ES/ER/TM-38

Approach and Strategy for Developing Human Health Toxicity Information for Contaminants of Concern at Sites Administered by the U.S. Department of Energy Oak Ridge Field Office Environmental Restoration Program

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CONTENTS

EXECUTIVE SUMMARY

Toxicity assessment is an important part of the risk assessment effort presently under way at U.S. Department of Energy Oak Ridge Field Office (DOE-OR) Environmental Restoration (ER) facilities. Four major tasks in the toxicity assessment process are (1) identification and prioritization of contaminants of concern at DOE-OR ER sites; (2) compilation and dissemination of toxicity values approved by the U.S. Environmental Protection Agency for the contaminants of concern and identification of contaminants requiring toxicity value development (i.e., reference doses, reference concentrations, and slope factors); (3) development of toxicity summaries; and (4) development of toxicity values. Prioritization of chemicals was the first step because resources are limited and because the chemicals that pose the greatest risk of human exposure need immediate assessment. Identifying and disseminating the toxicity values for the chemicals of concern is also important because these toxicity values are the basis for determining whether environmental levels are of concern. It is very important that all parties conducting health risk assessment for DOE-OR ER sites have the most current toxicity values so that risk assessment will be consistent. The toxicity summaries for the chemicals of concern briefly summarize what is known concerning the toxicity of each chemical and present the information in a way that is useful for the risk assessor. After existing toxicity values are located and the toxicity summaries prepared, the chemicals that have sufficient information to derive missing toxicity values can be identified. Where toxicity values are missing and the information is deficient to derive the values by conventional means, predictive toxicology methods will be employed.

1. PURPOSE

Human health risk assessments for hazardous waste sites combine dose estimates and toxicity estimates to quantitatively calculate the risks to human health posed by each contaminant of concern. For many contaminants of concern at U.S. Department of Energy Oak Ridge Field Office (DOE-OR) Environmental Restoration (ER) facilities, no toxicity estimates have been approved by the U.S. Environmental Protection Agency (EPA). At best, the lack of toxicity estimates has necessitated a purely qualitative approach for assessing risks posed by these contaminants. At worst, there has been no alternative but to place these contaminants in a ''black box" of unknown risk. The goal is to take the contaminants out of the black box, so that a quantitative approach to assessing risks to human health can be made. Thus, toxicity values will be developed for contaminants that are of concern at DOE-OR ER sites for which no EPA-approved values have previously been developed. The proposed research will not only benefit the DOE-OR ER Program, but it will also benefit environmental restoration programs across the country.

2. SCOPE

Toxicity values will be developed for both carcinogenic and noncarcinogenic toxic effects of chemicals of concern at DOE-OR ER sites. Radionuclides will be evaluated separately. Effects will be evaluated for the inhalation and ingestion routes of exposure. Effects involving dermal exposures will be considered separately. For noncarcinogenic effects, both subchronic and chronic effects will be quantified.

3. APPROACHES

Toxicity value development will involve four major tasks: (1) identification and prioritization of contaminants of concern at DOE-OR ER sites, (2) compilation and dissemination of EPA-approved toxicity values for the contaminants of concern and identification of contaminants requiring toxicity value development, (3) development of toxicity summaries, and (4) development of toxicity values using computerized literature searches and EPA methodology. Information on the relevant epidemiological or experimental studies and the toxic and/or carcinogenic effects will be compiled for all contaminants of concern at DOE-OR ER sites. These summaries will be made available to all parties involved in risk assessment at DOE-OR ER sites.

4. INTRODUCTION

One of the initial steps in the toxicity assessment phase of risk assessment consists of collecting or, when not available, calculating appropriate toxicity values for the chemicals under consideration. When available from EPA, reference doses (RfDs) and reference concentrations (RfCs) (for noncarcinogenic effects) and carcinogen slope factors (CSFs) (for carcinogens) will be identified for the chemicals of interest. An RfD or RfC is an estimate of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime or a portion of a lifetime (EPA 1989). Chronic RfDs and RfCs are developed to estimate acceptable long-term exposures (from 7 years to a lifetime); subchronic RfDs and RfCs are developed to estimate acceptable short-term exposures (2 weeks to 7 years). A CSF is an upper-bound estimate of the probability of a carcinogenic response for a given unit intake of a chemical over a lifetime (EPA 1989).

When RfDs, RfCs, and CSFs have been identified or developed, they can be compared to exposure estimates and the risk can be characterized. Initial risk assessment activities have shown that for only a few of the chemicals of concern at DOE-OR ER sites are all of the above-mentioned criteria available, and both the *Risk Assessment Guidance for Superfund: Volume I* (*RAGS*) (EPA 1989) and the risk assessment staff of EPA Region IV indicate the need for criteria to be developed for those chemicals having a toxicity that is not quantified for effective use by the risk assessor. In many instances, the chemical-specific toxicity data are not available, and therefore, no quantification is possible.

The toxicity assessment also includes a qualitative assessment of the toxic effects of the contaminants of concern at the site. A toxicity summary is compiled for all contaminants for which epidemiological, experimental, metabolic, or pharmacokinetic studies have been undertaken. The results and uncertainties associated with the studies are presented, and the likely human health effects for the various exposure routes and for possible sensitive subpopulations are described.

4.1 SOURCES OF TOXICITY VALUES AND OF GENERAL TOXICITY INFORMATION

A number of sources provide toxicity information for a variety of chemicals. The preferred EPA toxicity factors are verified RfDs (for oral exposures) or RfCs (for inhalation exposures) for noncarcinogenic effects and oral and inhalation CSFs or inhalation unit risks for carcinogenic effects. The *Integrated Risk Information System (IRIS*) (EPA 1991) provides the EPA-approved RfDs, RfCs, and CSFs. *IRIS* also provides health advisories from the EPA Office of Drinking Water, EPA regulatory action summaries, data on acute health hazards, and physical and chemical properties. *IRIS* is available on line and is updated approximately monthly.

If *IRIS* does not provide a verified value for a chemical, then the *Health Effects Assessment Summary Tables (HEAST)* (EPA 1992) should be consulted. *HEAST* is a compilation of toxicity values for chemicals that have been identified as being present at Superfund or Resource Conservation and Recovery Act sites and that have undergone some level of EPA review but have not received final EPA approval and, thus, are not on *IRIS*. These RfDs, RfCs, CSFs and unit risks should be used in the absence of verified values. *HEAST* summarizes in a tabular form information

from (1) health effects assessments, (2) health and environmental effects documents, (3) health and environmental effects profiles, (4) health assessment documents, and (5) ambient air quality criteria documents. *HEAST* not only provides general toxicity information but also directs readers to other current sources of information. *HEAST* is updated quarterly.

If no toxicity values are available for a contaminant, then the toxicity values may be derived independently using EPA methodology. Until such values are developed, the chemical should be addressed qualitatively in the risk assessment using EPA criteria documents (e.g., drinking water criteria documents, drinking water health advisory summaries, ambient water quality criteria documents, and air quality criteria documents) and toxicity summaries from the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR is assembling toxicology summaries for 275 hazardous substances that supply general toxicity information as well as the levels of exposure associated with lethality, cancer, and various other toxic effects.

4.2 EPA GUIDANCE ON THE DERIVATION OF TOXICITY VALUES

General guidance provided by *RAGS* for the generation of toxicity values is as follows.

- The relevance and scientific quality of the scientific studies considered for evaluating toxicity values are primary considerations in determining the validity of the final toxicity value generated.
- Human epidemiological studies are the favored source of information for toxicity factors. If these are inadequate for a quantitative assessment, then they should be used to support data from other studies.
- Experimental studies on nonhuman mammals (e.g., rats, mice, rabbits, guinea pigs, hamsters, dogs, and monkeys) are the second most favored source of information.
- Data from animal studies should, when available, be supported by metabolic and pharmacokinetic studies to ascertain the degree to which results from the particular animal species are applicable to humans. Data from cell culture or microorganism studies may be used as supporting evidence of carcinogenicity.
- If studies on more than one animal species are available, then studies on the animal species that are most relevant to humans should be considered. This decision should be based on metabolic and pharmacokinetic information and, in the case of inhalation experiments, on the respiratory anatomy and physiology of the respective species. If one species cannot be deemed the most appropriate, then the species that is most sensitive to the toxic effects of the chemical should be considered. For carcinogenic effects, the geometric mean of the CSFs derived from different studies on different species may be used.
- Experimental studies that involve doses similar to the environmental exposures expected are preferred. Long-term exposure studies are favored for determining long-term health effects.
- For the evaluation of noncarcinogenic effects, an uncertainty factor of 10 should be applied to the ‘‘no-observed-adverse-effects level” (NOAEL) [or, if this is not available, the ‘‘lowest-observed-adverse-effects level” (LOAEL)] when extrapolating from an animal species to humans to account for the possibility of humans being more sensitive to the particular chemical than the model animal species is. Other uncertainty factors that are often used include a factor of 10 to account for sensitive human subpopulations and up to a factor of 10 for (1) subchronic

to chronic exposures, (2) LOAEL to NOAEL, and (3) an incomplete to complete toxicity data base.

- For the evaluation of carcinogenic effects in the absence of specific information, one should assume that humans are equally sensitive to the effects as an animal species, taking into account differences in body weight. (One does not need to account for body weight differences for inhalation experiments for gases and vapors.)
- In the absence of sufficient toxicity information for a particular chemical, structural activity studies may, in some circumstances, be considered. These may enable derivation of a toxicity value from comparisons with structurally related chemicals.

5. IMPLEMENTATION STRATEGY

5.1 PRIORITIZATION OF CONTAMINANTS OF CONCERN FOR TOXICITY VALUE DEVELOPMENT

Over 120 chemicals have already been identified as being of potential concern at DOE-OR ER facilities. Because resources are limited, the list of chemicals of concern needs to be prioritized so that contaminants requiring immediate attention can be identified.

Two criteria have been selected for prioritizing chemicals: (1) whether the contaminant may have been released off site (contaminants in the off-site environment are assigned a high priority because the likelihood of public exposures is higher) and (2) the number of sites at which the contaminant has been identified as being of concern. Chemicals that have already been identified as being of concern at a number of DOE-OR ER sites are assigned a high priority, because they are likely to be of concern at many other sites that have not yet been characterized. Such contaminants are likely to play a major role in future risk assessment activities at DOE-OR ER sites. These two prioritization criteria have been applied to all contaminants of concern at six sites on the Oak Ridge Reservation (ORR). Contaminants are divided into four groups.

- **First priority.** Contaminants of potential concern off site and at two or more other sites (18 inorganics, 9 organics).
- **Second priority.** Contaminants of potential concern off site and at less than two other sites (8 inorganics, 21 organics).
- **Third priority.** Contaminants of potential concern at two or more sites but not off site (3 inorganics, 15 organics).
- **Fourth priority.** Contaminants of potential concern at only one site and not off site (7 inorganics, 46 organics).

Additional criteria will be used to further prioritize chemicals within each of the four categories. For example, higher priority will be assigned to contaminants that are known to be highly toxic or carcinogenic. For third and fourth priority contaminants of concern (i.e., contaminants that have not been identified as being of concern in the off-site environment), contaminants will be assigned high priority if they have been detected in the surface water or groundwater because of their potential for migrating to the off-site environment.

The preliminary list may also be modified as site characterization data become available from more sites. Certain contaminants initially assigned a low priority may be given higher priority if further studies indicate that they are likely to pose a significant threat to human health at DOE-OR ER sites. Schedules and time constraints in the Remedial Investigation/Feasibility Study process may also result in reprioritization, particularly if it is thought that excluding a chemical from a quantitative risk assessment because of the lack of toxicity values would result in an inadequate characterization of the true risks posed by a site. However, the competing needs of the risk assessment activities at different sites will mean that time constraints alone cannot dictate the prioritization of chemicals.

Further site characterization studies may also identify new contaminants that were not of concern at the initial six sites used to compile the original list. However, the initial indications are that most of the DOE-OR ER contaminants are already included in the list. Recent data for a number of additional sites at the Oak Ridge Y-12 Plant indicate only one further contaminant of concern. Preliminary data for the Paducah Gaseous Diffusion Plant indicate no further contaminants. Any new contaminants identified at additional sites will be added to the list and prioritized on a case-by-case basis.

5.2 COMPILATION AND DISSEMINATION OF EPA-APPROVED TOXICITY VALUES

5.2.1 Compilation

The next step in the process is to identify the EPA-derived toxicity values for chemicals of concern at DOE-OR ER facilities. Chemicals that have an oral RfD but no inhalation RfC (or vice versa) must be identified, as must those that have an oral but no inhalation CSF or unit risk value (or vice versa) and those that have no toxicity values at all. This step has already been completed for the toxicity values available from the most recent *IRIS* update and *HEAST* tables. Of the more than 120 chemicals, only one, methylene chloride, has been assigned a complete set of toxicity values [i.e., RfDs, RfCs and CSFs (or unit risks)]. As specified in *RAGS*, the Environmental Criteria and Assessment Office in Cincinnati, Ohio, and Research Triangle Park, North Carolina, will be contacted to determine if toxicity values are being developed for contaminants of concern at DOE-OR ER sites.

5.2.2 Dissemination

Because it is important that consistent approaches be adopted by all DOE-OR ER risk assessments, available toxicity values will be disseminated to all parties involved in risk assessment activities in the DOE-OR ER Program. The timely provision of a listing of the most current toxicity values can be accomplished by providing, on a regular basis, a table compiling the chemicals found in *IRIS* and *HEAST* with their corresponding toxicity values.

The second issue of the above table has already been released to risk assessors and project managers at all five DOE-OR sites [Oak Ridge K-25 Site, Oak Ridge National Laboratory (ORNL), Oak Ridge Y-12 Plant, Paducah Gaseous Diffusion Plant, and Portsmouth Gaseous Diffusion Plant]. The next release will occur when new *HEAST* data and *IRIS* updates have been received by the Biomedical and Environmental Information Analysis (BEIA) Section of the Health and Safety

Research Division. Comments and suggestions from recipients will be incorporated in all future releases where necessary.

5.3 DEVELOPMENT OF TOXICITY SUMMARIES

The toxicity assessment portion of the baseline risk assessment includes a description of the toxic effects of each chemical assessed. Because many DOE-OR ER contaminants are found at a number of different sites, an on-line toxicity summary data base including all DOE-OR ER contaminants of concern will be developed. Risk assessors at all five DOE-OR ER sites will be able to access the data base. This will prevent duplication of effort and will ensure consistency in risk assessment approaches across different sites. The data base will be updated periodically as more toxicological information becomes available and as more contaminants of concern are identified at DOE-OR ER sites.

Toxicity summaries have already been developed for a number of DOE-OR ER contaminants. These summaries consist of an executive summary that should be included in the ‘‘Toxicity Assessment’’section of the risk assessment. The remainder of the summary will be available as a reference source. The toxicity summaries also indicate the available data that can be used to derive missing toxicity values and identify data gaps, thus signaling the consideration of predictive toxicity.

5.4 DEVELOPMENT OF TOXICITY VALUES

Two approaches will be used to develop toxicity values for DOE-OR ER contaminants for which EPA has not developed values. For contaminants with sufficient toxicology data, the standard EPA methodology will be applied to derive RfDs, RfCs, and CSFs. A predictive toxicological approach will be applied for cases where sufficient data do not exist. This latter approach uses short-term data to predict carcinogenic effects. The predictive approach may also be used as a temporary means of evaluating lower priority DOE-OR ER contaminants until the standard EPA methodology has been applied.

5.4.1 Derivation of RfDs, RfCs and CSFs Using EPA Methodology

Computerized literature searches will be conducted to identify appropriate toxicity-related information, including unpublished studies submitted to EPA. In addition, the BEIA staff has written health-related summary and risk assessment documents for over 300 chemicals, and this information will be used as appropriate. For a number of chemicals, there will be insufficient information to develop reliable toxicity values. This insufficiency will be documented and sent to EPA. When there are sufficient data, EPA methodologies described in *RAGS* will be used to derive toxicity values for both noncarcinogenic and carcinogenic effects.

Once the toxicological data for a chemical have been evaluated, the resulting toxicity value will, following appropriate internal review, be submitted to EPA for approval along with documentation describing how the value was obtained. Included in this explanation will be a description of the types of effects of the chemical (e.g., noncarcinogenic, carcinogenic, mutagenic, reproductive, or developmental). The studies from which the values were derived will also be described. This description will include species, route of administration, dosages, frequency of

exposures, duration of exposures, and critical effect. The actual method of derivation will be reported along with references for the studies cited in the discussions.

5.4.2 Application of Predictive Toxicology

The Risk Analysis Section of the Health and Safety Research Division at ORNL has developed a relative potency model for predicting the carcinogenic potency of chemicals for which no EPA-derived CSFs are available. Previous models used to predict carcinogenic potency have relied on a single class of short-term data (e.g., mutagenicity data). The Risk Analysis Section's relative potency model uses several types of short-term toxicological data to predict carcinogenic potency. Validation studies show that variation in the carcinogenic potency estimates predicted for a number of carcinogens using the relative potency model explains over 90% of the variation in the actual estimates derived for those carcinogens. Theoretically, the model can also be adapted for predicting noncarcinogenic effects of chemicals. Validation studies will be performed for noncarcinogenic effects, and if these are successful, then the model will be used to develop toxicity values for noncarcinogenic as well as carcinogenic effects.

The relative potency model will be used as a temporary means of evaluating all priority chemicals that will not be evaluated using the standard EPA methodology. The predicted toxicity values derived by the model will only be applied in the ''qualitative" section of risk assessments, and the use of the values will be accompanied by explicit statements regarding their limitations. This approach will be used only when other approaches are inapplicable.

6. REFERENCES

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