CRITERIA FOR SELECTING TOXICOLOGICAL PROFILES FOR DEVELOPMENT

Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry
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I. 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.

Toxicological profiles provide an examination, summary, and interpretation of available toxicological and epidemiologica1 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, 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. The intended audiences for the toxicological profiles are environmental and health professionals in the private and public sector, and interested private organizations and groups.

II. Overview

In addition to preparing new profiles on hazardous substances, and as directed by CERCLA, section 104(i)(3), ATSDR reviews the published profiles periodically to determine if revision and 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 or created.

This document details literature evaluations that are employed during the process of toxicological profile selection. A candidate list is generated with inputs from various sources (see: Toxicological Profile Process). Substances on this candidate list undergo a literature evaluation to quantitatively evaluate available research and determine an information score for each substance. This information score is then used to prioritize the list of toxicological profiles to create or update.

III. Information Scoring

The availability of new studies that fill 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. For each update candidate, a reviewer will examine the literature published since the release of that profile, whereas for new profiles, the literature will be reviewed without date restrictions.

Studies are grouped into four categories: (1) epidemiological health effects, (2) toxicological health effects, (3) potential for human exposures, and (4) supplemental data.

For update candidates, 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 literature is evaluated using the same four categories. The information is qualitatively evaluated and no information score is calculated because all of the information is considered new. This review is compared to the quantitative information scores for the update candidates. All things being equal between a new substance and an update substance, the higher priority will be given to the new substance. This acknowledges 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.

Epidemiological Health Effect Data

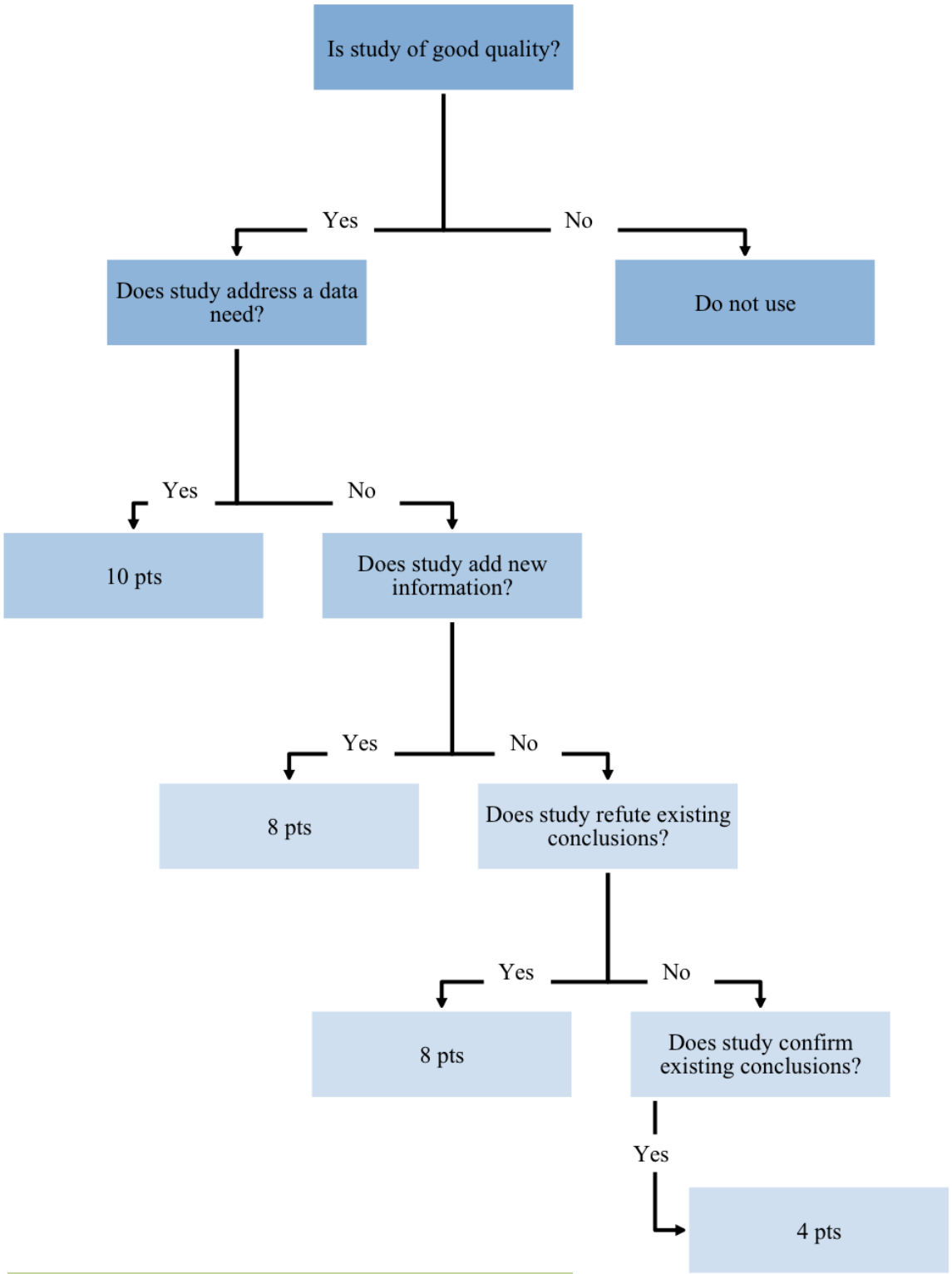
Human epidemiological studies can provide important information regarding the relationship between health effects and exposure to a hazardous substance. They can be an important tool when attempting to identify and characterize the health risks due to exposure to a hazardous substance. Despite inherent 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 (NRC 1984; Guidance for the Preparation of Toxicological Profiles, Attachment D). 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 are given greater weight in terms of scoring. Studies which refute existing information are 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 If information from the epidemiological studies is likely to support MRL derivation, then an extra eight points is added to the final score (see Appendix A and Figure 1).

Figure 1. Decision Tree for Evaluating Epidemiological Studies



Is information likely to support MRL derivation?
If yes, add an extra 8 pts. to final score.

Toxicological Health Effect Data

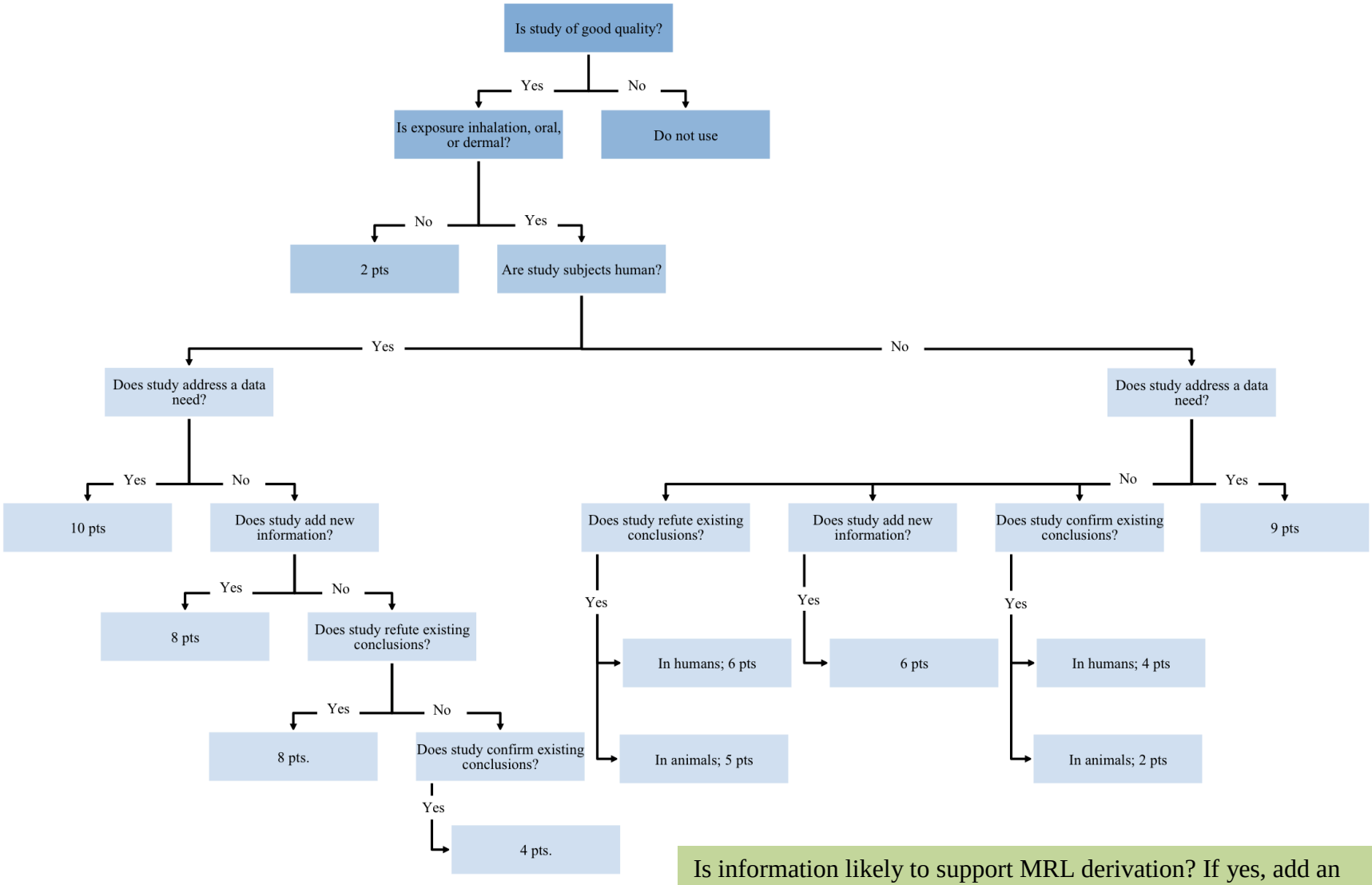
The health effects associated with levels of exposure to a substance are often determined in toxicological studies where either humans or animals were the subjects. Human and animal toxicological studies are useful for a thorough understanding of the health risk to humans exposed to hazardous substances. 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; Guidance for the Preparation of Toxicological Profiles, Attachment C). 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 (NRC 1984), 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 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. If information from the epidemiological studies is likely to support MRL derivation, then an extra eight points is added to the final score (see Appendix A and Figure 2).

Figure 2. Decision Tree for Evaluating Toxicological Studies



Is information likely to support MRL derivation? If yes, add an extra 8 pts. to final score.

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.

The toxicokinetics of a substance, including its absorption, distribution, metabolism, and excretion can significantly impact 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.

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 considered if the substance is produced in large quantities, widely used in the home or industry, or disposed of in the environment.

Table 1. Potential for Human Exposure (maximum points = 8)[1]		
Subcategories	Study provides new information?	Study confirms existing data?
Monitoring Information		
Levels in biological tissues:		
Populations near NPL[2] sites?	7.0 pts.	3.5 pts.
General population?	6.0 pts.	3.0 pts
Worker population?	5.0 pts.	2.5 pts.
Levels in environmental media:		
Populations near NPL sites?	6.0 pts.	3.0 pts.
General population?	5.0 pts.	2.5 pts.
Worker population?	4.0 pts.	2.0 pts.
Toxicokinetics Information	4.0 pts.	2.0 pts.
Environmental Fate Information	4.0 pts.	2.0 pts.
Bioavailability and Bioaccumulation	3.0 pts.	1.5 pts.
Chemical Release Information	3.0 pts.	1.5 pts.
Physical/Chemical Property Information	1.0 pts.	0.0 pts.

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

[2]National Priority List

Supplemental Data

Several other factors could also affect the risk assessment process and are considered. These may include new regulations, guidelines, or advisories, interactions with other chemicals, biomarkers of exposure, effect, and susceptibility, mechanisms of action, methods for reducing toxic effects, and physiologically based pharmacokinetic (PBPK)/pharmacodynamic models.

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.

Information about other factors, such as interactions with other chemicals, and biomarkers of exposure, effect, and susceptibility. Hence, studies addressing these areas are considered important.

Information on PBPK models quantitatively describe relationships among critical biological processes. PBPK models are increasingly used in risk assessments to predict the concentration of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species. Information pertaining to animal-to-human extrapolations can indicate if there will be a difference in the toxicity or toxicokinetics of a chemical between humans and animals and is thus important to the risk assessment process.

Criteria in this category are scored according to the information scoresheet (see Appendix A). Refer also to Table 2.

Table 2. Supplemental Data (maximum points = 5)[1]		
Subcategories	Study provides new information?	Study confirms existing data?
Regulations/Advisories/Guidelines	1.0 pts.	0.0 pts
Interactions with other chemicals	3.0 pts.	1.5 pts.
Biomarkers of exposure/effect/susceptibility	3.0 pts.	1.5 pts.
PBPK Modeling	4.0 pts	2.0 pts
Human-to-Animal Extrapolation	4.0 pts	2.0 pts
[1]Use highest subcategory score unless study addresses a data need (score 5 points).		

Scoring

For purposes of deriving the information score, each category (epidemiological health effect, toxicological health effect, potential for human exposure, and supplemental data) is assigned the score achieved by its highest scoring subcategory.

References

ATSDR. 2015. Support Document to the 2015 Priority List of Hazardous Substances that will be Candidates for 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

1. Health Effect Data: Epidemiological Studies (maximum = 18)				
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 information is likely to support a new MRL, add (8)				
Which MRL? Ref				

2. Health Effect Data: Toxicological Studies (maximum = 18)				
Number of studies				
Is exposure other than inhalation, oral, or dermal? If yes, score (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 information is likely to support a new MRL, add (8)				
Which MRL? Ref				

3. Potential for human exposure (maximum = 8)				
Does study address a data need? If so, score (8)				
Which data need? Ref				
If not, does study deal with:				
Toxicokinetics:				
	New (4)		Confirming (2)	
	Ref		Ref	
Monitoring information in humans (biological tissue):				
	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				

4. Supplemental Data (maximum = 5)	
Does study address a data need? If so, score (5)	
Which data need? Ref	

If not, does study deal with:			
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	
PBPK Modeling:			
	New (4)	Confirming (2)	
	Ref	Ref	
Human-to-Animal Extrapolation:			
	New (4)	Confirming (2)	
	Ref	Ref	

Total:

Other Considerations:

Evaluator: