CRITERIA FOR SELECTING TOXICOLOGICAL PROFILES FOR DEVELOPMENT

DIVISION OF TOXICOLOGY

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
U.S. PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Background

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), Section 104(i) [42 U.S.C. 9604(i)], as amended by the Superfund Amendments and Reauthorization Act [Pub. L. 99-499], directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) and the Administrator of the Environmental Protection Agency (EPA) to prepare a list of hazardous substances most commonly found at facilities on the National Priority List (NPL) and which, in their sole discretion, are determined to pose the most significant potential threat to human health. ATSDR is then to prepare toxicological profiles on these substances and assure the initiation of a research program to fill identified data needs associated with the substances.

Toxicological profiles are prepared for hazardous substances chosen based on the listing activities of the Quality Assurance Branch (QAB). These profiles provide an examination, summary, and interpretation of available toxicological and epidemiological studies on hazardous substances in order to ascertain the levels of significant human exposure to a given substance and the associated health effects. Information on toxicokinetics, biomarkers of exposure, effect, and susceptibility, interactions with other chemicals, environmental fate, levels in environmental media and biological tissues and fluids, physical and chemical properties, analytical methods, information regarding production, import, export, use, and disposal, and other subjects are also discussed in these

documents. Additional toxicological tests which may be needed to enhance the current knowledge of human health risk from exposure to hazardous substances are identified as "data needs" in the profiles. These "data needs" are prioritized by the Research Implementation Branch (RIB) to create "priority data needs". The new information provided through this activity is funneled back into the profile development process to fill in the gaps of knowledge.

The intended audiences for the toxicological profiles are the general public, environmental and health professionals in the private and public sector, and interested private organizations and groups.

Overview

In addition to preparing new profiles on hazardous substances, and as directed by CERCLA, section 104(i)(3), ATSDR reviews the published profiles no less often than once every three years to determine if revision and re-publication (updating) are warranted. The overall goal in updating the profiles is to enhance the risk assessment process to the greatest possible extent. To reach this goal, ATSDR has developed criteria for evaluating which profiles would benefit most from being updated. ATSDR considers certain factors important in making the determination regarding which new substances will be profiled and which profiles will be updated. These factors include:

1) Frequency of occurrence at NPL sites;

2) Toxicity;

3) Potential for human exposure;

4) The availability of new information.

The strength of each of these factors will be evaluated as described in the following sections. The general procedure used will be to assign scores to each of the factors listed above to derive a "profile need score", which is used to list substances in order of priority for profile development.

The updating of previously released profiles cannot be accomplished without considering the development of profiles on substances which have not yet been profiled. A determination must be made as to the relative benefits of updating a profile or developing a profile on a new substance. Therefore, new substances will also be scored and ranked along with the update candidates in order of priority for profile development.

ATSDR wishes to be responsive to public health needs as they arise. Therefore, requests from health agencies to develop profiles on specific substances of public health concern will be considered in making the final decision on the selection of profiles for development. Examples of such situations would be where the profile need score of a substance may not be high, yet its impact on human health and on risk assessment are of concern. In such cases, ATSDR may develop a profile even if the general quantitative procedure outlined in this document would ordinarily exclude it from consideration.

For each update candidate, a reviewer will examine the literature published since the release of that profile. Using the procedures described below, the reviewer will assign each substance an "information score." In the case of new substances, a default information score is assigned.

The information score will be combined with the scores for frequency of occurrence, toxicity, and potential for human exposure as derived previously by the QAB to derive the ATSDR Priority List of Hazardous Substances (ATSDR 1992). The new information score will be given equal weight with each of the other three scores to calculate a "profile need score".

The Profile Selection Committee will present to the Division Director a summary of all substances

evaluated, including the recommendation for each substance and the rationale for each recommendation.

A more complete discussion of each of the factors: frequency of occurrence, toxicity, potential for human exposure, and the availability of new information are discussed more completely below.

Method for Selecting Toxicological Profiles for Development

Frequency of occurrence, Toxicity, and Potential for Human Exposure

A notice of the availability of the Priority List of 275 Hazardous Substances was published by ATSDR on October 28, 1992 (57 FR 48801). This list is based on the most comprehensive information currently available and is revised on an annual basis as additional information is gathered. Substances are ranked in order of priority based on the individual scores for their frequency of occurrence at NPL sites, toxicity, and potential for human exposure, according to the

$$TOTAL\ SCORE = NPL\ FREQUENCY + TOXICITY + POTENTIAL\ FOR\ HUMAN\ EXPOSURE$$

following algorithm:

The procedures used to prepare this list are available (ATSDR 1992). The score and subsequent rank of a substance reflects the potential of the substance to impact human health and is a measure of these three factors combined and weighted equally.

Availability of New Information

When a profile is published, areas of research which need further exploration are noted in the profile. The ATSDR Substance-Specific Applied Research Program then identifies which of these "data needs" are "priority data needs". With time, data relevant to these areas is expected to

become available, either due to general development in the field, or as a direct consequence of the ATSDR Substance-Specific Applied Research Program. The availability of new studies that fill these defined data needs or in some other way contribute significantly to the understanding of the toxicology of the substance and increase the reliability of risk assessment is a critical element in the decision of which profiles to update. Studies which are not expected to contribute significantly to the risk assessment process are not weighted as heavily as those which are expected to impact the risk assessment process.

Studies are grouped into three categories: 1) Studies providing health effect data (including both epidemiological and toxicological studies), 2) Studies providing information regarding the potential for human exposure, and 3) Studies providing supplemental data.

Numerical values are assigned to represent a judgement of the relative importance of information in each category. Scores for each category will be combined to obtain an "information score". This will permit a comparison between profiles that is based on the significance of the information rather than the volume of literature.

In the case of new substances, or substances which have not been profiled, the "information score" is assigned. The score assigned will be one (1) greater than the maximum score found for all of the update candidates. For example, if after a review of the literature for a given pool of update candidates, the highest "information score" calculated is 21, then all new substances being considered would receive an "information score" of 22. This rationale gives greater weight to new substances, acknowledging that developing a profile on a new substance will fill a greater void in the pool of information available to health assessors than will updating a profile.

Specific descriptions of the process for assigning literature scores to update candidates are discussed below.

Health Effect Data

Epidemiology: Human epidemiological studies can provide important information regarding the relationship between health effects and exposure to a hazardous substance. They can be an important tool when attempting to identify and characterize the health risks due to exposure to a hazardous substance. Despite inherent study limitations, well conducted epidemiological studies are preferable over animal toxicological studies. In general, epidemiologic studies are given a higher priority than are toxicological studies on animals.

All new epidemiological studies which are located are evaluated for quality (The Chemical Manufacturers Association's Epidemiology Task Group 1991). The quality of a study is the first consideration in determining the importance of the new information. While the meeting of all of the guidelines for good epidemiology practice is ideal, it can be expected that most studies will not meet every guideline. Study limitations, however, may not always diminish the contribution of a study in understanding the adverse health effects resulting from human exposure to a hazardous substance and the levels of significant exposure.

If the quality of a study is determined to be adequate, it is evaluated using the Information Scoresheet (see appendix A). Refer also to figure 1. In general, epidemiological studies which address "data needs" or "priority data needs" are given greater weight in terms of scoring. Studies which refute existing information is also given greater weight, while studies which confirm existing information, although useful for supporting conclusions, are not weighted as heavily.

ATSDR considers the Minimal Risk Levels (MRLs) to be important in risk assessment, therefore, extra points are given to studies expected to impact MRL derivation.

Toxicology: The health effects associated with levels of exposure to a substance are often determined in toxicological studies where either humans or animals were the subjects. Human and animal toxicological studies are useful for a thorough understanding of the health risk to humans exposed to hazardous substances. In the ATSDR toxicological profiles, toxicological studies are interpreted to determine the significant risk associated with exposures. Clearly, it is essential to consider the strengths and limitations of the studies being evaluated. Quality toxicological studies are necessary for health professionals to make sound judgements on the public health implications of exposures to hazardous substances. Therefore, the study quality should be the first consideration in determining the importance of new information for understanding human health risk (NRC 1984). Studies which meet the optimal quality guidelines would be most useful; however, as with the epidemiological studies, not all studies will meet these standards. ATSDR may determine that the limitations of a study do not exceed its importance for better understanding the potential risk to humans.

If the quality of a study is considered to be adequate, the study is evaluated using the Information Scoresheet (see appendix A). Refer also to figure 2.

Studies with animals are more frequently available; however, evidence on the health effects from human exposures is preferred and is given greater weight.

In general, studies that address "data needs" or "priority data needs" are scored highest. Studies which refute previous conclusions are also scored highly, as are studies that add other types of new

information likely to impact risk assessment. Studies which confirm existing data or contain data less likely to impact risk assessment are given less weight and consequently, lower scores.

Human studies are weighted more heavily than are animal studies. Toxicological studies which use routes other than inhalation, oral, or dermal exposure are assigned minimal importance for evaluating the relevance to human health. Though considered in the procedure, these routes are of limited importance because inhalation, oral, or dermal routes of exposures are the most relevant to human exposure to substances at hazardous waste sites.

As with epidemiological studies, additional points are given to studies expected to impact MRL derivation.

Potential for Human Exposure

The potential for human exposure to hazardous substances in the environment is an important consideration in evaluating the risk a substance poses to human health. Therefore, this type of information is considered in the update process. However, this category is not given as high a priority as are health effect data from epidemiological and toxicological studies. Several areas of information (subcategories) are helpful in making the determination for the potential for human exposure. These areas include, but are not limited to, environmental and biological monitoring information, toxicokinetics, environmental fate, chemical release information, bioavailability, bioaccumulation, and chemical and physical properties.

As always, the quality of a given study is of paramount importance in determining whether it would add to the reliability of risk assessment. If the quality of a study is adequate, it is scored based on the criteria shown in the information scoresheet (see appendix A). Refer also to table 1. In general, greater weight is given to information which addresses a "data need" or "priority data need".

The toxicokinetics of a substance, including its absorption, distribution, metabolism, and excretion can significantly affect health effects caused by that substance. Therefore, toxicokinetic studies can enhance the risk assessment process.

Human exposure data (levels of hazardous substances or metabolites in biological tissues or in the environment) from appropriately selected populations or sites are of value for evaluating the public health implications because they provide a direct measurement of human exposure to hazardous substances. ATSDR focuses on determining the impact of hazardous substances at NPL sites on the surrounding human population. Therefore, the data on NPL sites are considered most valuable. Data on the general population is also rated highly. Occupational exposure data also contributes to our understanding of potential health effects in humans exposed to hazardous substances. However, caution must be taken in

Figure 1. Decision Tree for Evaluating Epidemiological Studies

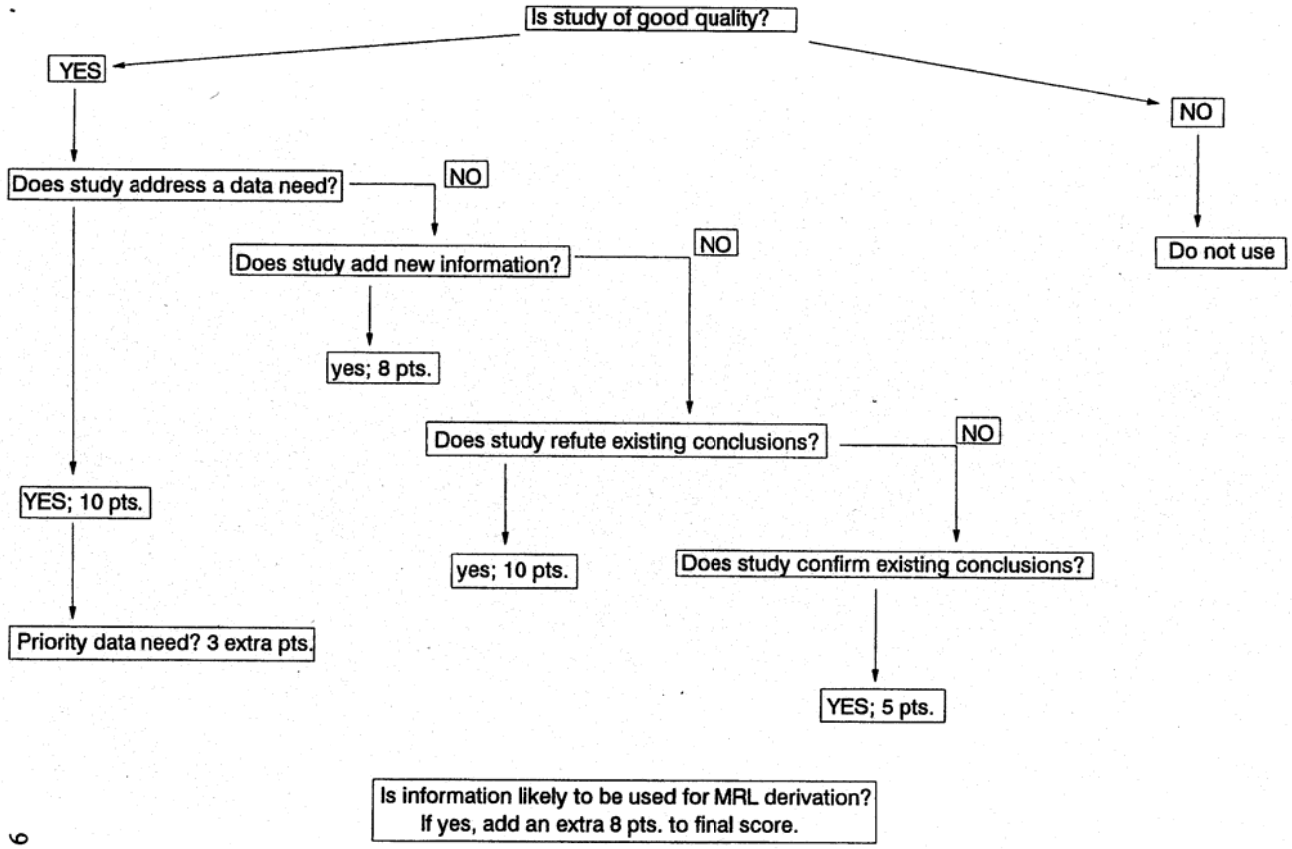
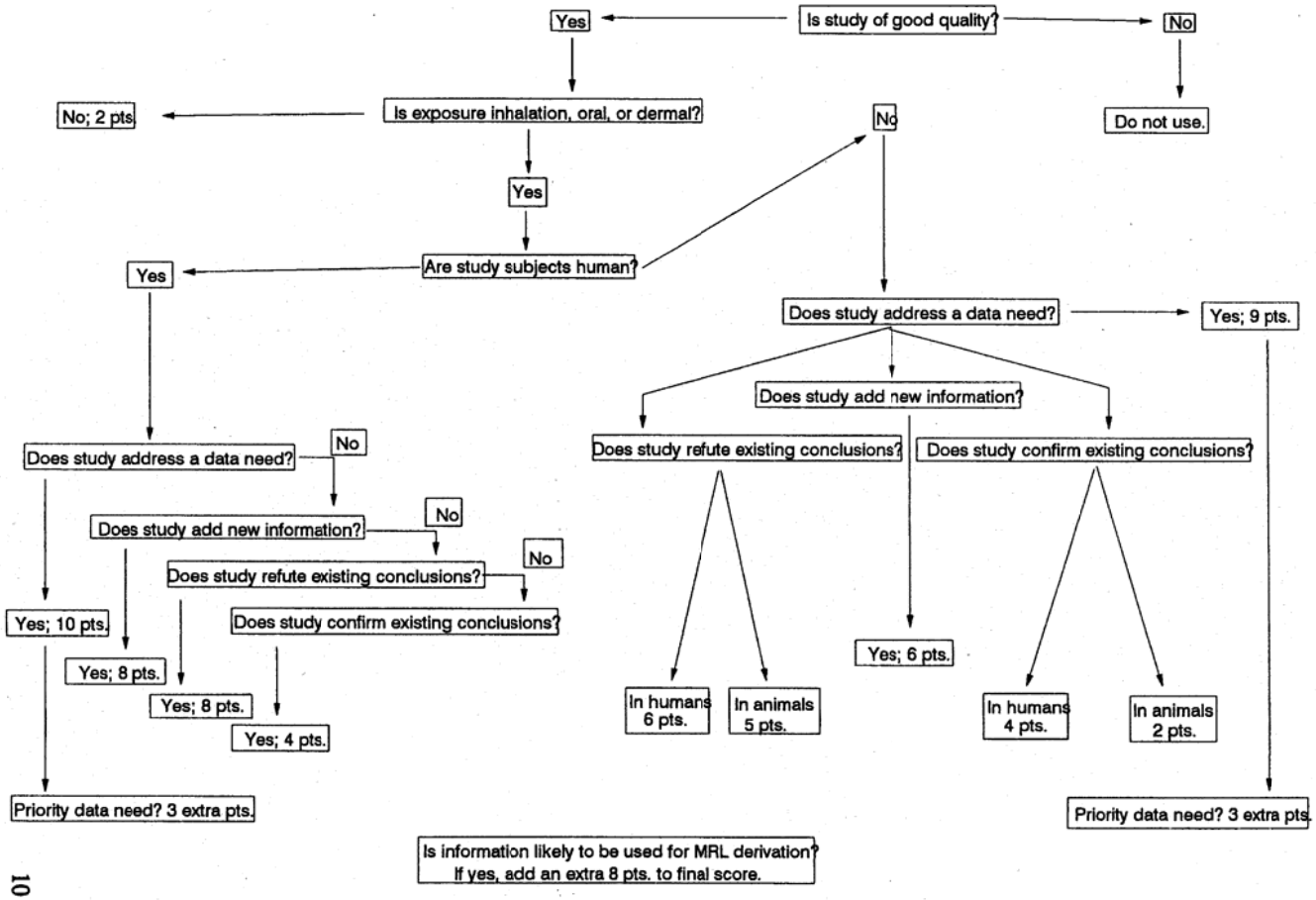


Figure 2. Decision Tree for Evaluating Toxicological Studies



interpreting occupational exposure data because of confounding factors such as simultaneous exposure to other chemicals in the workplace. In addition, workers are not representative of the general population which includes children, the elderly, and the infirm.

Information on the environmental fate of hazardous substances (partitioning between various environmental media, transport, transformation, or activation) contributes to our understanding of the persistence of these substances in the environment and how the potential for human exposure may be altered by these processes. New information on chemical and physical properties could also be helpful in estimating the environmental fate of a substance.

Data on bioavailability (the absorption of hazardous substances from contaminated air, water, soil, or plant material), and bioaccumulation (the bioconcentration and/or biomagnification in plants, aquatic organisms or animals) are useful for identifying relevant exposure pathways for humans.

In the absence of monitoring information, chemical release information (production, import, export, use, and disposal) may be used as a surrogate for potential human exposure. The potential for human exposure to a hazardous substance may be considerable if the substance is produced in large quantities, widely used in the home or industry, or disposed of in the environment.

Supplemental Data

Several other factors could also affect the risk assessment process and will be considered. These may include new regulations, guidelines, or advisories, the availability of new or improved analytical methods, interactions with other chemicals, biomarkers of exposure, effect, and susceptibility, mechanisms of action, and methods for reducing toxic effects.

The development of new regulations or advisories suggests that new evidence exists or that a re-evaluation of existing evidence has occurred. The supporting literature for such changes should be retrieved and evaluated as described above.

Improved analytical methods provide a more accurate determination of the levels of hazardous substances in the environment and in biological tissues. In addition, they may be useful in identifying biomarkers for human exposure or hazardous substances in additional environmental media. The new data should be included in the update of the profile if the method is considered of good quality (precision, accuracy, and recovery) and is an improvement over existing methods with regard to sensitivity and specificity.

Information about other factors, such as interactions with other chemicals, biomarkers of exposure, effect, and susceptibility, the mechanisms of action, and methods for reducing toxic effects can directly affect the evaluation of public health risk. Hence, studies addressing these areas will be considered. Criteria in this category are scored according to the information scoresheet (see appendix A). Refer also to Table 2.

Scoring

For purposes of deriving the information score, each category (health effect, potential for human exposure, and supplemental data) is assigned the score achieved by it's highest scoring subcategory. The information score is then derived by the addition of the three category scores. The most current scores for frequency of occurrence at NPL sites, toxicity, and potential for human exposure as determined by QAB will be combined with the information score to obtain a "profile need score" and rank substances in priority order for profile development.

PROFILE NEED SCORE = NPL FREQUENCY + TOXICITY + POTENTIAL FOR HUMAN EXP

Other Considerations

Input from the general public, environmental and health professionals in the private and public sector, and interested private organizations and groups is used to ensure that no critical information has been overlooked. ATSDR welcomes comments regarding both new and update profiles. Data from studies not generally available to ATSDR through the published literature are essential to the profile development process. Individuals and groups are encouraged to provide ATSDR with these studies.

In addition, the availability of studies describing alternative approaches to estimating risk, such as Quantitative Structure Activity Relationships (QSAR) or Physiologically Based Pharmacokinetic Modeling (PBPK) for a given substance will also be considered in the decision of which profiles to prepare and to update.

TABLE 1

POTENTIAL FOR HUMAN EXPOSURE (maximum points = 10)[1]		
SUBCATEGORIES	Study Provides New Information?	Study Confirms Existing Data?
Monitoring Information		
levels in biological tissues:		
Populations near NPL[2] sites?	7 pts.	3.5 pts.
General population?	6 pts.	3.0 pts.
Worker population?	5 pts.	2.5 pts.
levels in environmental media:		
Populations near NPL sites?	6 pts.	3.0 pts.
General population?	5 pts.	2.5 pts.
Worker population?	4 pts.	2.0 pts.
Toxicokinetics Information	4 pts.	2.0 pts.
Environmental Fate Information	4 pts.	2.0 pts.
Bioavailability and Bioaccumulation	3 pts.	1.5 pts.
Chemical Release Information	3 pts.	1.5 pts.
Physical/Chemical Property Information	1 pts.	0 pts.

[1] Use highest subcategory score unless study addresses a data need (score 7 points) or a priority data need (score 10 points).

[2] National Priority List

TABLE 2

SUPPLEMENTAL DATA (maximum points = 8 points)[1]		
SUBCATEGORIES	Study Provides New Information?	Study Confirms Existing Data?
Analytical Methods	3 pts.	1.5 pts.
Regulations/Advisories/Guidelines	3 pts.	1.5 pts.
Interactions with other chemicals	3 pts.	1.5 pts.
Biomarkers of exposure/effect/susceptibility	3 pts.	1.5 pts.
Mechanisms of action	4 pts.	2.0 pts.
Methods for reducing toxic effects	5 pts.	2.5 pts.

[1] Use highest subcategory score unless study addresses a data need (score 5 points) or a priority data need (score 8 points).

References

ATSDR. 1992. Support Document for the CERCLA 104 Priority List of Hazardous Substances that will be the Subject of Toxicological Profiles. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

NRC. 1984. Guidelines for Assessing the Quality of Individual Studies. In: Toxicity Testing: Strategies to Determine Needs and Priorities. National Research Council.

The Chemical Manufacturers Association's Epidemiology Task Group. 1991. Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research. J Occup Med 33(12):1221-1229.

APPENDIX A

INFORMATION SCORESHEET

COMPOUND_____

1a. Health Effect Data: Epidemiological Studies (maximum = 21)

_____ Number of studies_____

Does study address a data need? If so, score (10). _____

Which data need?_____ Ref_____

If study does not address a data need, is data:

New (8) ___ Confirming (4) ___ Refuting (8) ___ _____

Ref_____ Ref_____ Ref_____

If data need addressed is a "Priority Data Need," add (3). _____

If information is likely to be used for a new MRL, add (8). _____

Which MRL?_____ Ref_____

1b. Health Effect Data: Toxicological Studies (maximum = 21) _____

Number of studies_____

Is exposure other than inhalation, oral or dermal? (2) _____

Ref_____

If human subjects, does study address a data need? If so, score (10). _____

Which data need?_____ Ref_____

If study does not address a data need, is data:

New (8) ___ Confirming (4) ___ Refuting (8) ___ _____

Ref_____ Ref_____ Ref_____

If non-human subjects, does study address a data need? If so, score (9). _____

Which data need?_____ Ref_____

If not, does study:

Provide new information (6)? ___ _____

Ref_____

Confirm conclusions previously drawn from studies

In humans (4)? ___ In animals (2)? ___ _____

Ref_____ Ref_____

Refute conclusions previously drawn from studies

In humans (6)? ___ In animals (5)? ___ _____

Ref_____ Ref_____

If data need addressed is a "Priority Data Need," add (3). _____

If information is likely to be used for a new MRL, add (8). _____

Which MRL?_____ Ref_____

2. Potential for human exposure (maximum = 10)

_____

Does study address a data need? If so, score (7). _____

Which data need?_____ Ref_____

If not, does study deal with:

Toxicokinetics:

New (4) ___ Confirming (2) ___ _____

Ref_____ Ref_____

Monitoring information in humans (biol tissues):

Near NPL sites? New (7) ___ Confirming (3.5) ___ _____

Ref_____ Ref_____

General population? New (6) ___ Confirming (3) ___ _____

Ref_____ Ref_____

Worker population? New (5) ___ Confirming (2.5) ___ _____

Ref_____ Ref_____

Monitoring information in humans (environmental levels):

Near NPL sites? New (6) ___ Confirming (3) ___ _____

Ref_____ Ref_____

General population? New (5)___ Confirming (2.5) ___ _____

Ref_____ Ref_____

Worker population? New (4) ___ Confirming (2) ___ _____

Ref_____ Ref_____

Environmental fate:

New (4) ___ Confirming (2) ___ _____

Ref_____ Ref_____

Bioavailability and bioaccumulation:

New (3) ___ Confirming (1.5) ___ _____

Ref_____ Ref_____

Chemical release information:

New (3) ___ Confirming (1.5) ___ _____

Ref_____Ref_____

Physical/Chemical properties: New (1) ___ _____

Ref_____

If data need addressed is a "Priority Data Need," add (3). _____

3. Supplemental Data (Maximum = 8) _____

Does study address a data need? If so, score (5). _____

Which data need?_____ Ref_____

If not, does study deal with:

Improved analytical methods:

New (3) ___ Confirming (1.5) ___ _____

Ref_____ Ref_____

New or updated regulations, guidelines, advisories (1): _____

Ref_____

Interactions with other chemicals:

New (3) ___ Confirming (1.5) ___ _____

Ref_____ Ref_____

Biomarkers of exposure or effect:

New (3) ___ Confirming (1.5) ___ _____

Ref_____ Ref_____

Mechanism of action:

New (4) ___ Confirming (2) ___ _____

Ref_____ Ref_____

Methods for reducing toxic effects:

New (5) ___ Confirming (2.5) ___ _____

Ref_____ Ref_____

If data need addressed is a "Priority Data Need," add (3). _____

Total: _____

Other considerations (include references dealing with QSAR or PBPK treatment of the substance):

Evaluator: _____