validity and reasonableness of the quantitative derivation and the use of appropriate dose-response models.
- Discuss the extent to which the uncertainties associated with the assessment have been adequately characterized. Comment on the general presentation of uncertainties and whether uncertainties not directly captured in the aggregate Uncertainty Factor are adequately discussed in the "Statement of Confidence"
- Provide any other suggestions for improving the scientific credibility of the assessment.

Because the science and available information evolve, PPRTVs were initially derived with a three-year life-cycle that allowed for frequently used PPRTVs to be reassessed at the end of their three years and renewed or revised, as appropriate. However, PPRTVs are now moving towards a continuous update cycle. If an IRIS value becomes available for a chemical with a PPRTV, it will replace the PPRTV. Sometimes available information is not sufficient to derive a PPRTV, and some PPRTV support documents conclude that a PPRTV cannot be derived based upon the available information.

Other Sources of Toxicity Values

In addition to IRIS and PPRTVs, there are a number of other sources of toxicity values. The quality of these values varies widely and depends on the depth of the toxicity data base, the scientific quality and rigor of the underlying risk assessment and the scope of peer review. Such assessments are generally more acceptable when the methods used for the assessments have been previously established and publicly available and have been themselves peer reviewed. Some available values, such as ATSDR MRLs and Cal EPA criteria have undergone an extensive literature review, a rigorous data analysis using up to-date guidance and methods to derive a toxicity value, and have been thoroughly peer reviewed. However, it should be noted that ATSDR MRLs are limited to non-cancer effects only. At the other end of the spectrum, there may be chemicals with no values and little or no available toxicity information, or outdated studies which are no longer consistent with current methodologies and practices.

IRIS toxicity values are publicly available at http://www.epa.gov/iris/. The PPRTV database is not publicly available, but toxicity values for use on site-specific risk assessments from it may be obtained by contacting the EPA Superfund Program (in Headquarters or in an EPA Regional Office) and being placed on the PPRTV Registered User list. Upon request EPA will send PPRTV assessments to persons on this list. As discussed earlier, the OSRTI hierarchy describes these as Tier 1 and Tier 2 sources. As also discussed above, the OSRTI hierarchy describes other sources of toxicity values as Tier 3.

There appears to be no available database with a comprehensive list of potential values for compounds lacking IRIS values. Possible sources, by no means inclusive, include U.S. Federal Agencies, States, International Agencies (UN), Foreign Governments (Canada, Netherlands), and various non-governmental organizations. Potential pitfalls in these sources include values that are administrative and were not derived using risk assessment, values that include risk management considerations (MCLs), outdated values that were derived using outdated studies and analysis, or values for which documentation of the studies and the analysis of the studies that entered in to the derivation of the values are not available. In some cases, providing toxicity studies are available, a value may need to be derived de novo. Overall, developers of risk assessments need to independently assess the quality of such studies and corroborate data amongst pertinent studies to the extent possible. In this case, the study from which the value is derived (and all studies considered), the analysis of the studies, and calculations to derive the value should be provided to all interested parties. The analysis and derivation of the value should follow current guidance, and some form of peer review should also be included.

In some instances, no information on the chemical may be available. In this situation, an alternative is to identify a chemical surrogate and use its toxicity value as a surrogate for the chemical without data (source chemical). This approach, of course, introduces considerable uncertainty which must be discussed in any risk assessment using this surrogate value. An important point to consider in choosing a surrogate is identification of a chemical with a similar structure and metabolism to the source chemical.

Particularly important is the identification of metabolites associated with toxicity as well as similarities or differences in metabolism, disposition and elimination that exist between the two chemicals.

Identification of other available toxicity values is important, and chemicals should not be dropped from a risk assessment because of a lack of an available IRIS value. In the future, information may be developed as to the toxicity of the dropped chemical or it may have been removed from the suite of chemicals to be analyzed, thereby losing important data and causing the public, regulators and stakeholders to be deprived of potentially useful information. Important chemicals with an insufficient toxicity database should be referred to bodies such as the EPA or the National Toxicology Program for consideration for future testing.

Recommendations

The ECOS-DoD Sustainability Work Group generally supports the use of the OSRTI hierarchy to help identify human health toxicity values for use in site-specific risk assessments. Unless compelling scientific reasons suggest otherwise (e.g. newly published peer-reviewed scientific research), IRIS toxicity values would generally be used when available, and in the absence of IRIS values, then PPRTVs would generally be used. EPA, States and DoD recognize the obligation to protect human health and the environment pursuant to federal and state mandates by using the best available toxicity data and reserve the right to do so. The EPA, States and DoD advocate the use of the following preferences to identify or rank toxicity values. These may also be used when an agency or party would like to propose an alternative to a toxicity value. An understanding of the available sources of toxicity data and the strengths and weaknesses of each source is necessary to select the most appropriate toxicity value for use in a risk assessment, whether the chemical is an “emerging contaminant” with relatively little toxicity data available or a familiar contaminant with an evolving data set.

1. There should be a preference for transparent assessments (in which toxicity values are derived), that clearly identify the information used and how it was used.

2. There should be a preference for assessments which have been externally and independently peer reviewed, where reviewers and affiliations are identified. Other things being equal, there should also be a preference for assessments with more extensive peer review. Panel peer reviews are considered preferable to letter peer reviews.

3. There should be a preference for assessments that were completed with a previously established and publicly available methodology. Methodologies that themselves were externally peer reviewed are preferred over those that were not externally peer reviewed.

4. While there should be a preference for assessments using established methodologies to derive toxicity values, these methodologies should also be informed by the current best scientific information and practices. New assessment methodologies should provide reproducible results and meet quality assurance and quality control requirements.

5. There should be a preference for assessments that consider the quality of studies used, including the statistical power or lack thereof to detect effects; that corroborate data amongst pertinent studies; and that make best use of all available science.

6. There should be a preference for assessments and values which are publicly available or accessible. There may be a further preference for toxicity assessments that invited and considered public comment (as well as, but not in lieu of, external peer review).

7. Other things being equal, there should be a preference for toxicity values that are consistent with the duration of human exposure being assessed. For example, an externally peer reviewed subchronic reference dose (RfD) should be preferred to an externally peer reviewed chronic RfD when assessing an exposure of 2 years for non-cancer toxicity.

The Work Group supports as an overriding principle, that the States, EPA, DoD, and other risk assessors should not be seeking to identify higher or lower toxicity values. Rather, the effort should continue to be to identify the best, or most scientifically defensible, toxicity value. When an agency is unable to identify a scientifically defensible toxicity value, for example due to the lack of relevant toxicological studies or lack of an appropriate surrogate for a given chemical, the site-specific risk assessment should identify this as an uncertainty in the risk characterization.

The recommendations in this paper are intended for site-specific risk assessments that are currently in development or are started after publication of this Issue Paper. As mentioned earlier in this Issue Paper, other environmental programs and health and environmental agencies may have developed their own hierarchies and criteria for selecting toxicity values and conducting health risk assessments. Some States have developed their own specific toxicity values and risk assessment criteria which within their States regulatory framework may supplement or supersede US EPA guidance. The intent of this document is not to supersede such State regulations but rather to provide guidance and a suggested framework for identification and selection of toxicity criteria/values as the need arises. When there are challenges or questions regarding alternative toxicity values, we believe that following this systematic process for ranking values can facilitate resolution. Furthermore, using the preferences described above may help minimize disputes regarding human health toxicity values and we encourage their use.