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Development of Exposure Guidelines for Chronic Health Effects Following Acute Exposures to Toxic Industrial Chemicals: Implementation of a Toxidrome-Based Approach with Application to the Lower Pulmonary Toxidrome

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1 SUMMARY

1.1 Purpose

This white paper describes a toxidrome-based, subject matter expert (SME)-informed approach to estimate the long-term health effects following acute chemical exposure. It also details a feasibility study to implement the approach for the lower pulmonary toxidrome. The resulting health effect curves can—

- Serve as a basis for establishing exposure guidelines and for closing a current gap in U.S. Army Public Health Center (APHC) military exposure guidelines (MEGs);
- Inform modeling for the National Chemical Terrorism Risk Assessment (published by the Department of Homeland Security); and
- Allow long-term public health and economic consequences to be calculated and used to inform policies and preparedness decisions.

1.2 Abstract

Joint Publication (JP) 3-11 (Joint Chiefs of Staff 2013), *Operations in Chemical, Biological, Radiological, and Nuclear (CBRN) Environments*, requires commanders to minimize total risk in operational planning and execution. Incorporating MEGs into risk estimates can provide commanders with a mechanism to consider both short- and long-term chemical risks. Current MEGs address acute exposures that lead to acute effects and sub-chronic exposures that lead to chronic effects. However, the current MEGs do not directly address acute exposures leading to chronic effects. This problem is of particular concern regarding acute exposure to non-lethal concentrations of toxic industrial chemicals (TICs). This gap is a source of concern for planners in the medical community, as these effects may have implications for long-term protection of exposed military or civilian populations. For example, 20 years after the release of methyl isocyanate (MIC) from the Union Carbide facility in Bhopal, India, survivors have exhibited obstructive pulmonary disease and decreased lung function. There are also documented cases of chronic lung disease following acute exposure to high concentrations of ammonia and chlorine. Other TICs may have similar long-term health effects that should be considered as part of both operational planning and longer-term force health protection issues.

This paper describes in detail the toxidrome-based, SME-informed approach to deriving long-term health effect curves as the bases for long-term health effect guidelines. It also details the results of a feasibility study in which the approach was implemented for the lower pulmonary toxidrome. Ten SMEs participated in the feasibility study and provided quantitative estimates of the likelihood of long-term health effects given an acute health effect. As described in this document, consensus SME input can be combined with chemical-specific acute effect dose-response estimates to yield long-term health effect curves. The APHC can subsequently use these curves to derive guidelines for long-term health effects following acute chemical exposures.

1.3 Recommendations

As a feasibility study, analysis of the process and the results of the study is the first step in determining if the approach is viable and acceptable for developing the desired guidelines. Socialization and review phases are necessary to reach the final goal of an acceptable process that can be applied to other toxidromes. To that end, a thorough review of this process is recommended. Socialization of the approach is also recommended to collect input and gain additional buy-in of the approach from the wider technical community of medical, toxicology, and/or other appropriate experts.

2 REFERENCES AND TERMS

Appendix A provides the references cited, and the Glossary provides a list of acronyms and terms.

3 BACKGROUND

There is a need for estimates of the likelihood of long-term effects from acute exposures for both military and civilians. Currently this exposure/outcome paradigm is not taken into account for planning, preparedness, or mitigating adverse effects from chemical events. Three documents support the need for such estimates: Homeland Security Presidential Directive (HSPD)-22, *Domestic Chemical Defense,* HSPD -18, *Medical Countermeasures against Weapons of Mass Destruction,* and JP 3-11 (Joint Chiefs of Staff 2013), *Operations in Chemical, Biological, Radiological, and Nuclear (CBRN) Environments*. HSPD-22 (2007) requires a Chemical Terrorism Risk Assessment (CTRA) to implement threat awareness as a critical element of the Nation's domestic chemical defense policy. HSPD-18 (2007) directs that the Nation's medical countermeasure research, development, and acquisition efforts target threats that have potential for catastrophic impact on public health and are subject to medical mitigation. JP 3-11 requires military commanders to minimize total risk in operational planning and execution.

Estimates of long-term adverse health effects following acute exposure can be incorporated into assessments such as the CTRA, leading to a more robust assessment of risk from threat chemicals. Additionally, incorporating these estimates into guidelines such as MEGs can provide commanders with a mechanism to consider both short- and long-term chemical risks when assessing overall risk. Currently the CTRA addresses single short-term events and risks, while MEGs address acute exposures leading to acute effects and sub-chronic exposures leading to chronic effects. However, neither the CTRA nor the current MEGs directly address acute exposures leading to chronic effects. This gap is of particular concern regarding acute exposures to non-lethal concentrations of TICs. It is a source of concern for planners in the medical community, as these effects may have implications for the long-term protection of exposed military or civilian populations. For example, 20 years after the release of MIC from the Union Carbide facility in Bhopal, India, survivors have exhibited obstructive pulmonary disease and decreased lung function. There are also documented cases of chronic lung disease following acute exposure to high concentrations of ammonia and chlorine. Other TICs may have similar long-term effects that should be considered as part of both operational planning and longer-term force health protection issues.

A previously completed white paper titled *Development of Exposure Guidelines for Chronic Health Effects Following Acute Exposures to Toxic Industrial Chemicals* (Winkel 2014) focused on developing an approach to estimate acute exposures that lead to chronic effects based on literature data. As discussed in that report, predicting long-term effects following acute exposures proved challenging, as chronic effects are not studied as thoroughly as acute effects. Robust data on chronic (long-term) effects following acute chemical exposure is minimal and generally characterized by several challenges, including the following:

- Quantitative exposure details (concentration, duration) are rarely available (and when available, have wide ranges of uncertainty).
- Often only a small number of individuals are actually exposed (i.e., small sample sizes).
- There is usually minimal to no documented medical history of the subjects in a study. Lack of medical history can cloud the linkage of exposure to an effect, as potential confounding factors cannot be assessed.
- There are difficulties/inconsistencies in identifying long-term effects. For example, a given study may focus strictly on signs/symptoms as reported by individuals via survey responses, while another study may focus on results of pulmonary function tests (PFTs).
- There is no formal definition of a "chronic" or "long-term" effect. In the case of pulmonary exposures, for example, long-term effects could be defined as requiring the presence of physical symptoms or by the presence of irregular PFT results. Different approaches can lead to different responses (e.g., for a given population having the same acute injuries, the fraction having abnormal long-term PFT results may be vastly different than the fraction having long-term symptoms).

These findings are not necessarily surprising, as the available data are not derived from a traditional toxicology study but rather from accidental exposures. The use of such data requires an approach to manage the limited data. Winkel (2014) discussed such an approach when applied to chlorine. The approach addressed some limitations of the data set but could not overcome all of the challenges. Specifically, the inconsistencies in observed long-term effects for given acute injuries could not be resolved. Given this outcome for chlorine (considered to be a "data rich" chemical), the successful application of the developed approach to other chemicals was unlikely.

An alternative approach was proposed in a follow-on white paper titled *Development of Exposure Guidelines for Chronic Health Effects Following Acute Exposures to Toxic Industrial Chemicals – A Toxidrome-Based Approach* (APHC (Prov) 2016) (see section 4 for details on the approach). The white paper aimed to address the issue of limited data by collecting toxidrome-based input from SMEs to bridge the data gap. Such an approach has greater applicability across chemicals as it relies on SME evaluation and judgments, which are based on personal expertise/experience and any amount of available literature data. The present white paper discusses the results of a feasibility study in which this toxidrome-based, SME-informed approach was implemented for the lower pulmonary toxidrome.

4 OVERVIEW OF THE TOXIDROME-BASED, SME-INFORMED APPROACH AND APPLICATION TO THE LOWER PULMONARY TOXIDROME

A toxidrome is defined as a constellation of signs and symptoms, or a particular clinical presentation, which suggests a particular kind of toxic insult. This section provides an overview of the toxidrome-based, SME-informed approach to establishing long-term health effect curves following acute exposures (see **Figure 1**) as well as details on its implementation for the lower pulmonary toxidrome (inhalation exposure route). While the steps of approach have been presented in a previous white paper (APHC (Prov) 2016), they are presented again here to reflect minor changes based on reviewer comments to the previous white paper and updates after having completed the feasibility study. Following some important preliminary discussions, **Section 4.4** presents the steps in detail.

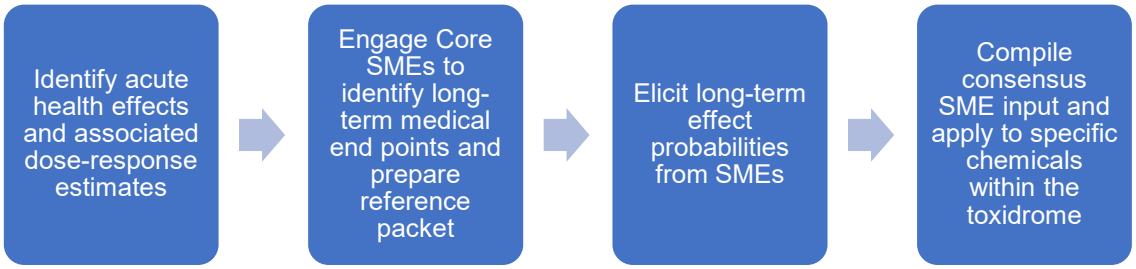


Figure 1. Overview of the Toxidrome-Based, SME-Informed Approach to Establishing Long-Term Health Effect Curves Following Acute Chemical Exposure

Note that for the purposes of this effort, a long-term health effect is defined in this effort as an adverse, non-acute health effect that arises following acute (i.e., one-time) exposure. The effects to be considered are analogous to chronic health effects often described in the literature—but are the result of an acute rather than chronic exposure. **Section 4.5** provides detailed, toxidrome-specific long-term effects.

4.1 Core and Value SMEs

As described previously, the biggest obstacle to establishing long-term effect curves for acute exposures is the limited reliable long-term health effect data in the literature. The process described in this white paper utilizes SMEs to fill this data gap. A qualified SME was considered to be an individual who is knowledgeable of the long-term effects associated with the given toxidrome (e.g., a medical toxicologist, or, for the feasibility study, a pulmonary toxicologist) and capable of making quantitative judgments on the likelihood of long-term effects because of an acute exposure.

This document refers to both “Core SMEs” and “Value SMEs.” Core SMEs are individuals participating in all four steps of the process. The expertise of Core SMEs is required to frame the study and prepare the appropriate materials for the participation of Value SMEs in Steps 3 and 4 (Appendix B provides prepared materials). Value SMEs are individuals involved only in Steps 3 and 4. The expertise of Value SMEs is required to quantify the likelihood that a given acute injury results in a long-term health effect. All Core SMEs also serve as Value SMEs. Subject matter expert involvement is explained in further detail as the steps of the process are described in subsequent sections of this document. Appendix C identifies feasibility study Core and Value SMEs.

4.2 Toxidrome Selection

The Department of Defense (DOD) and Department of Homeland Security (DHS) selected the lower pulmonary toxidrome for several reasons. First, there are several chemicals within this toxidrome that are of interest to DOD and DHS, including chlorine. Second, there are dose-response estimates for chemicals in this toxidrome (such as Sommerville et al. 2012). Third, the mechanism of toxicity for chemicals in this toxidrome is well understood. Finally, identifying SMEs to participate in the study was presumed to be straightforward, as chemicals that affect the lower pulmonary region are of interest and concern to numerous government and non-government entities. Toxidrome selection was determined at a meeting attended by DOD and DHS personnel in October 2015, with the study to be conducted in fiscal year 2016.

While there are a significant number of chemicals that fit into the lower pulmonary toxidrome, a limited number were selected based upon acute effects, long-term effects, and data availability. **Table 1** lists specific chemicals within this toxidrome that were considered by Core SMEs in their preparation of reference materials for the larger group of Value SMEs.

Table 1. Lower Pulmonary Toxidrome Chemicals Considered by Core SMEs in the Feasibility Study

Chemical Name		
Bromine	Ethyl isocyanate	Perchloromethyl mercaptan
Chlorine	Hexachlorocyclopentadiene	Perfluoroisobutene
Chlorine dioxide	Hydrogen selenide	Phosgene
Chloropicrin	Methyl isocyanate	Thiophenol
Dimethyl sulfate	Oxides of nitrogen	Hexachloroethane (HC) smoke

An advantage of a toxidrome-based approach is that additional lower pulmonary chemicals not listed in **Table 1** can leverage the results of this study, provided they are similar in mechanism. Examples include other chemicals categorized as lower pulmonary compounds by the DHS Chemical Security Analysis Center (CSAC) CTRA program, such as chloroform, cyclohexyl isocyanate, and phosphine. Thus, the chemicals listed in **Table 1** should not be considered as the only chemicals to which the results of this feasibility study apply.

4.3 An Additional Note on Toxidromes

The concept of toxidromes (or toxic syndromes) is recognized as a means of categorizing chemicals based upon the medical symptoms presented after an exposure. As implied by this definition, a toxidrome does not necessarily imply the same toxic mechanism of action. Thus, further sub-groupings (or sub-toxidromes) within a given toxidrome may be warranted to account for different mechanisms of action. An extreme application of this concept of sub-toxidromes would theoretically involve each chemical being evaluated independently. One of the goals of this effort is to simplify the data collection process such that it can ultimately be completed for all chemicals of concern to DOD and DHS. Thus, sub-toxidromes are used only as appropriate. In the implementation of the process for the lower pulmonary toxidrome, participating SMEs identified no sub-toxidromes.

The concept of toxidromes is critical to the assumptions of the process described in this document. For example, as explained above, the process assumes that all chemicals in a toxidrome (or sub-toxidrome) have the same mechanism of action. It is further assumed that similar acute injuries caused by different chemicals within the same toxidrome have the same probability of causing a given long-term health effect typical to that toxidrome. This assumption, when combined with unique, chemical-specific acute dose-response estimates and SME-elicited probabilities (described in **Section 4.7**), allows for estimation of long-term effect health effect curves.

4.4 Step 1 – Identify Acute Health Effects and Associated Dose-Response Estimates

Step 1 in the process is to identify acute health effects for a short-term exposure to one or more chemicals within the selected toxidrome by the selected exposure route. All chemicals within a toxidrome (or sub-toxidrome if appropriate) are assumed to have a mode of action that leads to the same toxic

mechanism and thus are assumed to result in the same health effects upon exposure.[1] Within the lower pulmonary toxidrome, the mechanism of action is the formation of acids and other compounds that can cause irritation and damage cellular integrity. At sufficiently high doses, the damage can result in pulmonary edema. It is also pertinent in Step 1 to determine if sub-toxidromes within the selected toxidrome are necessary. As mentioned in **Section 4.3**, Core SMEs identified no sub-toxidromes during the feasibility study. Furthermore, acute dose-response estimates are essential for chemicals within the toxidrome, as the estimation of the long-term health effects will be based on acute dose-response relationships. If they do not exist, and there is a desire to estimate long-term effect curves, the relationships must be determined. In the case of lower pulmonary chemicals, multiple sources, including Sommerville et al. (2012), have estimated acute dose-response relationships for several chemicals for lethal and severe acute injuries and for the CTRA program for life-threatening, severe, and mild/moderate acute injuries.

In the completion of the feasibility study, Core SMEs categorized acute health effects into the following groups: mild, moderate, severe, and life-threatening. These groups and their definitions, provided in **Table 2**, were proposed by the Core SMEs and are consistent with definitions used by DHS and APHC. It is anticipated that these groups will be used in any future implementations of this approach.

Table 2. Acute Health Effect Groups and Definitions

Health Effect Grouping	Definition
Mild	Non-disabling, largely reversible effects that do not impair performance; individuals are not expected seek medical attention but may need to provide self-care.
Moderate	Effects that are 1) reversible that alter organ function or impair performance; or 2) irreversible and do not alter organ function or impair performance (for this toxidrome, such acute moderate effects may range from changes in epithelial cell type to scarring on x-ray without clinical impairment). Individuals may seek medical attention.
Severe	Effects that alter organ function or impair performance and may be irreversible, though treatable. Severe acute effects require medical attention, but are not expected to cause death acutely. Severe long-term effects may result in a decreased life expectancy.
Life-threatening	Effects that are a threat to the individual's life and will result in death if left untreated. Note that the life-threatening category was not included as part of long-term effects. This definition is meant to apply to acutely life-threatening effects, whereas any long-term effect that could ultimately result in a decreased life expectancy is categorized as severe.

Use of the groupings and definitions presented in **Table 2** is beneficial in several ways. First, acute dose-response estimates are more likely to be available for different categories of symptom severity (e.g., mild, severe) as opposed to single health effects or symptoms (e.g., cough, dyspnea). Second, existing acute exposure levels and guidelines utilize similar groupings or can be derived from health effect curves that exist for these groupings. Similar groupings are also used by assessments such as the CTRA. The groupings in **Table 2** also facilitate SME tasking in this feasibility study. Finally, grouping acute symptoms permits the process to be applied in a more systematic way if expanded to include future toxidromes/chemicals.

[1] Note that the exposure (exposure concentration and time) required to elicit those health effects will vary among chemicals within the toxidrome.

Using the acute health groupings and definitions presented in **Table 2**, the Core SMEs identified the acute symptoms and findings shown in **Table 3**. Note that these descriptions include a combination of symptoms, clinical findings, test results, and therapy-related decisions and assessments.

Table 3. Acute Health Effects Identified for the Lower Pulmonary Toxidrome

Health Effect Grouping	Definition
Mild	• Cough that resolves with removal from exposure, though may recur with deep breathing or heavy exertion in the first few hours • Dyspnea and/or wheezing that resolve with removal from exposure, without inhaled beta-agonist treatments • Laboratory and imaging studies are not indicated • Acute care evaluation is not necessary
Moderate	• Cough that diminishes with rest within 24 hours • Dyspnea and/or wheezing that resolve with one or two inhaled beta-agonist treatments • Laboratory and imaging studies, if obtained, are non-specific (e.g., mild hyperglycemia, hypokalemia, and leukocytosis consistent with “stress effect” and increased interstitial markings or small areas of atelectasis on cx-ray) • Patients are likely to be discharged from the Emergency Department or Observation status within 24 hours
Severe	• Persistent or easily triggered cough, dyspnea, and wheezing that require continuous humidified oxygen delivery and multiple nebulized beta-agonist treatments; intravenous corticosteroids are indicated • Room air oxygen saturation is decreased • Chest x-ray may demonstrate increased interstitial markings or minor consolidation • Hospitalization is indicated
Life-threatening	• Severe cough, dyspnea, and wheezing are present despite therapy as described for severe exposure • Decreased oxygen saturation is present, despite supplemental oxygenation • Decreased mental status is likely • Hypercarbia and metabolic acidosis are expected • Positive-pressure ventilatory support is required • Airway management is complicated by high peak airway pressures and decreased venous return, leading to peripheral edema and hypotension • Chest x-ray or chest computed tomography (CT) demonstrates pulmonary edema. Atelectasis, cystic changes, and areas of consolidation may occur

Should the toxidrome-based, SME-informed approach be expanded to other toxidromes, a table similar to **Table 3** can be produced for those toxidromes.

4.5 Step 2 – Core SME Research Phase to Identify Long-Term Health Effects; Prepare Reference Packet

Step 2 of the process requires Core SMEs to—

- Obtain and review scientific literature relevant to the prevalence of long-term health effects from acute exposures to chemicals in the selected toxidrome;
- Identify toxidrome-specific long-term health effects; and
- Summarize relevant literature as part of a reference packet to be used by Value SMEs in Step 3 of the process.

4.5.1 Literature Search and Review

The literature search strategy included multiple search routes in an attempt to identify any relevant references. Battelle Memorial Institute completed an initial search using only chemical names (the chemicals listed previously in **Table 1**) and very general terms: "inhalation," "toxicology," "long-term," "long-term health effect," "chronic," "chronic health effect." This initial search covered several relevant science/toxicology databases accessed through Dialog and STN® search services. Battelle identified potentially relevant titles/abstracts from this search for subsequent review by the Core SMEs. The APHC performed a similar search of Defense Technical Information Center database but no additional relevant literature was identified. Following an analysis of these initial search results, the Core SMEs then developed a more focused strategy that included specific long-term effects.[2] These follow-up searches were conducted through the following searching services:

- PubMed (http://www.ncbi.nlm.nih.gov/pubmed)
- Web of Science (https://webofknowledge.com/)
- TOXLINE (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm)
- SUMSearch2 (http://sumsearch.org/)

Core SMEs identified potentially relevant titles/abstracts from these searches. In addition to the online search tools listed above, Core SMEs completed a review of toxicological overview documents. These documents were previously completed reviews that summarized literature relevant to a given compound and included the following:

- Agency for Toxic Substances and Disease Registry Toxicological Profiles (http://www.atsdr.cdc.gov/toxprofiles/index.asp) – chlorine, dimethyl sulfate, hexachlorocyclopentadiene, oxides of nitrogen, and phosgene
- International Programme on Chemical Safety (IPCS) Environmental Health Criteria Monographs (http://www.inchem.org/pages/ehc.html) – chlorine, dimethyl sulfate, hexachlorocyclopentadiene, oxides of nitrogen, and phosgene
- IPCS Poisons Information Monographs (http://www.inchem.org/pages/pims.html) – bromine, chlorine, and oxides of nitrogen

Finally, the feasibility study leveraged potentially relevant chlorine literature from Winkel (2014).

Core SMEs reviewed all potentially relevant articles/reports in their entirety. Where appropriate, Core SMEs also obtained and reviewed references cited in the articles/reports. The Core SMEs reviewed these second-generation articles and their reference lists, selecting additional articles for full-text review where appropriate. The lack of a reproducible search strategy raises the possibility of having missed relevant articles. However, the inability to find sufficient literature through a more reproducible route is likely a reflection of the lack of available and relevant information on this subject. Furthermore, the

[2] These searches included specific long-term effects including organizing pneumonia, fibrosis, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, asthma, tracheal stenosis, and restrictive lung disease. The terms "Graniteville" and "Bhopal" were also used to identify literature from those accidental releases.

consistency and repeated citations of the selected articles/reports should provide an adequate basis for assessing the English literature.

4.5.2 Identification of Long-Term Health Effects

The review of the relevant literature was used to identify relevant long-term health effects. Using the same health groupings and definitions presented in **Section 4.4** (with the exception of the life-threatening category), the Core SMEs identified long-term symptoms and findings for the lower pulmonary toxidrome (see **Table 4**). After some discussion, the Core SMEs determined that life-threatening long-term health effects were not an applicable category, as life-threatening implies a more immediate/acute state. Also, note that the identified long-term effects are restricted to those involving the selected toxidrome. In conducting the feasibility study, for example, the Core SMEs identified only the pulmonary effects of exposures. The process is not designed to ignore other effects but rather to focus the scope of the effort onto a single type of effect.[3]

Table 4. Long-Term Health Effects Identified for the Lower Pulmonary Toxidrome

Health Effect Grouping	Definition
Mild	• Decreased exercise tolerance and conditioning • Physical exam is likely normal • Mild obstructive findings (from baseline or in comparison to population norms) are present on formal PFT
Moderate	• Dyspnea on exertion, with or without wheezing, is present • If wheezing is present, treatment with inhaled beta-agonists, or chronically with cromolyn sodium and/or inhaled corticosteroids is effective for symptom relief and improves obstructive PFT results
Severe	• Debilitating shortness of breath with little exertion • May require use of ambulatory, supplemental oxygen to maintain oxygen saturation >90% • Imaging studies show cystic changes and fibrosis • PFTs demonstrate both obstructive and restrictive findings; either may predominate • PFT obstructive findings do not significantly reverse with inhaled beta-agonist

4.5.3 Preparation of Reference Packet

Step 2 requires the preparation of a reference packet to inform Value SMEs of the process and relevant literature. The reference packet includes a reference document with the following content:

- Introduction and overview of the feasibility study process
- High-level background/primer on toxicology concepts associated with the selected toxidrome
- A mapping diagram of acute to long-term health effects
- Description of the literature search and review process, with summaries of the most relevant literature identified by Core SMEs

Appendix B provides a copy of the reference document produced for the lower pulmonary toxidrome.

[3]Additional effort would be required to conduct a comprehensive assessment of all long-term effects (i.e., effects in addition to pulmonary effects) from an acute exposure. Each unique mechanism/effect would require its own specific analysis.

The diagram in the reference document (reproduced in **Figure 2**) maps the symptom-based and physiologic mechanism-based summary of the progression from acute to chronic health impacts. The Core SMEs generated the diagram to help Value SMEs visualize their contributions to the process. Each blue arrow in the figure represents an individual quantitative estimate required of a Value SME. As shown in **Figure 2**, the feasibility study required Value SMEs to provide 12 different estimates (explained in more detail in **Section 4.6**).

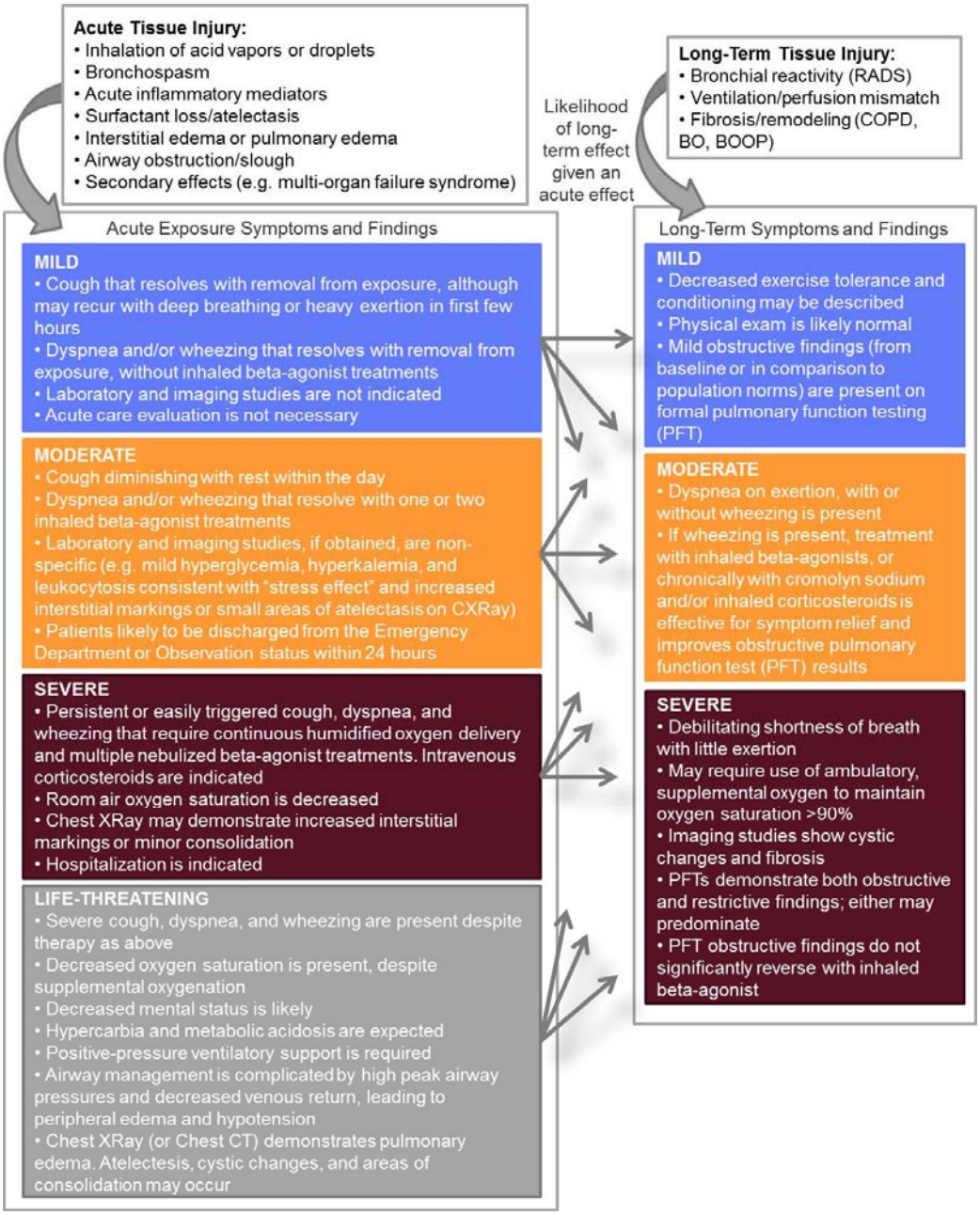


Figure 2. Mapping of Acute to Long-Term Health Effects in the Lower Pulmonary Feasibility Study

The reference packet included access to the most relevant references summarized in the reference document. Providing full-text access was deemed critical to SMEs desiring a detailed review of the most relevant literature to inform their contributions to the study. The reference packet also included an Excel® workbook tool to provide input. The various spreadsheets within the workbook are explained in greater detail in the reference document (reproduced in Appendix B).

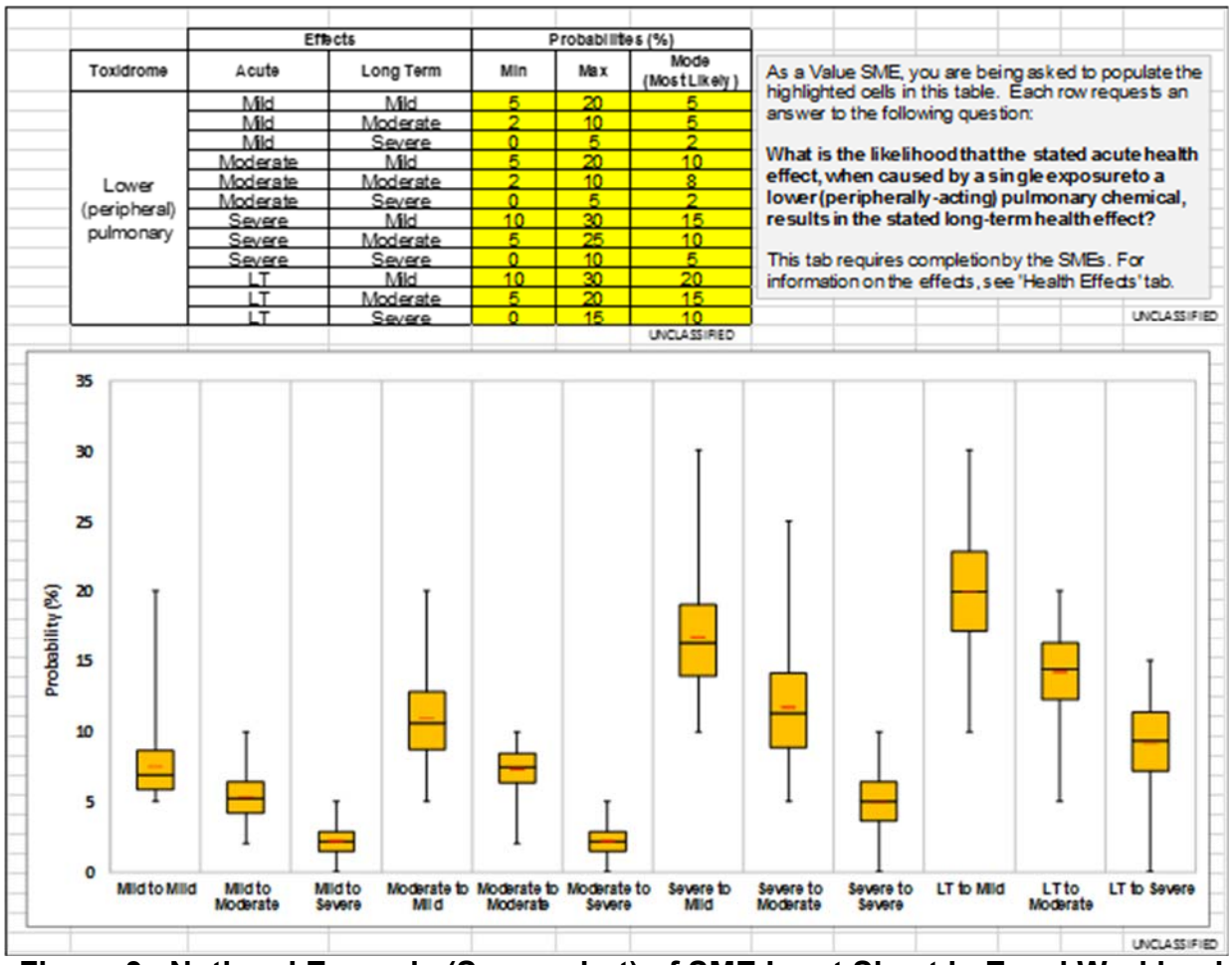
4.6 Step 3 – Elicit Long-Term Effect Probabilities from SMEs

The approach assumes that similar acute injuries caused by different chemicals within the same toxidrome (or sub-toxidrome) have the same probability of causing a given long-term health effect typical to that toxidrome. Step 3 requires Value SMEs to define the likelihood of an individual exhibiting the long-term effects described in Step 2 given the acute effects identified in Step 1. More specifically, Value SMEs are instructed to provide a quantitative likelihood (0 to 100%) for any connection in the mapping diagram (**Figure 2**) between an acute health effect grouping (mild, moderate, severe, or life-threatening) and a long-term health effect grouping (mild, moderate, or severe). All estimates elicited in the feasibility study were differential rather than cumulative (i.e., an estimate pertains only to the probability of mild long-term effects, not the probability of mild or greater long-term effects).

The elicitation effort is rooted in the methodology of the Delphi Method (Adler and Ziglio 1996). Specifically, Value SMEs were directed to define the set of long-term health effect probabilities independent of other SMEs participating in the effort. Upon receipt and combination of all SME input (explained in Step 4 in **Section 4.7**), the SMEs convened to view the combined result. The SMEs then worked to reach a consensus on the combined result, including identifying/resolving any SME inputs deemed invalid.

Ten Value SMEs (see Appendix A) participated in the feasibility study for the lower pulmonary toxidrome. Their involvement was initiated through an orientation teleconference in which an overview of the study process was provided. The SMEs were then provided with the reference packet created in Step 2 and allotted approximately 2 weeks to provide their estimates. Support was also provided on an as-needed basis via e-mail or phone to assist with SME questions.

Input was collected in a manner intended to ease the time burden on SMEs while also capturing the uncertainty associated with the estimates. Specifically, SMEs were instructed to provide each estimate as a betaPERT distribution, a “user-friendly” distribution with a straightforward parameterization (minimum, maximum, and “most likely” (or mode) values for each estimate). All SME input was provided on the “SME Input” sheet of the Excel workbook within the reference packet, as shown **Figure 3** with notional data. In this sheet, each row represents one of the acute/long-term combinations (e.g., the last highlighted row corresponds to the likelihood of a life-threatening acute health effect resulting in a severe long-term health effect). Below these inputs is a box plot. Each box corresponds to one of the SME inputs and provides a visualization of the SME input values (e.g., the first box in the figure corresponds to the first row of requested input). In this figure and subsequent box plots in this document, the top and bottom borders of the boxes represent the 25th and 75th percentiles (the box is the interquartile range). The solid line in the box represents the median or 50th percentile. The whiskers extend to the minimum and maximum of the distributions. Additional sheets in the Excel workbook provided to the SMEs offered optional visualization tools for the SMEs to use in making their estimates (these additional sheets are explained in the reference document in Appendix B).



Toxidrome	Effects		Probabilities (%)		
	Acute	Long Term	Min	Max	Mode (Most Likely)
Lower (peripheral) pulmonary	Mild	Mild	5	20	5
	Mild	Moderate	2	10	5
	Mild	Severe	0	5	2
	Moderate	Mild	5	20	10
	Moderate	Moderate	2	10	8
	Moderate	Severe	0	5	2
	Severe	Mild	10	30	15
	Severe	Moderate	5	25	10
	Severe	Severe	0	10	5
	LT	Mild	10	30	20
	LT	Moderate	5	20	15
	LT	Severe	0	15	10

Figure 3. Notional Example (Screenshot) of SME Input Sheet in Excel Workbook Accompanying the Reference Packet

All SMEs completed the SME Input tab for the lower pulmonary toxidrome independent of one another and provided their inputs directly to study personnel. Where appropriate, study personnel iterated with SMEs if there were questions regarding input. **Figure 4** shows an example of individual SME Input (SME 1). See Appendix D for similar figures for all SMEs.

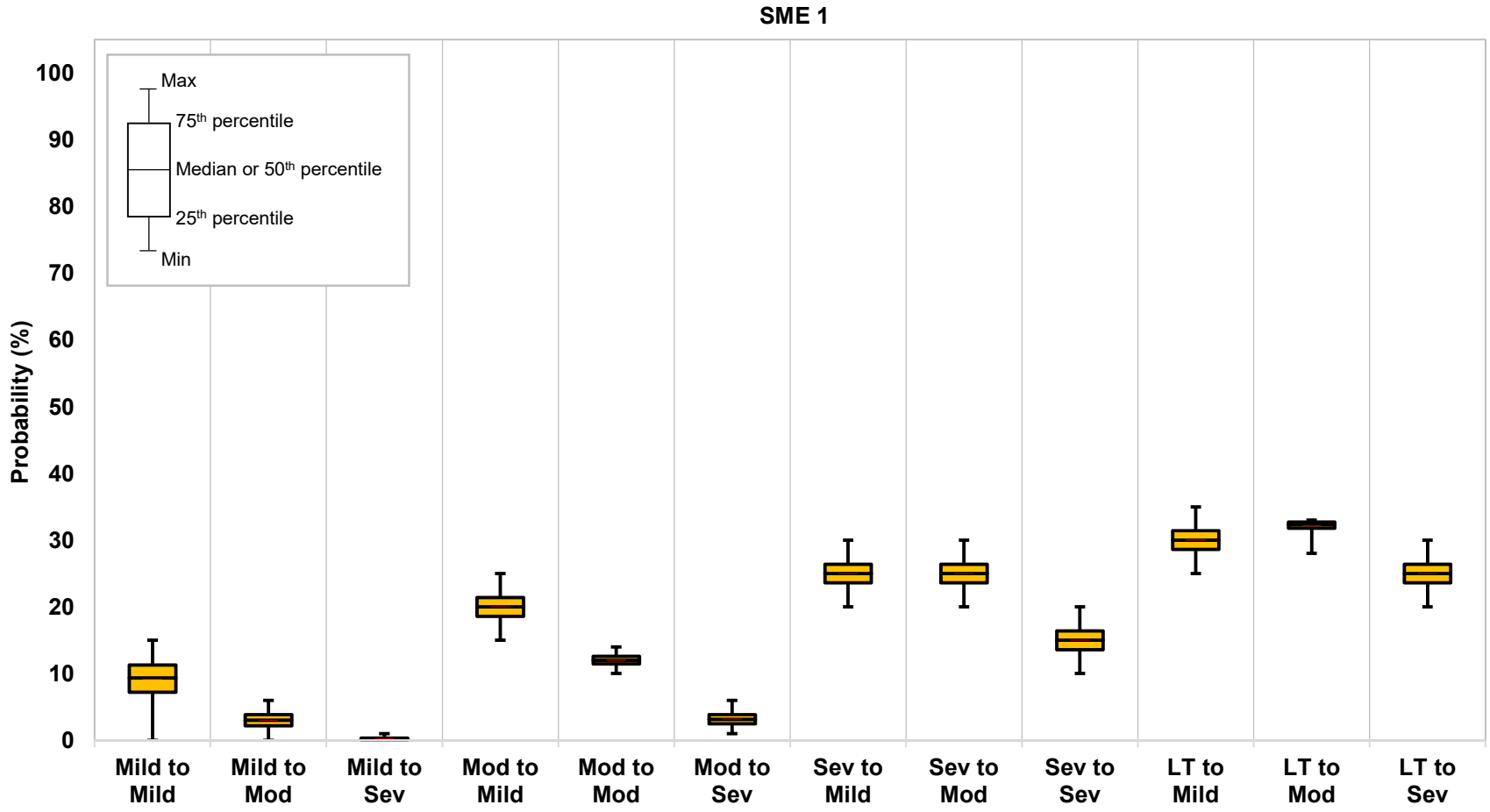


Figure 4. SME1 input to the Feasibility Study

4.7 Step 4 – Compile Consensus SME Input and Apply Consensus Distributions to Chemicals within the Toxidrome

The individual SME input collected in Step 3 is combined into a series of single, representative distributions in Step 4. Step 4 also includes fitting and parameterizing these distributions. Finally, the distributions are applied to chemicals within the toxidrome to create long-term health effect curves.

4.7.1 Compilation of SME Input into Representative Distributions

Participating SMEs convened via WebEx® meeting and reviewed anonymized individual inputs and the resulting consensus inputs (see **Figure 5** through **Figure 16**). **Figure 5**, for example, identifies individual SME estimates of the likelihood that an acute exposure to a chemical in the lower pulmonary toxidrome resulting in mild acute health effects will result in mild long-term effects (where the health effects are described in **Table 3** and **Table 4**).

The x-axis labels in these figures (SME 1, SME 2, etc.) illustrate how the anonymity of the SMEs was preserved (though SMEs were permitted to reveal their identities during the discussions). The average or "AVG" box on the far right of each figure is the representative distribution of all component SME input. Each AVG box was constructed from draws of each of the component distributions.

The SMEs reviewed the figures for each acute/long-term combination (i.e., for each blue arrow in **Figure 2**) and held an open discussion to reach a consensus on the resulting summary distribution. The SMEs explained their assignments at their own discretion during the discussion period, offering their interpretations of literature, insight from personal experience, etc. The SMEs asked questions about the input of other SMEs and revised their inputs at their own discretion (up to 1 week after the WebEx was allotted to provide revised inputs in light of meeting discussions). Two SMEs were unable to attend the review meeting; these SMEs were contacted after the meeting about values that were questioned by the meeting attendees. Following the receipt of updated values, updated summary figures were distributed to the group for review prior to finalization.

Note that the input of SME10 was not included in the review meeting. There were errors in the SME10 input that could not be corrected prior to the review meeting. After the meeting, SME10 made corrections and, following discussion with the sponsors, the input was included with the exception of outlier estimates for which justification was not obtained (i.e., some of SME10's estimates were well outside the range of the other SMEs, and the justification for that input could not be obtained by the conclusion of the study). As a result, SME10 input to all mild acute estimates (mild to mild, mild to moderate, and mild to severe) was removed from the study and did not contribute to the representative distribution.

Figure 5 through **Figure 16** represents the final individual inputs and consensus distributions as agreed upon by the SMEs. The figures are presented below in groups of three (where a given group contains the same acute exposure estimates [e.g., mild acute to mild long-term, mild acute to moderate long-term, and mild acute to severe long-term]).

4.7.1.1 Acute Exposures Resulting in Mild Acute Health Effects

Figure 5 through **Figure 7** identifies the individual and representative SME estimates for the mild acute to mild long-term, mild acute to moderate long-term and mild acute to severe long-term combinations, respectively. Similar to previously presented boxplots, the top and bottom borders of the boxes in these and subsequent figures represent the 25th and 75th percentiles. The solid line in the box represents the median or 50th percentile. The whiskers extend to the minimum and maximum of the distributions. As

explained earlier in this section, there is no input from SME10 in this figure. Appendix E provides a high-level summary of the discussions for these mild acute effect estimates.

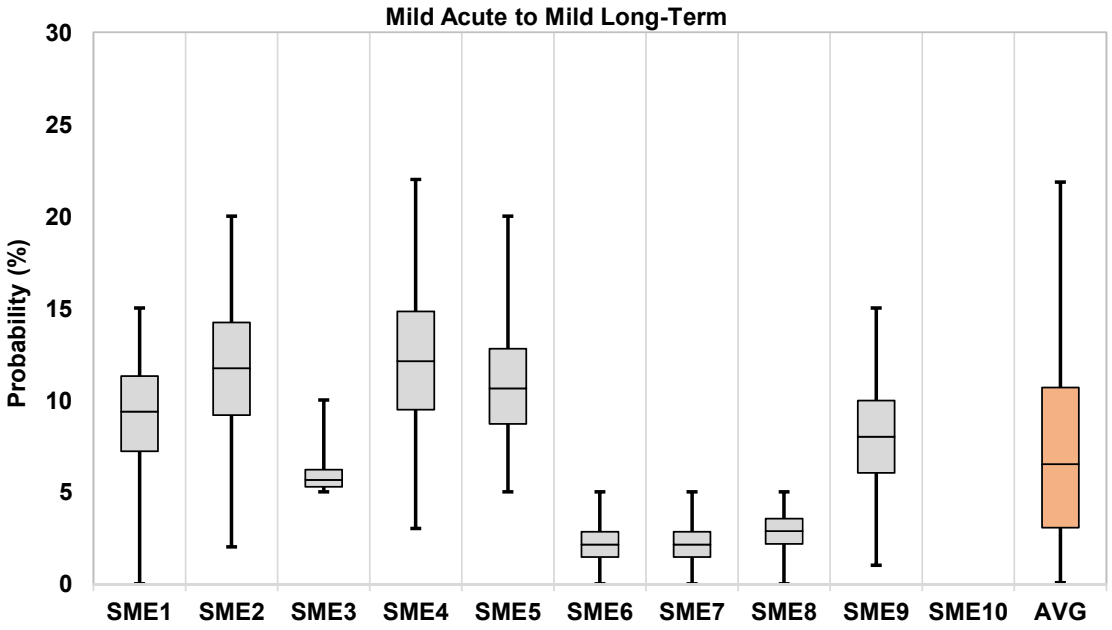


Figure 5. Individual and Consensus SME Estimates of the Likelihood of a Mild Long-Term Effect Given a Mild Acute Effect

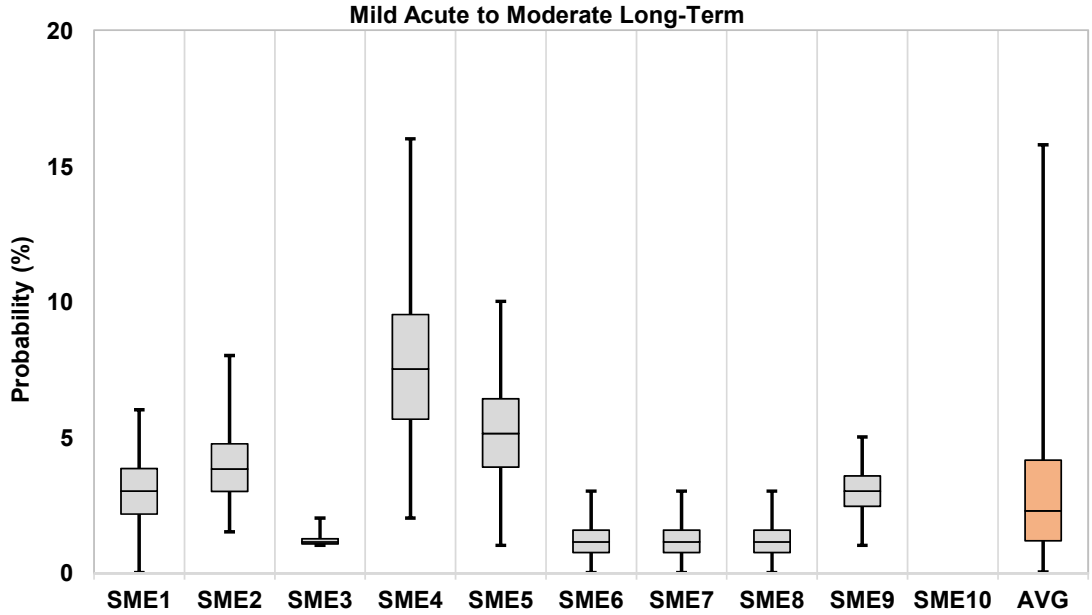


Figure 6. Individual and Consensus SME Estimates of the Likelihood of a Moderate Long-Term Effect Given a Mild Acute Effect

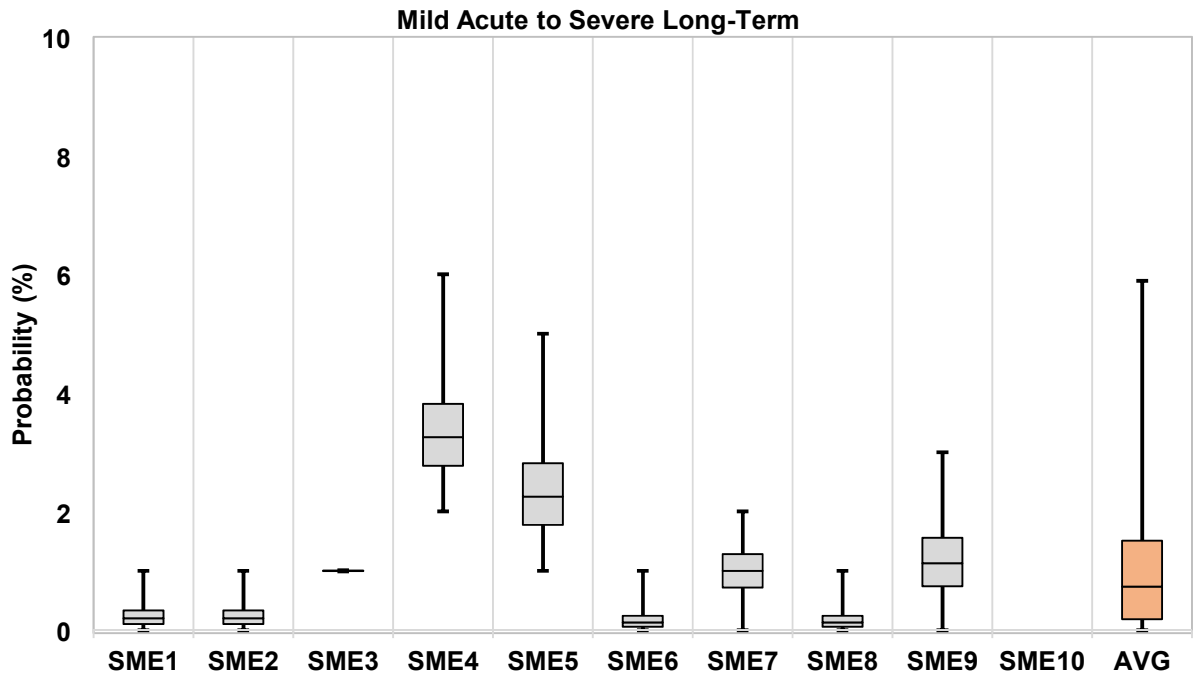


Figure 7. Individual and Consensus SME Estimates of the Likelihood of a Severe Long-Term Effect Given a Mild Acute Effect

4.7.1.2 Acute Exposures Resulting in Moderate Acute Health Effects

Figure 8 through **Figure 10** identifies the individual and representative SME estimates for the moderate acute to mild long-term, moderate acute to moderate long-term, and moderate acute to severe long-term combinations, respectively. Unlike previous figures, the input of SME10 was retained for this and all subsequent acute to long-term combinations. Appendix E provides a high-level summary of the discussions for these moderate acute effect estimates.

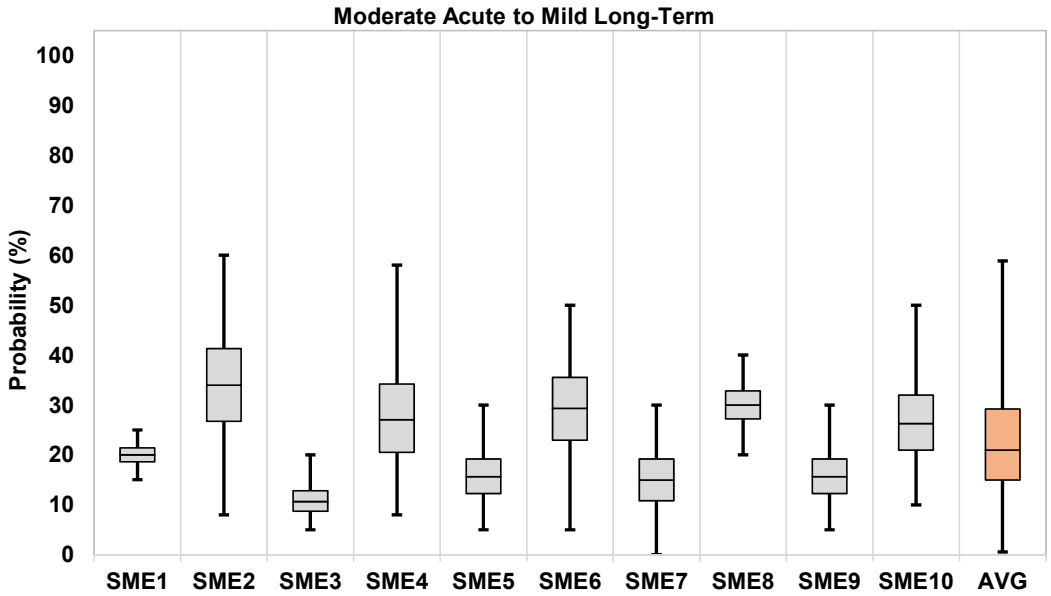


Figure 8. Individual and Consensus SME Estimates of the Likelihood of a Mild Long-Term Effect Given a Moderate Acute Effect

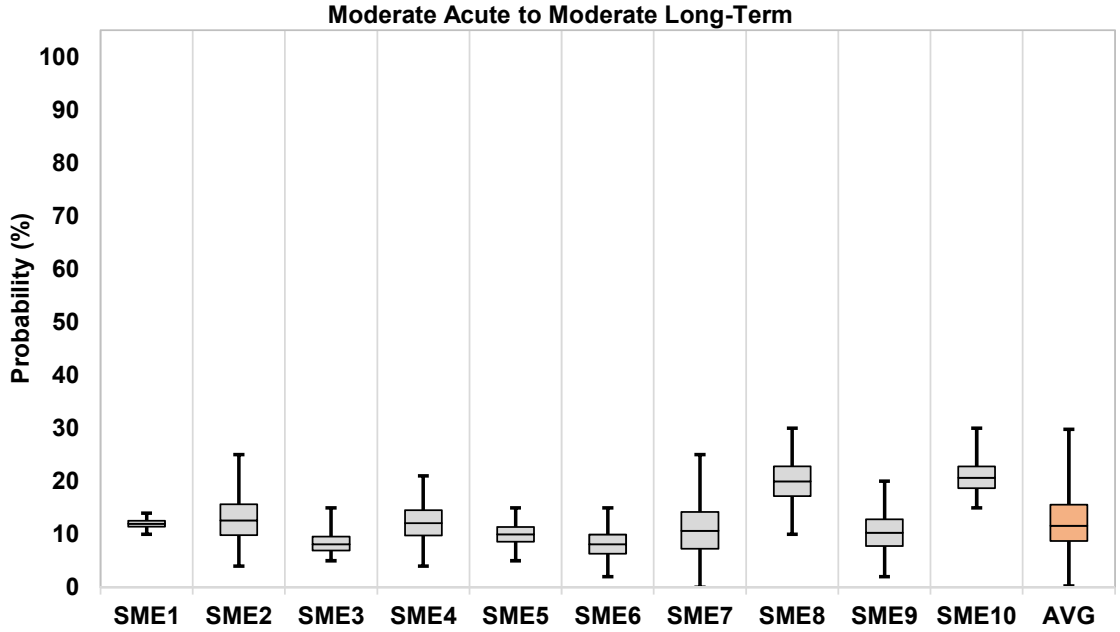


Figure 9. Individual and Consensus SME Estimates of the Likelihood of a Moderate Long-Term Effect Given a Moderate Acute Effect

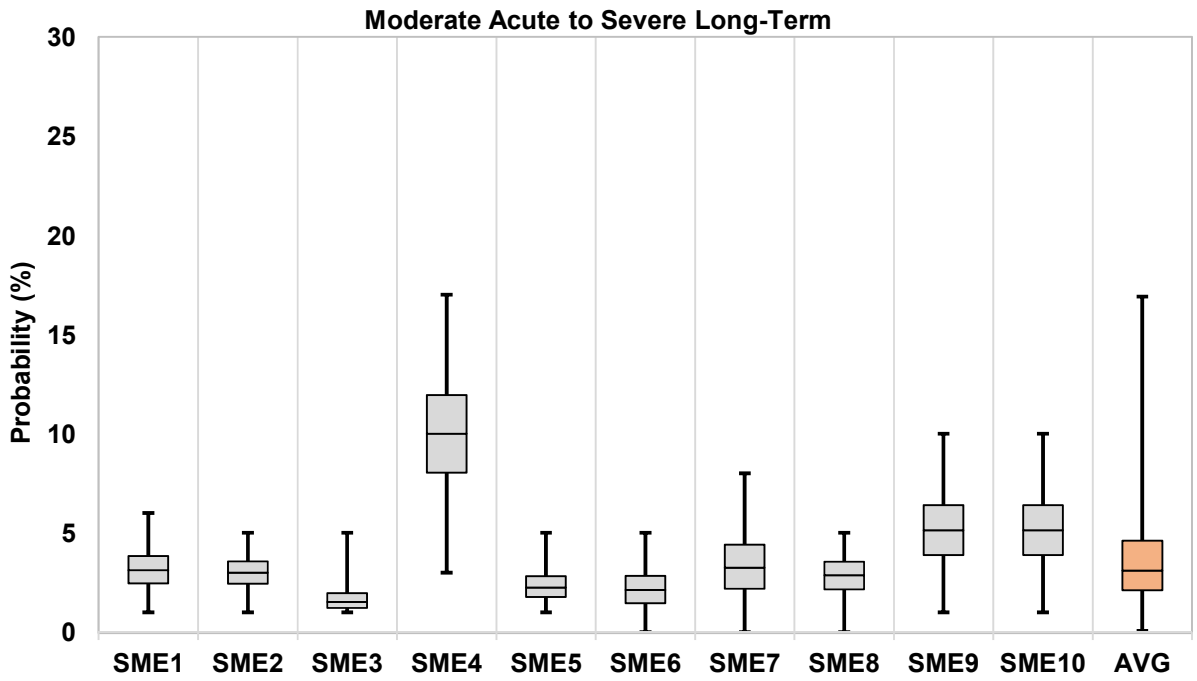


Figure 10. Individual and Consensus SME Estimates of the Likelihood of a Severe Long-Term Effect Given a Moderate Acute Effect

4.7.1.3 Acute Exposures Resulting in Severe Acute Health Effects

Figure 11 through **Figure 13** identifies the individual and representative SME estimates for the severe acute to mild long-term, severe acute to moderate long-term, and severe acute to severe long-term combinations, respectively. Appendix E provides a high-level summary of the discussions for these severe acute effect estimates.

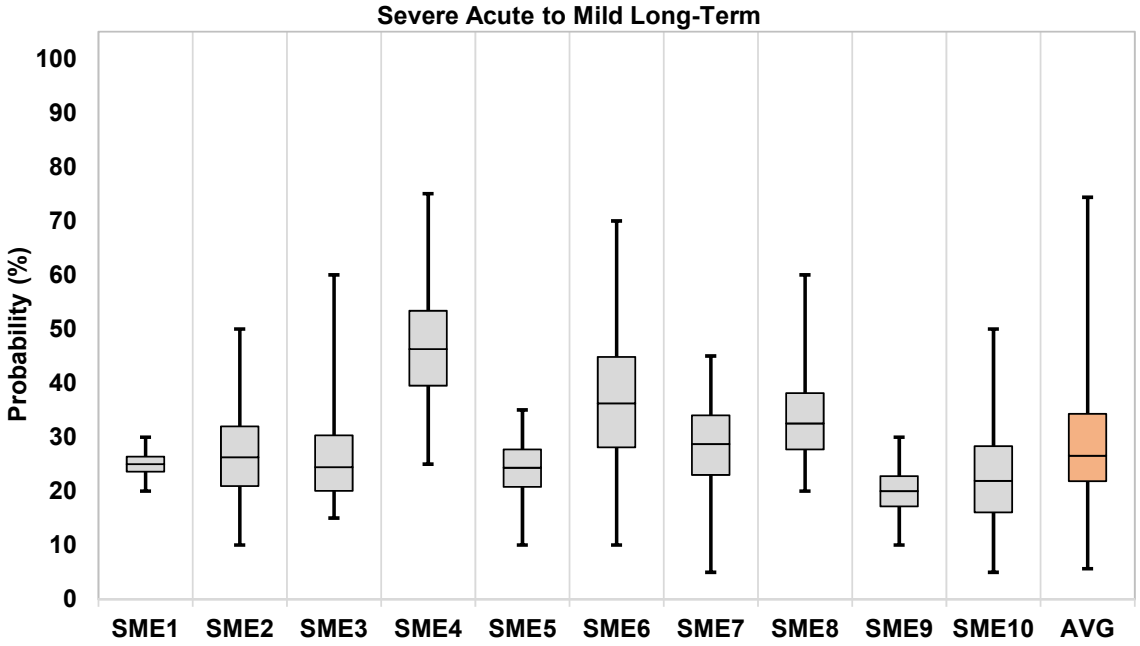


Figure 11. Individual and Consensus SME Estimates of the Likelihood of a Mild Long-Term Effect Given a Severe Acute Effect

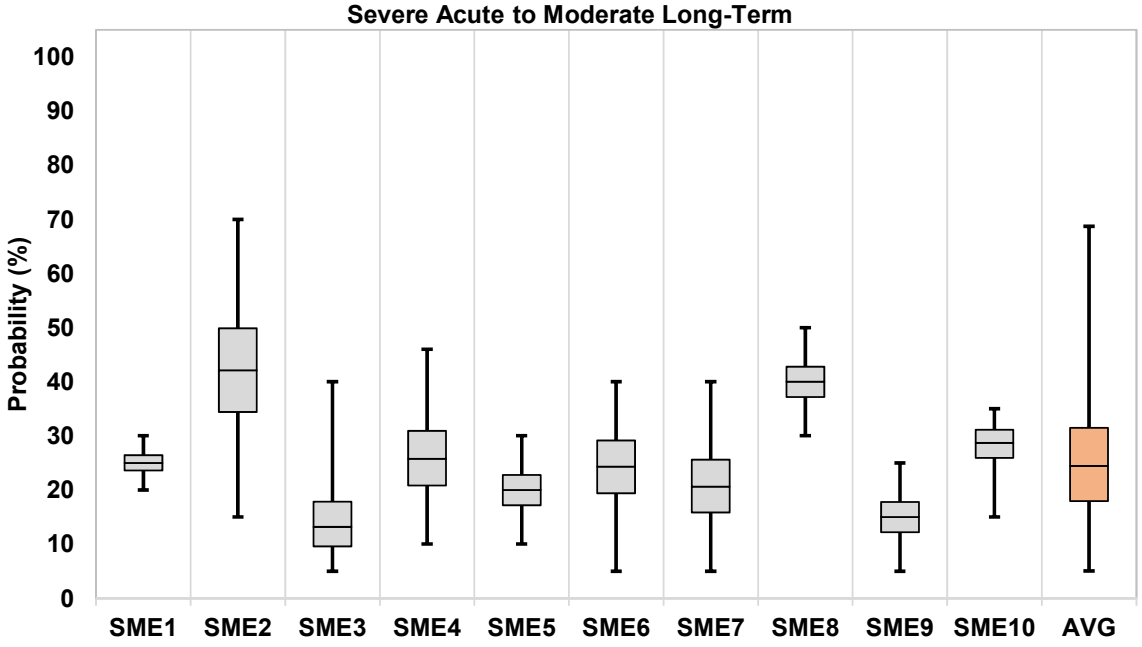


Figure 12. Individual and Consensus SME Estimates of the Likelihood of a Moderate Long-Term Effect Given a Severe Acute Effect

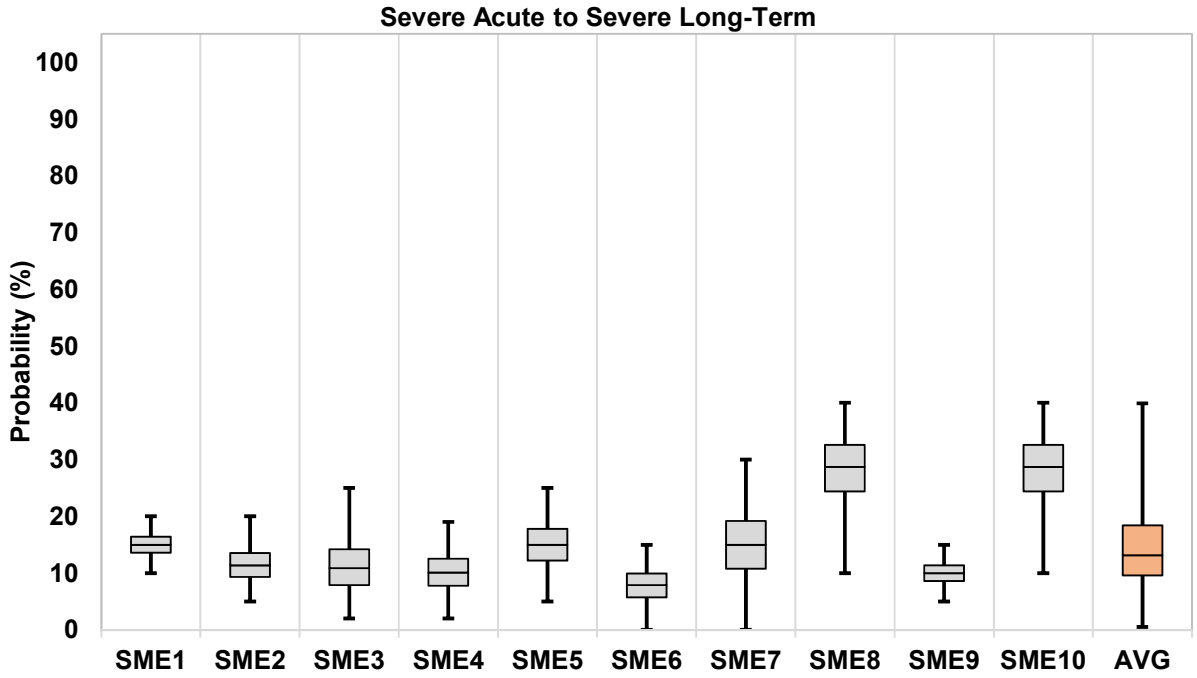


Figure 13. Individual and Consensus SME Estimates of the Likelihood of a Severe Long-Term Effect Given a Severe Acute Effect

4.7.1.4 Acute Exposures Resulting in Life-Threatening Acute Health Effects

Figure 14 through **Figure 16** identifies the individual and representative SME estimates for the life-threatening acute to mild long-term, life-threatening acute to moderate long-term, and life-threatening acute to severe long-term combinations, respectively. Appendix E provides a high-level summary of the discussions for these life-threatening acute effect estimates.

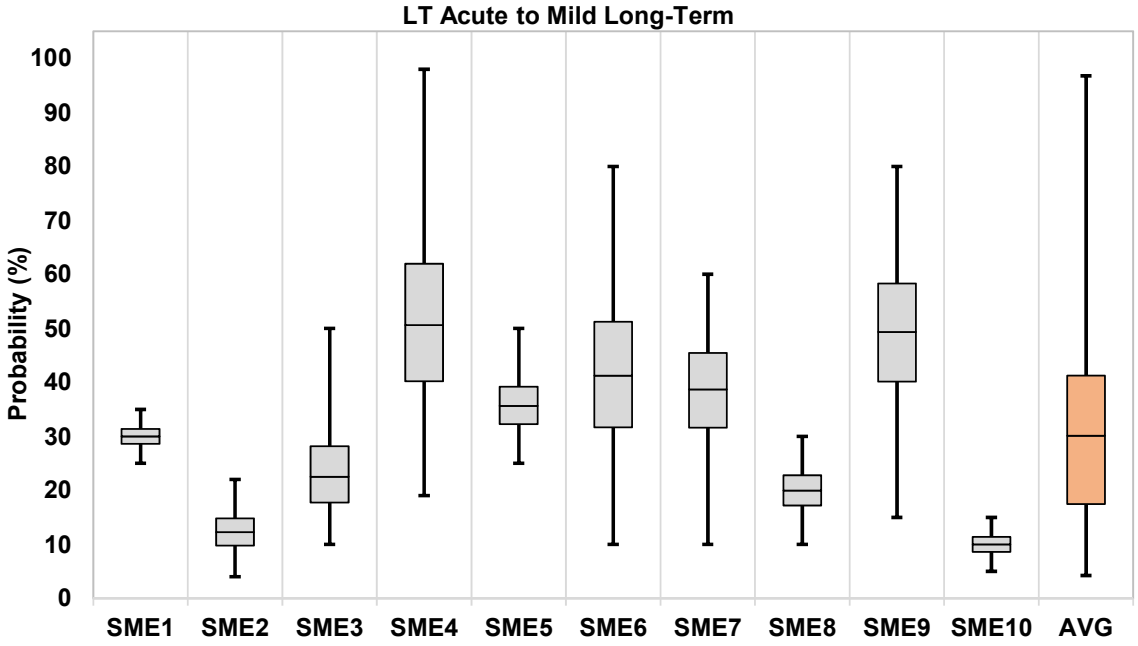


Figure 14. Individual and Consensus SME Estimates of the Likelihood of a Mild Long-Term Effect Given a Life-Threatening Acute Effect

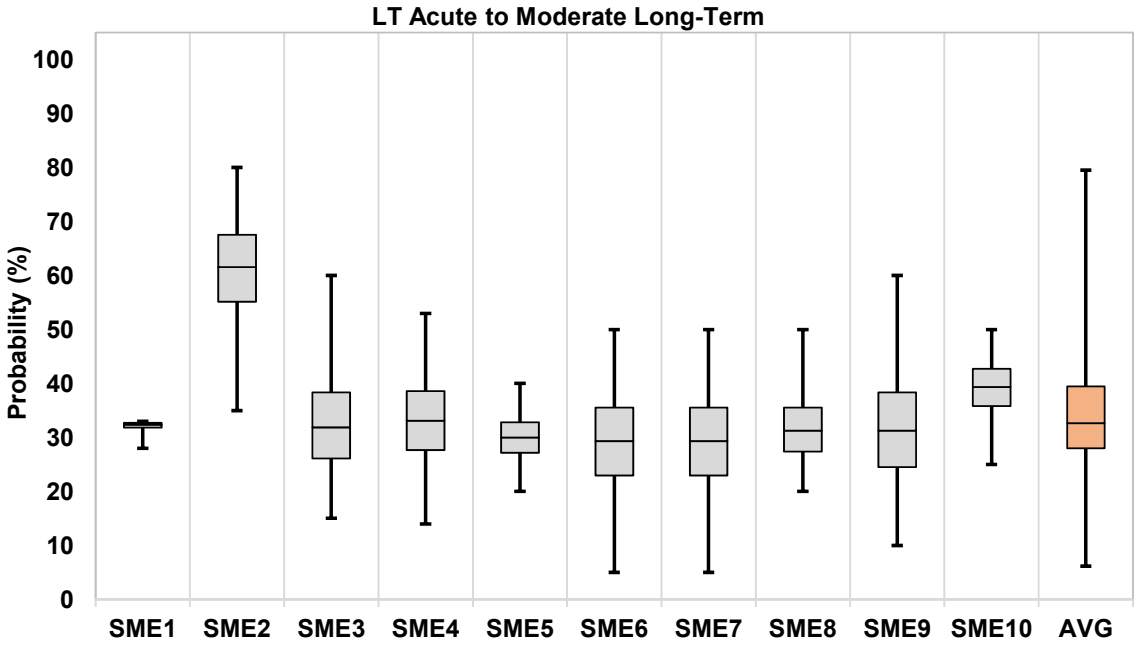


Figure 15. Individual and Consensus SME Estimates of the Likelihood of a Moderate Long-Term Effect Given a Life-Threatening Acute Effect

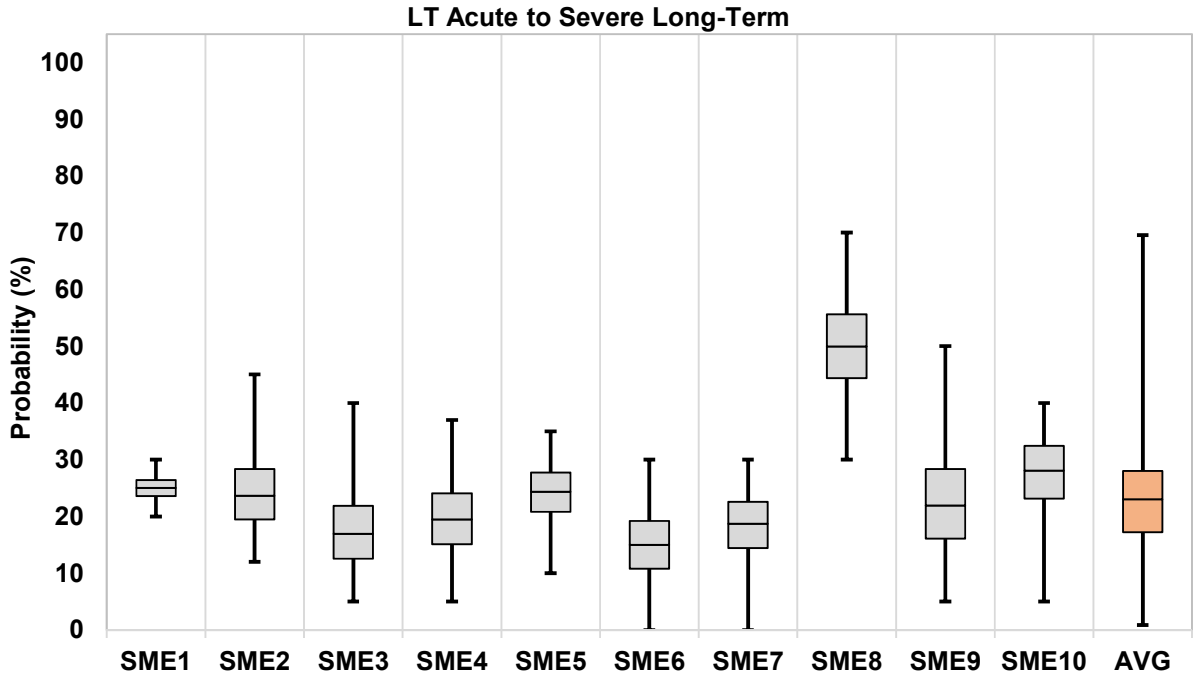


Figure 16. Individual and Consensus SME Estimates of the Likelihood of a Severe Long-Term Effect Given a Life-Threatening Acute Effect

4.7.1.5 Summary of SME Consensus Distributions

Figure 17 illustrates the raw consensus SME distributions collected in the feasibility study. Of most interest may be the monotonically decreasing triplicates for mild, moderate, and severe acute effects but not for life-threatening acute effects (this triplicate exhibits an inverted-U shape). The SMEs discussed this shape at length during the life-threatening acute effect portion of the meeting, with some of them favoring the monotonically decreasing trend and others favoring the inverted U shape (with one also favoring a monotonically increasing trend). Following the figure, **Table 5** identifies the parameters of the raw consensus SME distributions.

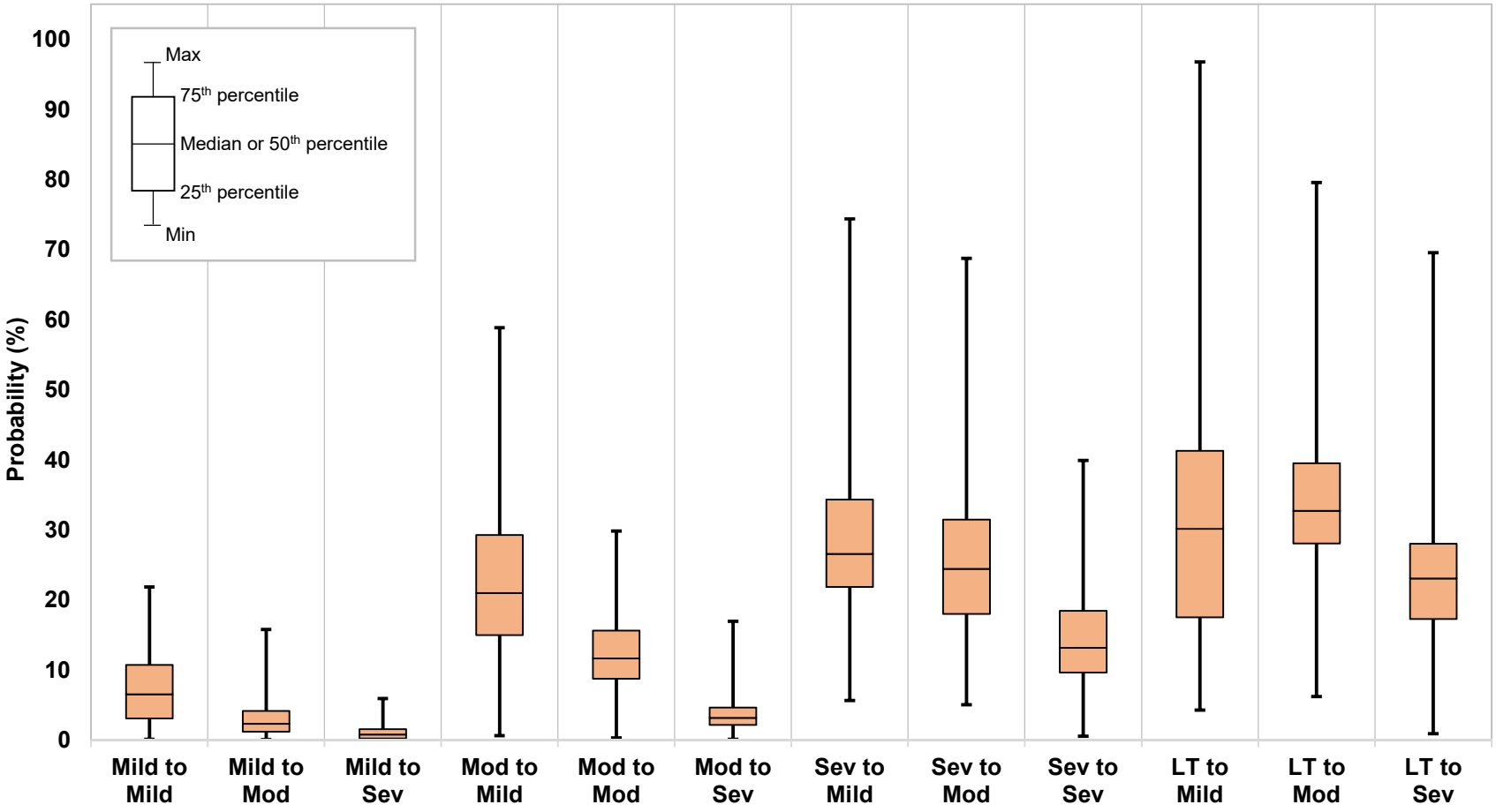


Figure 17. Raw Consensus SME Estimates Collected in the Feasibility Study

As mentioned previously, all values provided by SMEs were differential (not cumulative). Thus, the values illustrated by **Figure 17** (and listed in **Table 5**) can be viewed as bins in which acutely exposed individuals would be categorized in terms of the likelihood of long-term effects. For example, using the moderate acute triplicate in **Figure 17**, the medians are 21%, 12%, and 3%. Thus, using these median values, should 100 individuals exhibit moderate acute injuries following an acute exposure to a lower pulmonary chemical, an estimated 21% would exhibit mild long-term health effects, 12% would exhibit moderate long-term health effects, and 3% would exhibit severe long-term health effects (64% would not exhibit long-term health effects).

Table 5. Parameters of the Raw SME Consensus Distributions for all Acute Effect Triplicates

Acute to Long-Term Combinations	Raw SME Consensus Distribution Parameters			
	Mean	SD	Min	Max
Mild to Mild	7.2	4.5	0	22
Mild to Moderate	3.0	2.5	0	16
Mild to Severe	1.1	1.1	0	6
Moderate to Mild	22	10	0	60
Moderate to Moderate	13	5.2	0	30
Moderate to Severe	3.9	2.7	0	17
Severe to Mild	29	11	5	75
Severe to Moderate	26	11	5	70
Severe to Severe	15	8.0	0	40
Life-threatening to Mild	31	16	4	98
Life-threatening to Moderate	35	12	5	80
Life-threatening to Severe	24	11	0	70

4.7.2 Fitting Consensus Distributions and Accounting for Distributions in which Probability is Not Conserved

The consensus distributions shown in **Figure 17** were constructed from draws of each of the component distributions. Thus, the boxes shown in the figure are not defined by a common distribution but instead by a complex function defined by characteristics (e.g., multiple peaks) of the 10 component distributions. These complex functions are difficult to use in subsequent computations. Therefore, they were fit to a best-fit common distribution to produce computationally tractable distributions. For this process, the consensus distributions were parameterized to truncated log-normal distributions using the "NonLinearModelFit" curve-fitting function in the Wolfram Mathematica 10.4 program. Each fitted distribution was truncated at the minimum and maximum of its component distributions.

The fitted distributions present an additional challenge: in estimating the probabilities for a given acute health effect triplicate (e.g., severe to mild, severe to moderate, and severe to severe), there are potential draw combinations that sum to greater than 100% (i.e., probability is not conserved). As discussed later in the lessons learned section of this document (**Section 5.2**), this issue can be addressed in future implementations of the process by requiring that SMEs provide cumulative rather than differential values. For the present analysis, the issue can be addressed by working only with the mean values (the sums of

which do not exceed 100%), or by applying a correction or adjustment to the individual or consensus distributions. Potential correction options considered include the following:

- Scale the maxima of the fitted distributions to ensure that the sums of the maxima for a given acute injury triplicate do not exceed 100%. This option preserves the medians as the more important feature of the consensus distributions and the scaling is accomplished by reducing the maxima relative to each maximum's magnitude until the sum equals 100%. Note that some medians are also reduced as part of the scaling process, but not reduced as significantly as in other options.
- Scale the minima, medians, and maxima of the fitted distributions to ensure that the sums of the maxima for a given acute injury triplicate do not exceed 100%. This option is similar to the first option, although all features of the distribution (minimum, medians, and maximum) are reduced prior to the re-fit. This option focuses on preserving the relative relationships between a given distribution's minimum, mean, and maximum (e.g., the median is one-half of the maximum) and the scaling maintains these ratios in a manner that conserves probability. However, the medians of the scaled distributions can be reduced significantly.
- Each of the above strategies can also be applied to the component distributions prior to generation of the consensus distribution and subsequent fitting process.
- Parameterize SME elicited results using multivariate distributions. Using a multivariate distribution, such as a Dirichlet distribution (a multivariate form of the beta distribution), would provide a mechanism for incorporating the constraint of the triplicate not exceeding 100% and eliminate the need for an additional scaling procedure.
- Sampling schemes can be employed with the fitted distributions such that only valid sets of probability are used in an analysis (i.e., re-sample if probability is not conserved). This approach best preserves the consensus distribution as-is and ignores results that are not possible—such an approach results in a slight thinning of the tail of the consensus distribution. Note that this approach is an adjustment that occurs in the application of the existing fitted distributions rather than altering the distributions.
- Sampling schemes can be employed with the fitted distributions such that the probability is capped once 100% probability is achieved. For example, suppose the life-threatening acute triplicate draws were 70%, 60%, and 50%, for severe, moderate, and mild long-term health effect probabilities, respectively. Depending on the implementation of the capping method, multiple sets of adjusted values are possible. If the capping order is from severe to mild, then the adjusted values would be 70%, 30%, and 0%, whereas if the capping order is from mild to severe, then the adjusted values would be 0%, 50%, and 50%. One way to mitigate this issue is to randomize the order of the capping procedure, which can be easily implemented into the algorithm of this method. As with the previous correction option, this adjustment occurs in the application of the existing fitted distributions rather than altering the distributions.

As mentioned, the need for these adjustments can be eliminated in future implementations of this process by eliciting cumulative distributions from SMEs. The analysis of the present data set will utilize fitted consensus SME distributions that have been scaled according to the first option listed above. The first option was selected due to simplicity and the desire to preserve the medians as the more important feature of the data. Should the data from this study be used in future applications, consideration of the most appropriate adjustment (or exclusive use of the means) is recommended.

Figure 18 illustrates the consensus SME distributions following the fitting and scaling procedures as previously described. Following the figure, **Table 6** lists the mean, standard deviation, minimum, and maximum for each fitted and scaled SME distribution (note that this same information was presented for the raw SME consensus distributions in **Table 5**).

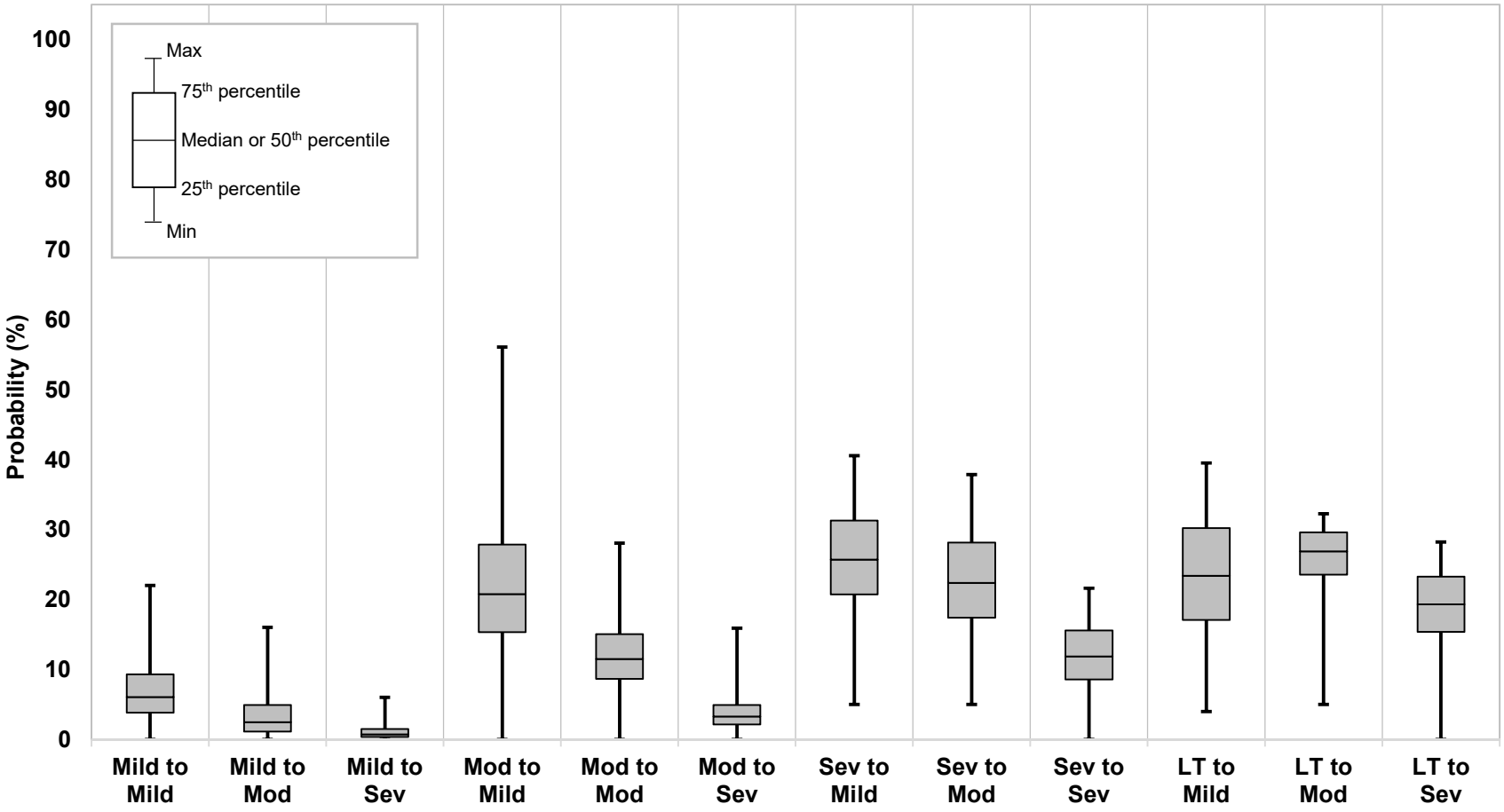


Figure 18. Fitted and Scaled SME Consensus Distributions

Table 6. Parameters of the Fitted and Scaled SME Consensus Distributions for all Acute Effect Triplicates

Acute to Long-Term Combinations	Fitted and Scaled SME Consensus Distribution Parameters			
	Mean	SD	Min	Max
Mild to Mild	7.1	4.3	0	22
Mild to Moderate	3.7	3.4	0	16
Mild to Severe	1.3	1.7	0	6
Moderate to Mild	22	9.7	0	56
Moderate to Moderate	12	4.9	0	28
Moderate to Severe	3.9	2.4	0	16
Severe to Mild	26	7.0	5	41
Severe to Moderate	23	7.1	5	38
Severe to Severe	12	4.5	0	22
Life-threatening to Mild	24	8.2	4	40
Life-threatening to Moderate	26	4.1	5	32
Life-threatening to Severe	19	5.0	0	28

4.7.3 Application of Consensus Distributions to Chemicals within the Toxidrome

The consensus distributions acquired in Step 4 are applied to the chemical-specific dose-response estimates collected in Step 1 to produce the long-term health effect curves. This step of the process was not completed during the SME elicitation and review phase to avoid SMEs using the resulting long-term health effect curves to bias their inputs to the study. All figures in this document depicting a long-term health effect curve were constructed using a cumulative representation of the fitted and scaled consensus distributions. For example, a mean mild long-term health effect curve was constructed by summing the means of the mild, moderate, and severe means (and thus the curve represents mild or worse long-term health effects). A mean moderate long-term health effect curve was constructed by summing the means of the moderate and severe means (and thus the curve represents moderate or worse long-term health effects). Severe curves are essentially differential curves because there is no subsequent long-term health effect category. The minimums and maximums are constructed similarly and thus represent very low-probability extremes. Alternative sampling schemes could be employed in the use of these distributions. For example, sampling could be correlated within a given quartile across distributions or completely uncorrelated. Each approach would result in different representations of the long-term health effect curves.

Figure 19 and **Figure 20** illustrate the application of the severe acute effect to moderate long-term effect distribution. The blue lines in these figures are based on an existing probit estimate for severe acute chlorine injury (provisional probit data from Sommerville et al. [2012])[4]. At any given value for log10(dose), the acute probit curve identifies the corresponding probit value (**Figure 19**), which equates to a probability of injury (**Figure 20**). Using the cumulative representation of the fitted and scaled consensus SME distribution obtained from this feasibility study for the likelihood of moderate long-term health effects resulting from a severe acute injury, a series of moderate (or worse) long-term health effect

[4] Note that the referenced dose-response data in this document (from Sommerville et al. (2012) and the Chemical Terrorism Risk Assessment) assume a toxic load model. Thus, this figure and subsequent figures utilize the toxic load model in calculation of dose.

curves can be constructed (red lines). The solid red line represents the mean of the distribution, and the dashed lines represent the minimum and maximum of the distribution. The points on long-term effect lines are constructed for a given log10(dose) by simply multiplying the acute effect probability and the consensus distribution probability (mean, minimum, or maximum) (an in the case of **Figure 19**, converting to the probit scale).

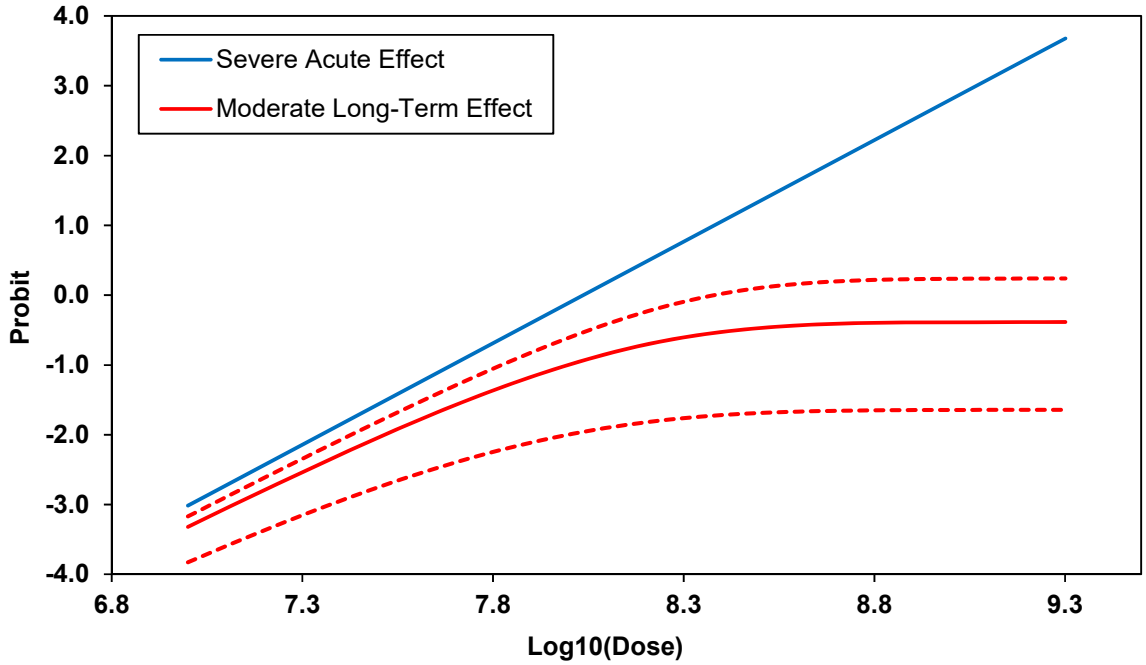


Figure 19. Moderate Long-Term Health Effect Curve Derived from an Existing Severe Acute Effect Probit Curve for Chlorine

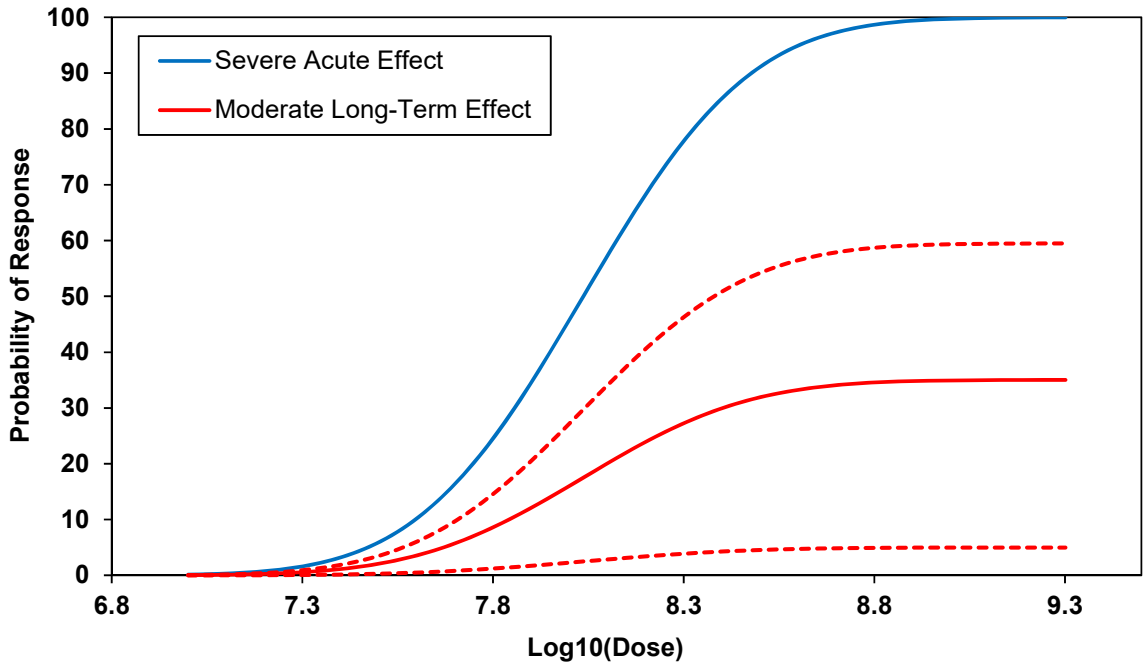


Figure 20. Moderate Long-Term Dose-Response Curve Derived from an Existing Severe Acute Effect Dose-Response Curve for Chlorine

As shown in **Figure 19**, the shape of the long-term health effect curves is different from that of the acute probit curve. The acute curves are generally developed from a probit analysis of dose-response data (such as the S-shaped curve shown in **Figure 20**, which is based on the same data as **Figure 19** except the y-axis has been converted from a probit scale to a probability scale). The long-term health effect curves represent a constant reduction in probability (e.g., 35% for the solid red line) across the S-shaped curve, producing its own (flatter) S-shaped curve. The new S-shaped curve reaches a plateau at a value equal to the probability of the long-term health effect, which in this example (using the mean) is 35% (as shown in **Figure 20**). The corresponding probit transform plateaus at a value equal to the probit transform of 35% (or −0.39 on a probit scale, as shown in **Figure 19**). There is no simple linear representation of the long-term health effect curve (i.e., it is not a probit curve and thus has no probit parameters). However, knowledge of the representative distribution allows for straightforward calculation of the probability of a long-term effect from the acute effect probit parameters. More specifically, the probability of acute effect is first determined according to the acute effect probit parameters. The acute effect probability is then reduced by the elicited probability of a long-term effect resulting from that acute effect.

Figure 21 is similar to **Figure 19**, except that mild (green) and severe (orange) long-term health effect curves have been added to the figure. The mild and severe curves were constructed in the same manner as discussed above for the moderate curve. Note that only the means are shown to avoid overcrowding the figure. Using the curves in **Figure 21** and assuming a log10(dose) of 8 (the gray dashed line in the figure), the resulting cumulative probabilities of long-term health effects are approximately 29% (mild or worse), 16% (moderate or worse), and 6% (severe). Inherent to these likelihoods is the probability that a severe acute effect has occurred. It should also be noted that other acute injuries may occur at this dose, and that these other injuries have their own set of distributions for long-term health effects. Thus, an

overall estimate of long-term health effects requires more analysis than what is provided by **Figure 21**. This topic is addressed in later in this section.

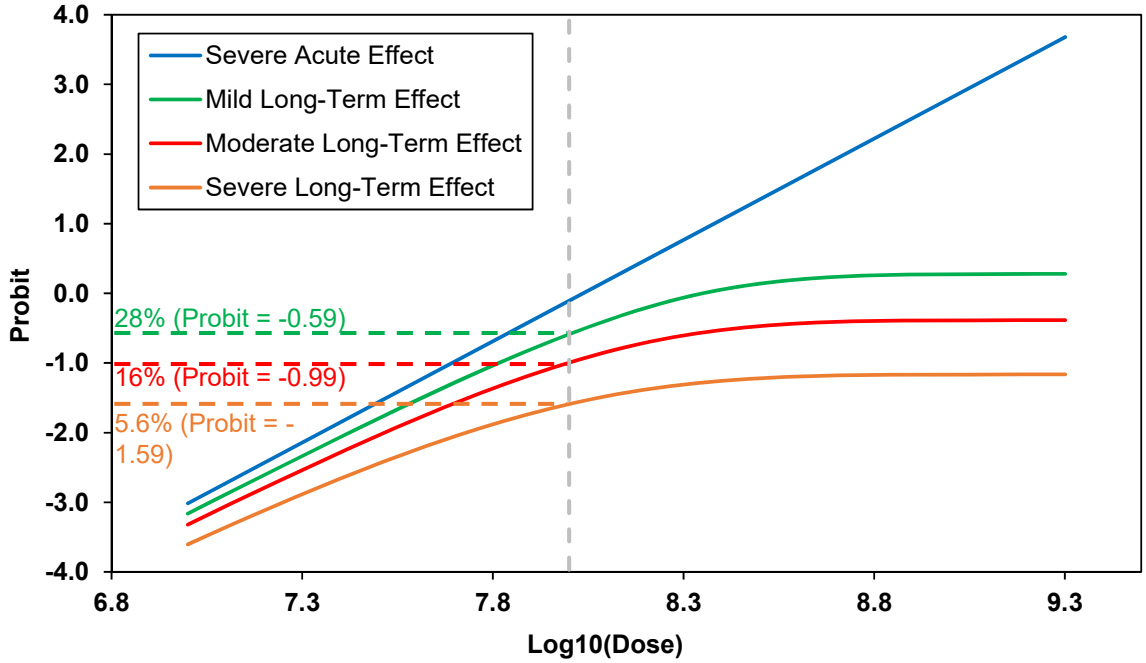


Figure 21. Mild, Moderate, and Severe Long-Term Health Effect Curve Derived from an Existing Severe Acute Effect Probit Curve for Chlorine

Because this process is conducted on a toxidrome basis, the results can be applied to all chemicals within the toxidrome. The underlying assumption that drives this statement (and the overall approach) is that similar acute effects caused by different chemicals within the same toxidrome can be characterized as having the same probability of causing long-term health effects. As shown in **Figure 22**, for example, long-term health effect curves similar to that shown in **Figure 19** for chlorine can also be generated for additional chemicals in the lower pulmonary toxidrome—phosgene and nitrogen dioxide. The plots on the right side of **Figure 22** are similar to the plot in **Figure 19** and show the acute (blue) and long-term (red) probit curves for chlorine, phosgene, and nitrogen dioxide. The acute probit curves for all chemicals were constructed using the provisional probit parameters from Sommerville et al. (2012).

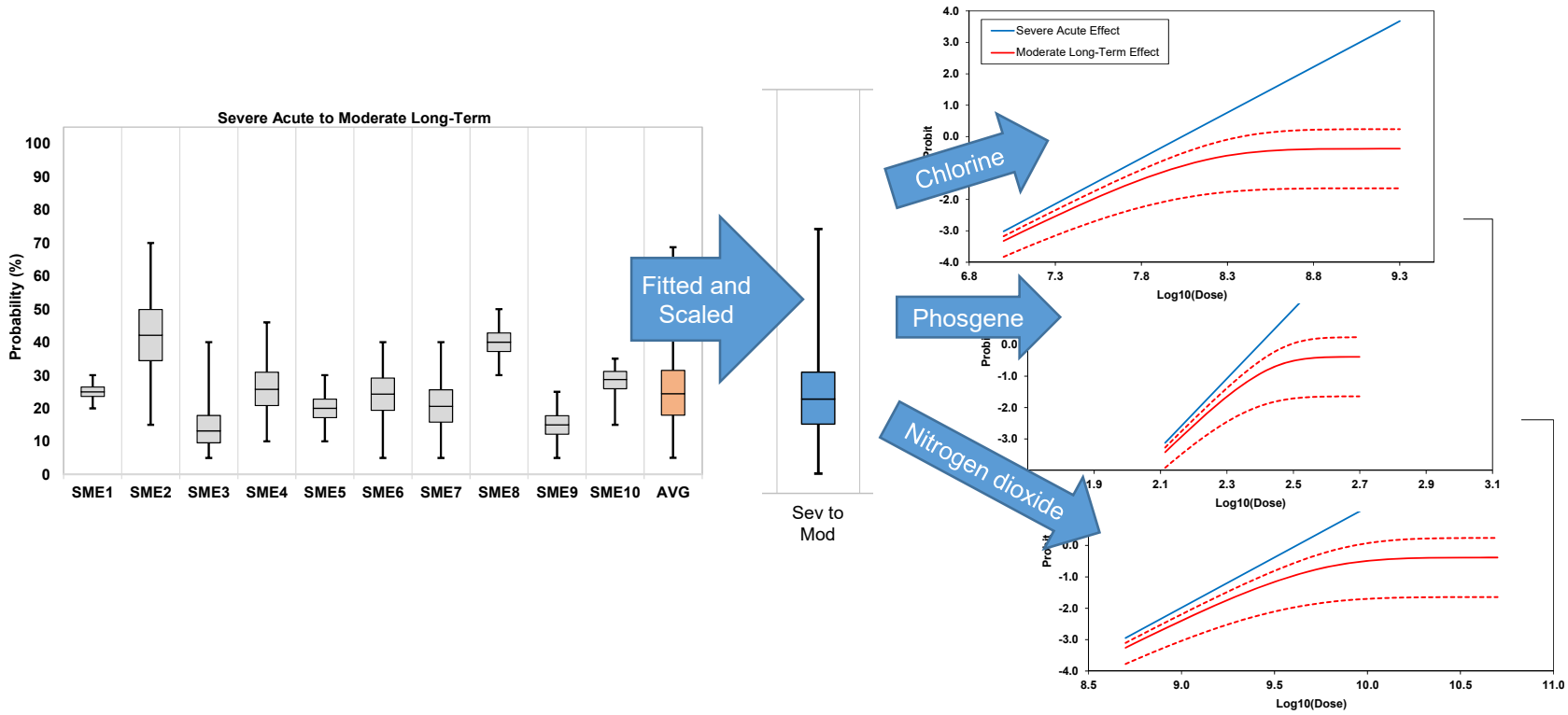


Figure 22. Conceptual Approach to Deriving Long-Term Health Effect Curves for Multiple Chemicals in a Toxidrome from Existing Severe Acute Effect Probit Curves

The process is also independent of the source of acute dose-response estimates. For example, **Figure 24** shows the same plots similar to those in **Figure 22** for chlorine (**Figure 23**) and phosgene (**Figure 24**), but using probit curves from the CSAC CTRA program. The flexibility of the process to be independent of dose-response estimates is advantageous in that any updates to acute dose-response data will not prohibit the use of the results of this process (provided that the injury type definitions are applicable).

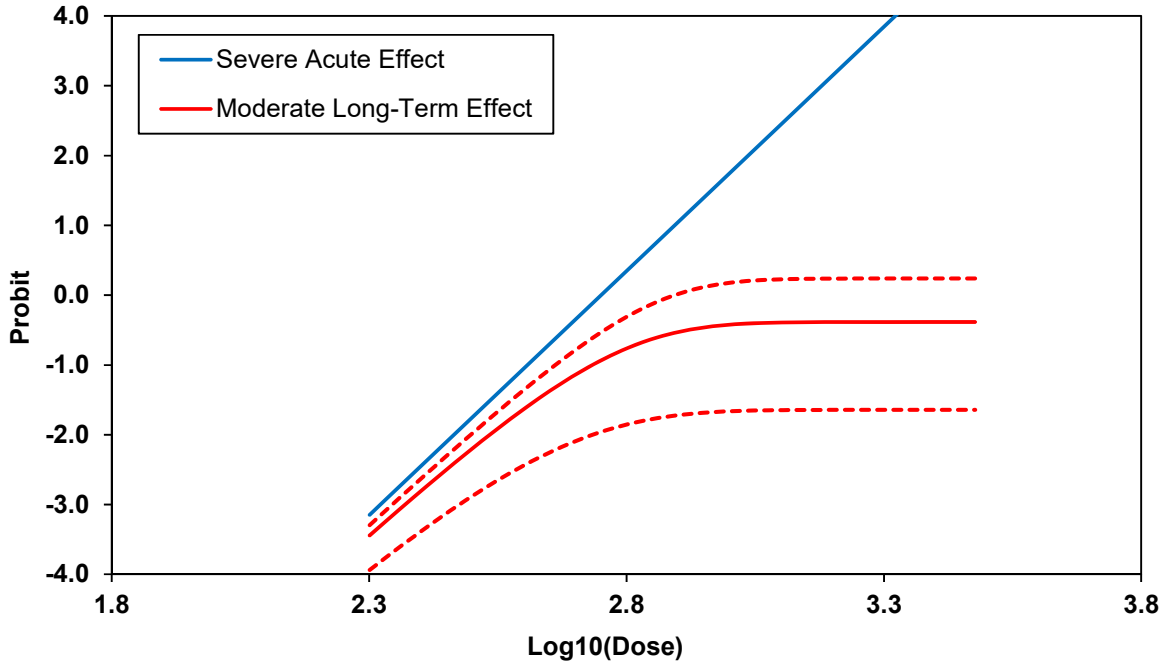


Figure 23. Moderate Long-Term Health Effect Curve Derived from Alternative Existing Severe Acute Effect Probit Curves for Chlorine

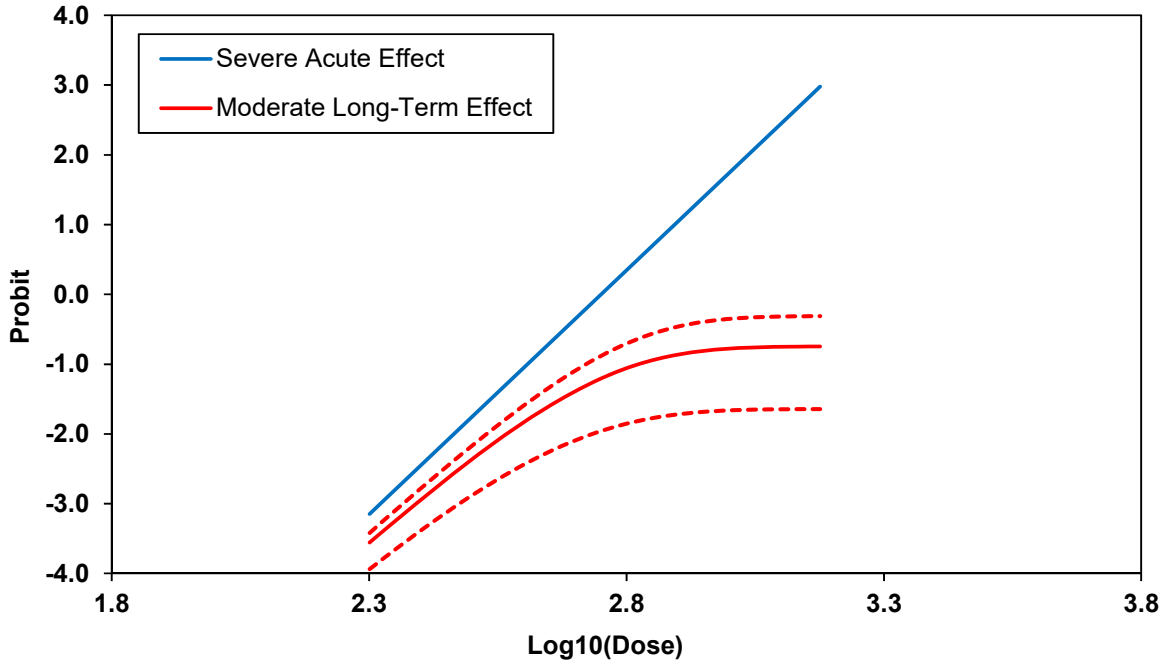


Figure 24. Moderate Long-Term Health Effect Curve Derived from Alternative Existing Severe Acute Effect Probit Curves for Phosgene

While the long-term health effect curves shown in the figures above are useful, it is important to remember that they are specific to an existing acute effect. In these figures, the long-term health effect curves are specific to severe acute injuries. However, the likelihood of long-term health effects from other acute injuries must also be considered. **Figure 25** provides an example of acute effect probit curves with significant overlap for a range of log10(dose) values. The probit curves are based on data from the CTRA program for phosgene, and the mild/moderate CTRA injury type is assumed to correspond to the moderate acute effect type as defined in this document.

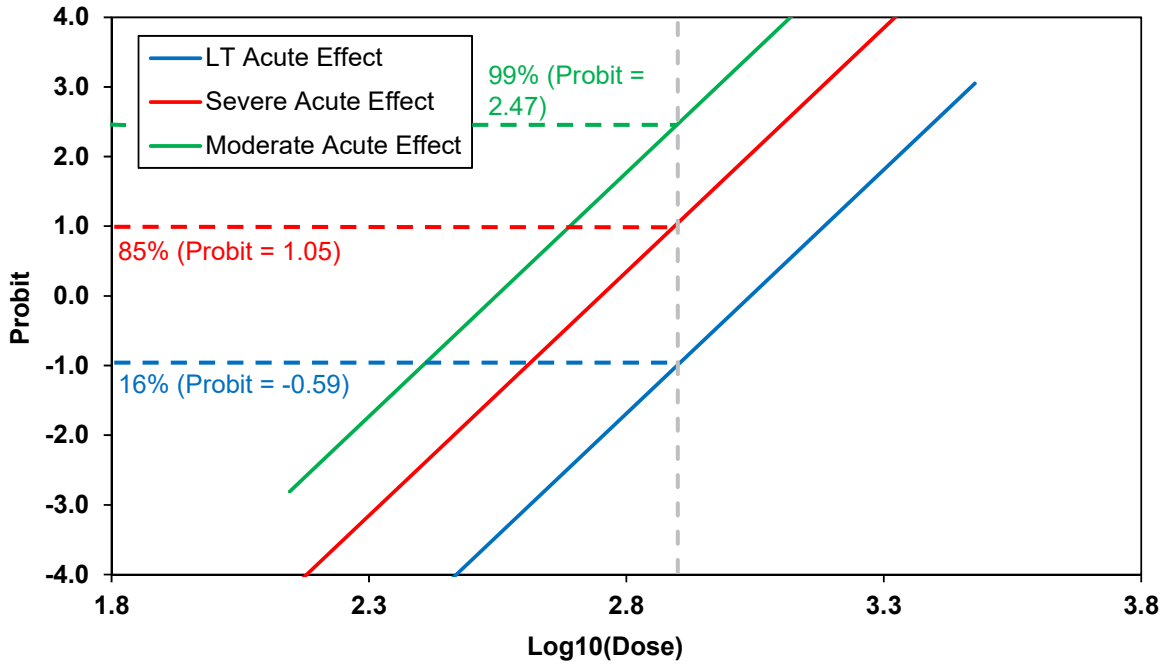


Figure 25. Existing Acute Effect Probit Curves for Phosgene Indicating Significant Overlap at Identical Dosages

As depicted in **Figure 25**, a log10(dose) value of 2.9 corresponds to acute effect probabilities of 99% (moderate), 86% (severe), and 16% (life-threatening). These percentages are inclusive of more severe injury types (e.g., 99% likelihood of moderate or worse acute health effects). Adjusting these figures to differential probabilities yields 14% (moderate only), 69% (severe only), and 17% (life-threatening only). Each curve in **Figure 25** has its own triplicate of long-term health curves. Thus, each long-term health effect type must be summed across all acute effect types. Applying the means of the fitted and scaled consensus SME distributions obtained in the feasibility study to the differential probabilities and summing across all acute effect types yields the long-term health effect curves shown in **Figure 26**.

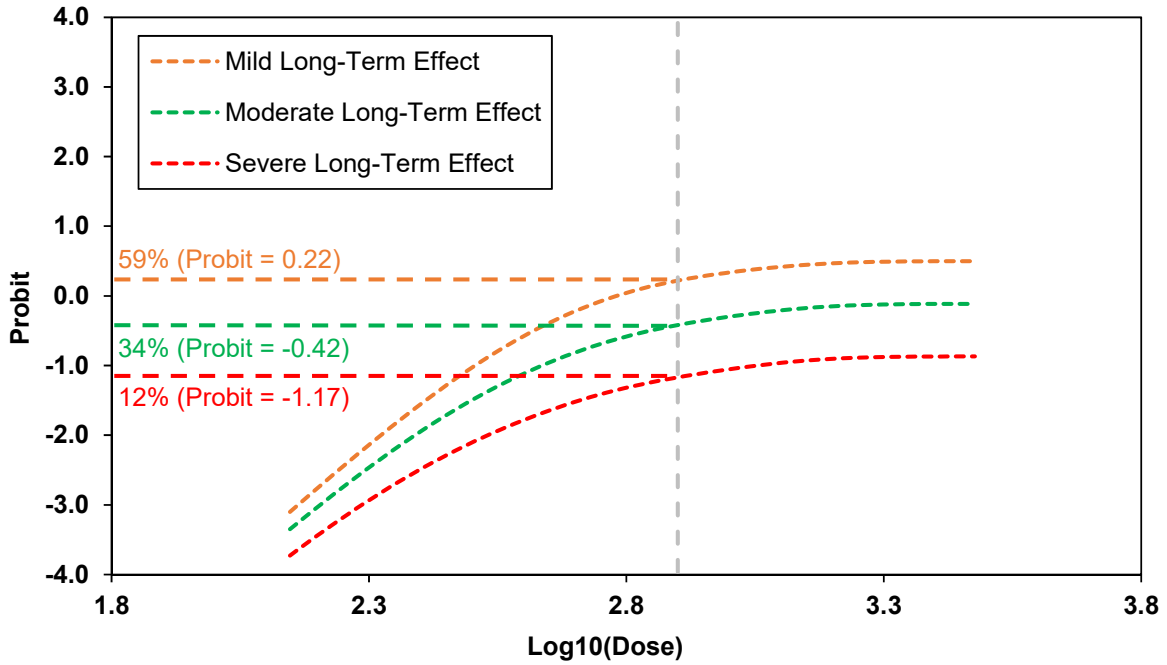


Figure 26. Existing Acute Effect Probit Curves and Summed Mild, Moderate, and Severe Long-Term Health Effect Curves for Phosgene

As noted in the example from the preceding paragraph, a log10(dose) value of 2.9 yields differential acute effect probabilities of 14% (moderate only), 69% (severe only), and 17% (life-threatening only). The means of the cumulative representations of the fitted and scaled consensus SME distributions for mild long-term health effects are as follows: 39% (moderate to mild), 61% (severe to mild), and 69% (life-threatening to mild). Thus, at a log10(dose) of 2.9, the mild long-term health effect probability is (14% x 39%) + (69% x 61%) + (17% x 69%) = 59%. This probability value corresponds to a probit of approximately 0.22 (and is consistent with the dotted orange line in **Figure 26**). As illustrated in the figure, the moderate and severe long-term health effect probabilities are 34% and 12%, respectively. As with the acute probit curves, the long-term curves are cumulative and can be used to calculate differential probabilities as needed. **Figure 27** illustrates both the acute effect probit curves and long-term health effect curves. Appendix F contains figures that are similar to **Figure 27** for other lower pulmonary chemicals and are based on probit estimates from the CTRA program. Note that the shape of the long-term health effect curves is variable and depends on the chemical-specific acute probit parameters, including the spacing between the acute curves.

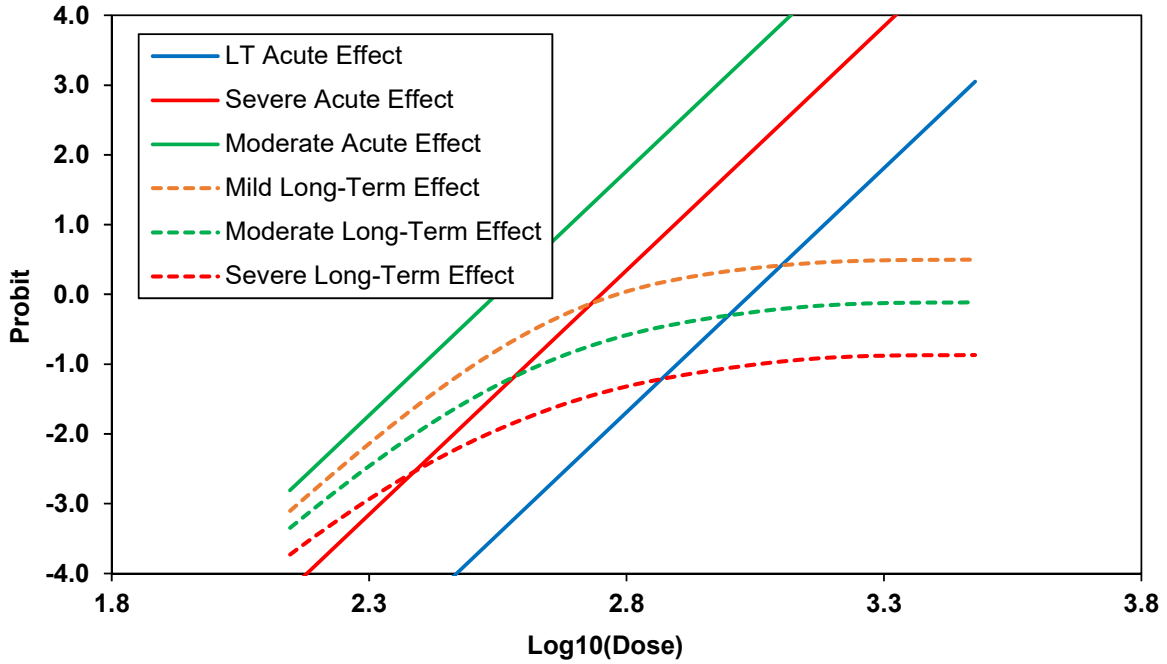


Figure 27. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Phosgene

The chemical-specific long-term health effect curves such as those shown in **Figure 26** and **Figure 27** for phosgene are the most important outputs of the process described in this document. These chemical-specific health curves, while not based directly on dose-response data, can be used in the same manner as the probit curves in the same figure. For users seeking to establish long-term health effect guidelines, it is presumed that such guidelines can be derived from specific percentiles selected from a given long-term health effect curve. For example, in deriving existing marginal MEGs for acute health effects following acute exposures, the guideline is ideally defined as the Effective Dose in 16% of those exposed (ED16) of a mild acute health effect curve. The long-term health effect curves generated by the feasibility study allow for the same type of approach to long-term effects of acute exposures. For users not wanting to establish guidelines but rather desiring to add fidelity to consequence estimates (such as risk assessors), the curves can be used directly as part of consequence estimates. Such users can calculate the probability of an acute effect for a given dosage or exposure contour and then compute the corresponding long-term health effect consequences. Finally, the results of the study can also be used to better identify individuals (deployed military or otherwise) for health surveillance based on health effects experienced following chemical acute chemical exposure.

5 PROCESS LIMITATIONS AND LESSONS LEARNED FROM THE FEASIBILITY STUDY

5.1 Process Limitations

The process described in this document involves assumptions and limitations that the following describe:

- The long-term health effect curves are not based on long-term health effect dose-response data. While the curves function similarly to probit curves, they are not based on experimental data but rather on SME input as defined in this document including relevant assumptions.
- All chemicals within a toxidrome are assumed to have the same toxic mechanism for the endpoint of interest. The process allows for sub-toxidromes to accommodate cases where a higher level toxidrome grouping is not sufficient. Because all chemicals within a toxidrome are assumed to have the same toxic mechanism, it is assumed that the chemicals will have the same health effects upon exposure.
- Similar acute injuries caused by different chemicals in the same toxidrome (or sub-toxidrome) are assumed to have the same probability of causing long-term health effects. This assumption is critical and underlies the entire process, as the SME-elicited probabilities are used to link acute and long-term health effects across an entire toxidrome.
- The process assumes that acute health effects are a primary predictor for long-term health effects. It is recognized that there may be other potential predictors of long-term effects, though they may not easily map to the modeled acute effects. For example, decreases in forced expiratory volume in one second (FEV1), the extent and time course of treatment received, and patient history may show potential in this regard. However, these factors are not easily mapped to the acute categories built into the process. Thus, SMEs classified such predictors into the existing categories according to their best expert judgment.
- The process assumes that given the dearth of literature data to support the development of long-term health effect curves and subsequent guidelines, SME elicitation represents a viable solution to bridging the data gap and meeting the need for an interim guideline until more appropriate data are generated.

It is also important to note for the purpose of establishing guidelines that without acute effect dose-response data as shown in the figures in **Section 4.7.3**, long-term health effect curves cannot be derived. Establishing long-term health effect guidelines in such cases would likely have to be accomplished through a low-resolution approach.

5.2 Feasibility Study Lessons Learned

Implementation of the toxidrome-based, SME-informed approach described in this document for the lower pulmonary toxidrome resulted in several lessons learned as listed below:

- The SME-elicited distributions are best collected as cumulative distributions. As seen throughout **Section 4**, cumulative distributions are more appropriate for use in Step 4 of the process. Furthermore, the use of cumulative distributions prevents the need for any scaling or adjustments to address invalid sets of acute triplicates (i.e., those for which probability is not always conserved). Note that the differential representation of these distributions is easily obtained. In addition, completing the fitting procedure prior the review meeting (rather than after) would enable SMEs to review the exact distributions that will be outputs of the study.
- Information regarding the nature of SME estimates as correlated or uncorrelated should be collected (i.e., is the uncertainty of SME estimates correlated or random across a given acute injury triplicate?). Knowledge of the SME approach will enable an appropriate sampling scheme to be adopted in the application of the consensus distributions.
- Additional one-on-one support to participating SMEs should be made available to mitigate the receipt of invalid distributions and minimize the time burden on SMEs. One-on-one support would also enable a more detailed understanding of the process and the inputs by participating SMEs.
- Allotting more than 2 weeks for Value SME input will ensure sufficient time to provide input. Pending available resources, incorporating results summary echoes back to SMEs within their

input sheet may also be helpful (e.g., “based on your inputs, XX% of individuals experiencing life-threatening acute effect will experience a long-term effect”).

- The SMEs identified several sources of potential confusion that can be mitigated:
    - Clearer descriptions of effect definitions during the orientation teleconference (potentially through discussions led by the Core SMEs) will mitigate the risk of misinterpreting them later and having to update input after the review meeting.
    - Clarification of how to interpret the extremes was suggested as beneficial to some SMEs. For example, 0% should be interpreted as no possibility of long-term health effects and 100% should be interpreted as long-term health effects being a certainty.
    - Clarification that the approach assumes that an individual or population has an acute effect (exhibited by the listed endpoint effects) was suggested as beneficial to SMEs. The fraction of individuals exposed but not exhibiting acute effects is not a factor in the denominator of any of the probabilities being estimated.

To the extent possible, the above lessons learned will be implemented into future applications of the process to improve the study outputs and the SME experience.

6 CONCLUSIONS AND RECOMMENDATIONS

This document details an approach to estimating the long-term health effects following acute chemical exposures and describes a feasibility study to implement the approach for the lower pulmonary toxidrome. The approach is designed to overcome data limitations identified in previous efforts. The four steps of the approach have been described in detail and a series of figures illustrating the utility of study outputs have been presented.

As a feasibility study, analysis of the process and the results of the study is the first step in determining if the approach is viable and acceptable for developing the desired guidelines. Socialization and review phases are necessary to reach the final goal of an acceptable process that can be applied to other toxidromes. To that end, a review of this process is recommended for the following:

- To ensure that the steps, underlying assumptions, and limitations of the process are acceptable.
- To ensure that the health effect definitions used in the process form an acceptable basis for use in establishing long-term health effect guidelines.
- To determine if existing hazard severity levels (negligible, marginal, critical) are appropriate/desired long-term health effect guideline levels.
- To establish an approach or hierarchy to linking the desired hazard severity levels and the long-term health effect curves (e.g., should a marginal long-term guideline be derived as the ED16 mild or moderate long-term health effect curve, is there a hierarchy or bounding approach if not all long-term health effect curves are available). Note that there are unique features of the derived curves that must be considered. Specifically, the long-term curves (unlike the acute probit curves) plateau at some probability and thus may not always meet a selected ED percentile

Additional external peer review and socialization of the approach is recommended to gain buy-in from the wider technical community of medical, toxicology, and/or other appropriate experts.

APPENDIX A

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APPENDIX B

REFERENCE PACKET PROVIDED TO PARTICIPATING SMEs

Table of Contents

B-1 Project Background

Chronic adverse health effects that result from acute exposures to chemical weapons is an issue of increasing concern to many government agencies, including Department of Defense (DOD), Department of Homeland Security (DHS), and Department of Health and Human Services. These effects can have long-ranging impact on medical, economic, and disaster response planning and the protection of exposed military or civilian populations.

Toxic Industrial Chemicals (TICs) such as chlorine have been used as weapons against soldiers and civilians in our most recent wars and conflicts. Other TICs (e.g., ammonia, sulfur dioxide, phosgene) have been identified by multiple agencies as chemicals of high concern for their potential use as a weapon against military and/or civilian populations. Chemical warfare agents such as the organophosphate sarin are also of concern; sarin was used in the 1995 Tokyo subway attack.

Current guidelines for chemical exposures address short-term effects following short-term exposures, and long-term (chronic) effects following long-term exposures. However, there are no published guidelines for long-term effects following short-term chemical exposures. To address this gap, the U.S. Army Public Health Center (APHC) is collaborating with the DHS Chemical Security Analysis Center (CSAC) to—

- Develop an approach for determining the risk of chronic adverse health effects following acute exposure to inhalation hazards; and
- Use this approach to develop appropriate values for inhalation hazards and other threat chemicals of high concern to the military and other agencies.

Previous efforts have documented the development of an analytical approach to estimating acute chlorine exposures that lead to chronic effects, specifically for chlorine. Establishing guidelines for long-term effects following acute exposures is challenging, as chronic effects are not studied as readily or as thoroughly as acute effects. There are very limited human data available for modeling long-term effects following short-term chemical exposures, and animal studies do not always address this exposure/effect paradigm.

To bridge this gap, an alternative approach was developed to address the issue of limited data by collecting toxidrome-based input from subject matter experts (SMEs). Note that a toxidrome is a constellation of signs and symptoms, or a particular clinical presentation, which suggests a particular kind of toxic insult. This document describes a feasibility study supported jointly by the APHC and the CSAC. The feasibility study implements this toxidrome-based, SME-informed approach to estimating acute exposures that lead to chronic effects. This document provides the following information to assist participating SMEs in this study: an overview of the approach with

instructions for SMEs (Section B-2), background on relevant physiology and toxicology (Section B-3), a focused discussion on health effects to the toxidrome of interest (Section B-4), and a discussion of pertinent literature (Section B-5). As discussed in Section B-2, an Excel workbook is included in addition to this reference packet. SMEs are to provide input in the Excel workbook and return to the Technical point of contact (POC) (David Winkel – winkeld@battelle.org).

B-2 Overview of the Toxidrome-Based, SME Informed Approach

This section provides an overview of the steps of the toxidrome-based, SME-informed approach to developing guidelines for long-term health effects following acute exposures. Specific instructions on how Value SMEs are involved in the process are also presented. Note that although all four steps of the process are presented, the first two steps have already been completed, and Value SMEs only participate in portions of the final two steps. Finally, it should also be noted that the present feasibility study is an implementation of this approach for only peripherally-acting lower pulmonary chemicals via the inhalation exposure route (i.e., a single toxidrome and exposure route combination).

B-2.1 Step 1 – Identify acute, non-lethal health effects and associated dose-response estimates

Step 1 is the identification of acute, non-lethal medical health effects for a short-term exposure to chemicals within the selected toxidrome by the selected exposure route. *Because all chemicals within a toxidrome are assumed to have the same toxic mechanism, it is assumed that the chemicals will have the same health effects upon exposure.*[5] Of course, the dose or exposure resulting in those effects will vary among chemicals in the toxidrome. The acute, non-lethal medical effects (including symptoms and findings) identified for the peripherally-acting lower pulmonary chemicals via the inhalation exposure route can be found in the mapping diagram presented in Section 2.2.

It is further assumed that a given acute health effect caused by different chemicals within the same toxidrome has the same probability of causing a given long-term health effect typical to that toxidrome. As will be shown later, the estimation of the long-term effect guidelines will be guided by acute dose-response relationships. Thus, it is

[5] The creation of toxidrome sub-groupings is permitted to handle exceptions to this assumption in which there are appreciable differences in mechanisms. An extreme application of the concept of sub-groupings would result in each chemical within a toxidrome being assigned to its own sub-group. However, a goal of this effort is to simplify the data collection process such that it can ultimately be completed for all chemicals of concern to DOD and DHS – thus, grouping is preferred where reasonable. Note that for the particular toxidrome and exposure route combination selected for this feasibility study (peripherally-acting lower pulmonary chemicals via the inhalation exposure route), no sub-toxidromes were established.

essential that dose-response estimates exist for chemicals within the toxidrome. Health effects are grouped into effect categories (such as mild and severe) to increase the likelihood that dose-response data are available. While "cough" is a health effect for the pulmonary toxidrome, for example, it can be difficult to identify dose-response estimates specific to only cough. Such estimates will likely group coughing with other respiratory symptoms. The health effect groupings used in this feasibility study are mild, moderate, severe, and life-threatening. It is envisioned that these groupings would continue to be used in future implementations of the process. The groups can be defined as follows (note that these definitions are used for both acute and long-term effects, as reflected in the definitions)[6]:

- Mild - Non-disabling, largely reversible effects that do not impair performance; individuals not expected seek medical attention but may need to provide self-care.
- Moderate - Effects that are 1) reversible that alter organ function or impair performance; or 2) irreversible and do not alter organ function or impair performance (for this toxidrome, such acute moderate effects may range from changes in epithelial cell type to scarring on X-Ray without clinical impairment). Individuals may seek medical attention.
- Severe - Effects that alter organ function or impair performance and may be irreversible, though treatable. Severe acute effects require medical attention, but are not expected to cause death acutely. Severe long-term effects may result in a decreased life expectancy.
- Life-threatening - Effects that are a threat to the individual's life and will result in death if left untreated. Note that the life-threatening category was not included as part of long-term effects. This definition is meant to apply to acutely life-threatening effects, whereas any long-term effect that could ultimately result in a decreased life expectancy is categorized as severe.

While acute dose-response estimates are necessary for the completion of the process, these estimates are not provided as part of this reference document. Inclusion of this information would allow participating SMEs to provide likelihood estimates based on the resulting long-term health effect curves. To preserve the integrity of the process, only notional dose-response estimates are provided in this reference packet and accompanying Excel tool. The notional data will prevent the feasibility study outputs (i.e., the resulting long-term health effect curves) from being used to inform SME inputs.

[6] Definitions were based on reviews of existing acute definitions from multiple sources, including DHS CSAC Chemical Terrorism Risk Assessment (CTRA) definitions and National Research Council (NRC) review of a risk analysis model (NRC report available at: http://www.nap.edu/catalog/6205/assessment-of-exposure-response-functions-for-rocket-emission-toxicants), as well as review by the Government POCs

B-2.2 Step 2 – Engage Core SMEs to identify long-term health effects and prepare reference materials

Step 2 of the process is to engage a core group of medical/toxicology SMEs that are capable of and comfortable with: 1) identifying long-term medical health effects for the given toxidrome; and 2) exploring/understanding the linkage between the acute and long-term medical health effects. For the purposes of this effort, a long-term health effect is defined in this effort an adverse, non-acute health effect that arises following an acute (i.e., one-time) exposure. The effects to be considered are analogous to chronic health effects often described in the literature – but are the result of an acute rather than chronic exposure. As with acute health effects, long-term health effects are categorized into levels of severity. Note that this feasibility study is concerned only with the pulmonary effects of these exposures – the process is not designed to ignore other effects, but simply focus the scope of the effort onto a single type of effect.

The Core SMEs involved in this feasibility study are listed in **Table B-1**.

Table B-1. List of Core SMEs

SME	Organization/Affiliation	Education/Experience
Terry Gordon, PhD	New York University School of Medicine	Expertise in inhalation toxicology, air pollution, genetic susceptibility, and occupational health.
James M. Madsen, MD, MPH, COL(ret), MC, USA	US Army Medical Research Institute of Chemical Defense	Board-certified in anatomic pathology, clinical pathology, occupational medicine, and medical toxicology. He has taught and published extensively, especially on the medical management of chemical-warfare-agent casualties.
Charles McKay, MD, FACMT	American College of Medical Toxicology	Board-certified in Medical Toxicology, Emergency Medicine, and Internal Medicine with training in anatomic pathology. Medical Director of a regional Poison Center and SME participant in CTRA Medical Mitigation model data collection effort.

For this feasibility study, the Core SMEs identified long-term health effects based on references/knowledge of toxic mechanisms as well as literature describing the potential for these effects. **Figure B-1** shows the resulting list found in the mapping diagram. The figure depicts a mapping of the symptom-based and physiologic mechanism-based summary of this progression from acute to chronic health impacts.

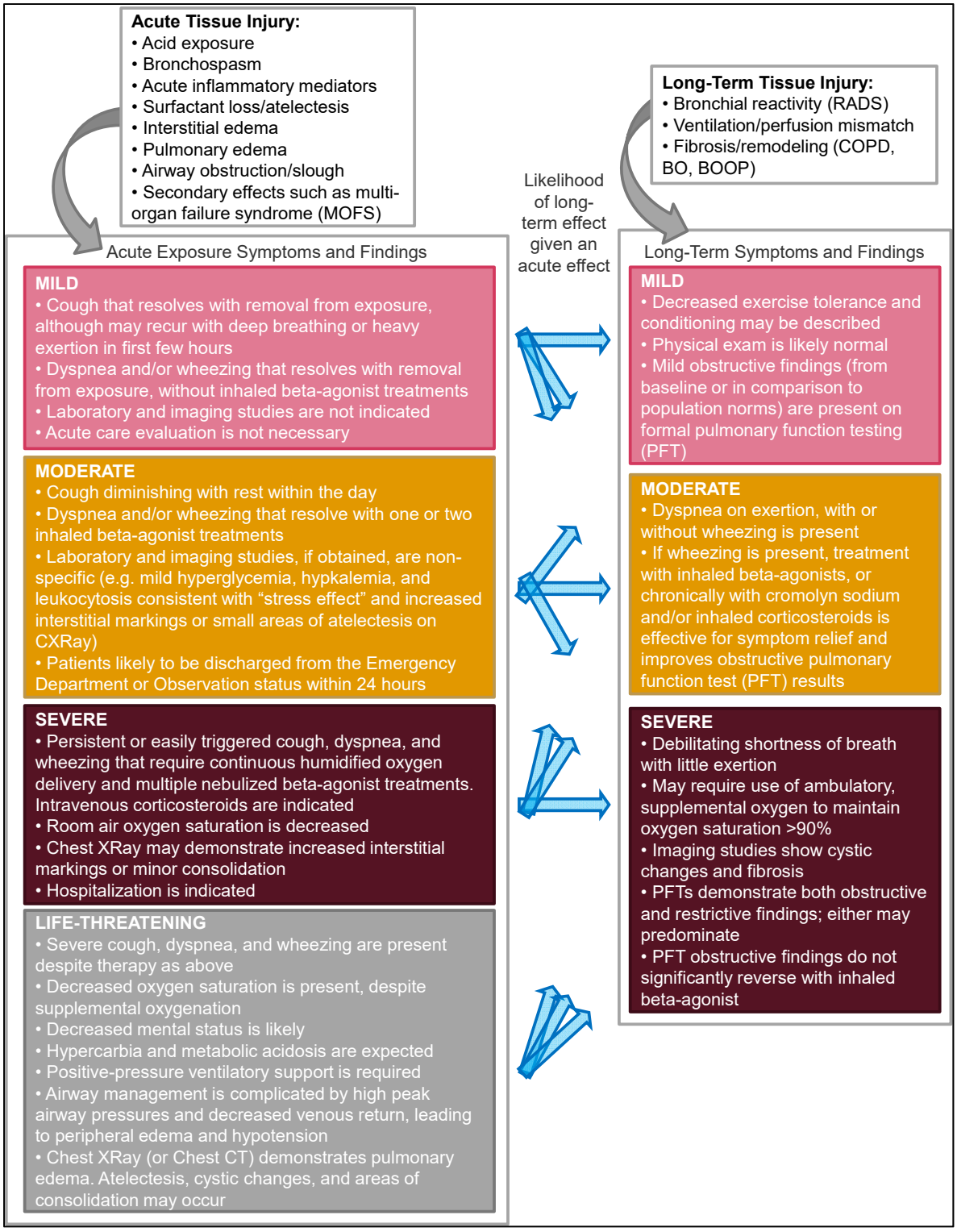


Figure B-1. Mapping of Acute to Long-Term Health Effects in this Feasibility Study

B-2.3 Step 3 – Elicit Long-Term Health Effect Probabilities from Value SMEs

In Step 3, Value SMEs will quantitatively define the likelihood of an individual exhibiting the long-term health effects described in Step 2 given the acute health effects identified in Step 1. *Specifically, it is requested that Value SMEs provide a quantitative likelihood for any connection in the diagram between an acute health effect grouping (mild, moderate, severe, or life-threatening) and a long-term health effect grouping (mild, moderate, or severe).* Information to assist in making these estimates is provided in the subsequent sections of this reference document (Sections 3 through 5), prepared by the Core SMEs as part of Step 2.

Figure B-1 shows multiple values (i.e., one estimate for each acute/long-term combination) will be elicited for the toxidrome of interest (each connection represents an estimate). Thus, 16 separate likelihoods are being elicited. It is worth reiterating that because this approach is toxidrome-based, these estimates apply to all chemicals in the toxidrome (i.e., estimates are not made on a chemical-by-chemical basis). This toxidrome-level estimate is consistent with the assumptions identified in Step 1:

- All chemicals within a toxidrome are assumed to have the same toxic mechanism.
- Similar acute health effects caused by different chemicals within the same toxidrome have the same probability of causing the long-term health effects of that toxidrome.

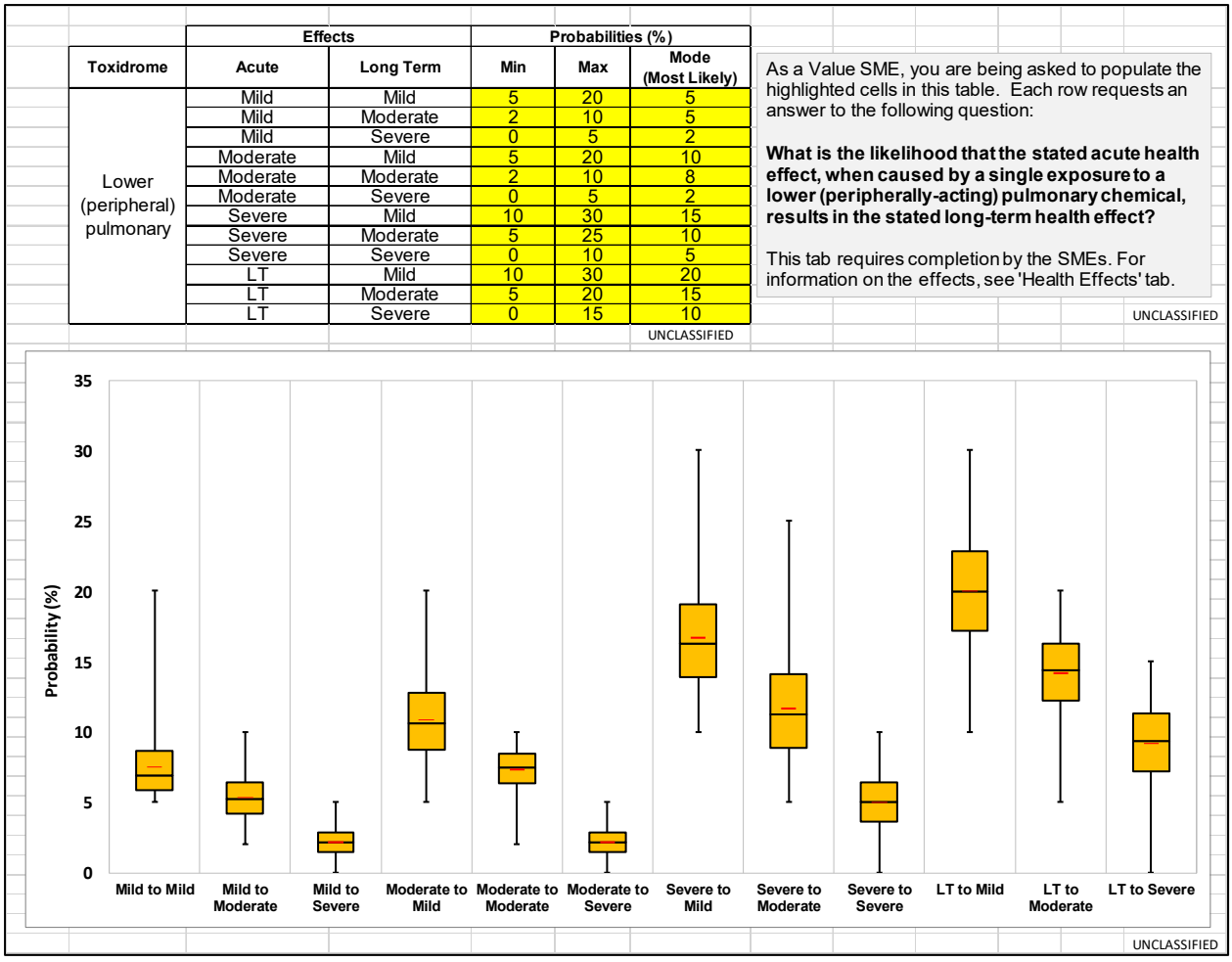
Using Sections 3 through 5 of this reference document as well as their own expertise and experience, Value SMEs will populate the connections of the mapping of acute health effects to long-term health effects. Input will be recorded in a manner intended to ease the burden on SMEs while also capturing the uncertainty associated with the estimates. Specifically, SMEs will be asked to provide three parameters – a minimum value, maximum value, and most likely value for each estimate. These values will be recorded in the "SME Input – Individual" Excel workbook (provided to all SMEs) as inputs to a betaPERT distribution. The workbook has the following tabs to facilitate SME involvement in the elicitation process:

- SME Input – SMEs will provide their likelihood estimates on the 'SME Input' tab in the highlighted cells. Each row represents one of the acute/long-term combinations (e.g., the last highlighted row corresponds to the likelihood of a life-threatening acute health effect resulting in a severe long-term health effect). Below these inputs is a figure with a series of box plots. Each box plot corresponds to one of the SME inputs and provides a visualization of the SME input values (e.g., the first box plot in the figure corresponds to the first row of requested input).

- Health Effects – The 'Health Effects' tab provides a list of the various health effects associated with each grouping. It is essentially a reproduction of the mapping diagram in **Figure B-2**.
- Distribution Visualization PDF – This visualization tab provides an alternative to the box plot illustration of a betaPERT distribution[7]. Although it is not linked to the SME Input tab, SMEs can enter up to two different sets of betaPERT distribution parameters and view the resulting PDFs
- Step 4 Preview – This tab provides a preview of how the results of the feasibility study can be applied to acute health effect dose-response estimates to produce long-term health effect dose-response estimates. The SME can enter a potential combined distribution (i.e., the result of the feasibility study) and the dose-probit and dose-response curves for a series of hypothetical chemicals will be updated to illustrate the resulting long-term health effect curves that are generated.

Screenshots of the SME Input and Distribution Visualization PDF tabs are shown in **Figure B-2** and **Figure B-3**, respectively.

[7] A betaPERT distribution has a shape similar to that of a normal or log-normal distribution (depending on how its parameters are defined). It is useful for exercises such as this one, in that it produces what is considered to be a realistic shape without requiring specification of the more-difficult-to-define mean and standard deviation parameters.



Toxidrome	Effects		Probabilities (%)		
	Acute	Long Term	Min	Max	Mode (Most Likely)
Lower (peripheral) pulmonary	Mild	Mild	5	20	5
	Mild	Moderate	2	10	5
	Mild	Severe	0	5	2
	Moderate	Mild	5	20	10
	Moderate	Moderate	2	10	8
	Moderate	Severe	0	5	2
	Severe	Mild	10	30	15
	Severe	Moderate	5	25	10
	Severe	Severe	0	10	5
	LT	Mild	10	30	20
	LT	Moderate	5	20	15
	LT	Severe	0	15	10

Figure B-2. Screenshot of SME Input Tab of "SME Input – Individual" Excel Workbook

Beta PERT Distribution Visualization

On this tab, users can enter up to two sets of betaPERT distribution parameter values (min, max, and mode) and view the PDF of the resulting distributions, as well as percentile data. This tab only serves to help visualize distributions.

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Parameter	Parameter Set 1 (Blue Line)	Parameter Set 2 (Red Line)
Distribution Type	betaPERT	betaPERT
Min	2	5
Max	20	20
Mode	15	10

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Percentile (%)	Value	Value
0.1	4.0	5.3
5	7.8	6.6
25	11.4	8.7
50	14.0	10.6
75	16.2	12.8
95	18.4	15.7
99.9	19.8	18.6

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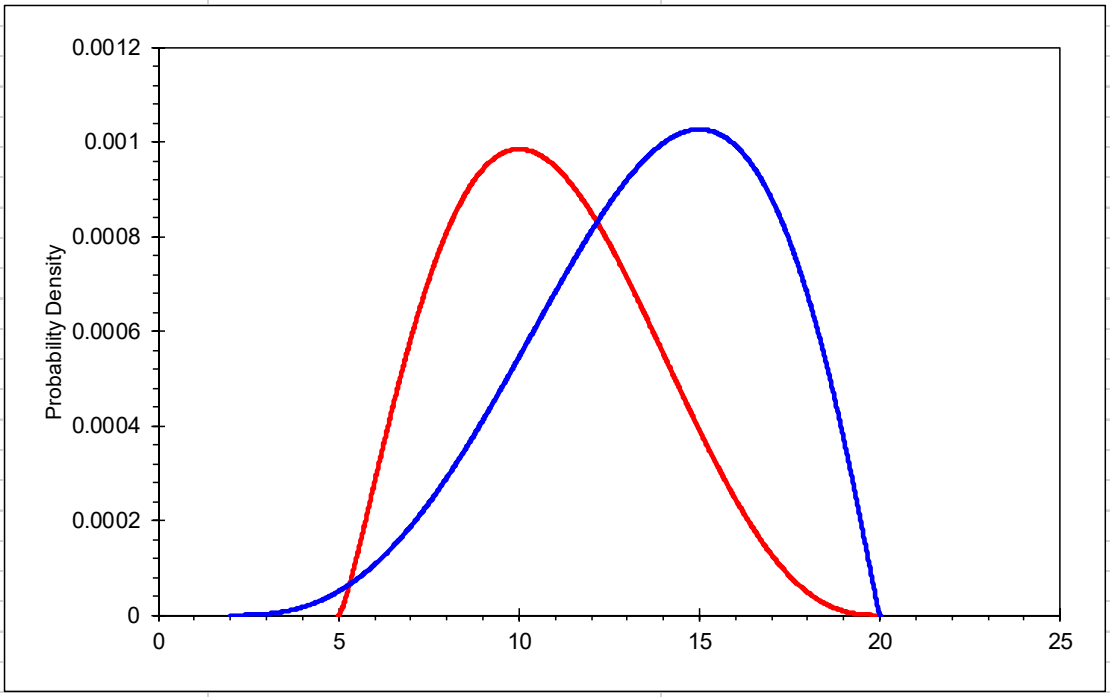

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Figure B-3. Screenshot of Distribution Visualization – PDF Tab of "SME Input – Individual" Excel Workbook

To eliminate potential bias during the SME input phase, discussion amongst SMEs is prohibited. SMEs will generate estimates independently and return the Excel file to the project POCs for compilation with other SME input. Completed Excel files are due by noon Eastern Standard Time on 29 August to David Winkel (winkeld@battelle.org).

B-2.4 Step 4 – Elicit Long-Term Health Effect Probabilities from Value SMEs

After all Value SME input is collected in Step 3, the input will be combined by the feasibility study personnel into a single, combined distribution for each elicited value (i.e., for each acute/long-term combination) in Step 4. The Value SMEs will be convened for a WebEx/telecon review meeting and presented with the individual (anonymized) and combined distributions for review and discussion (such as that seen in **Figure B-4**).

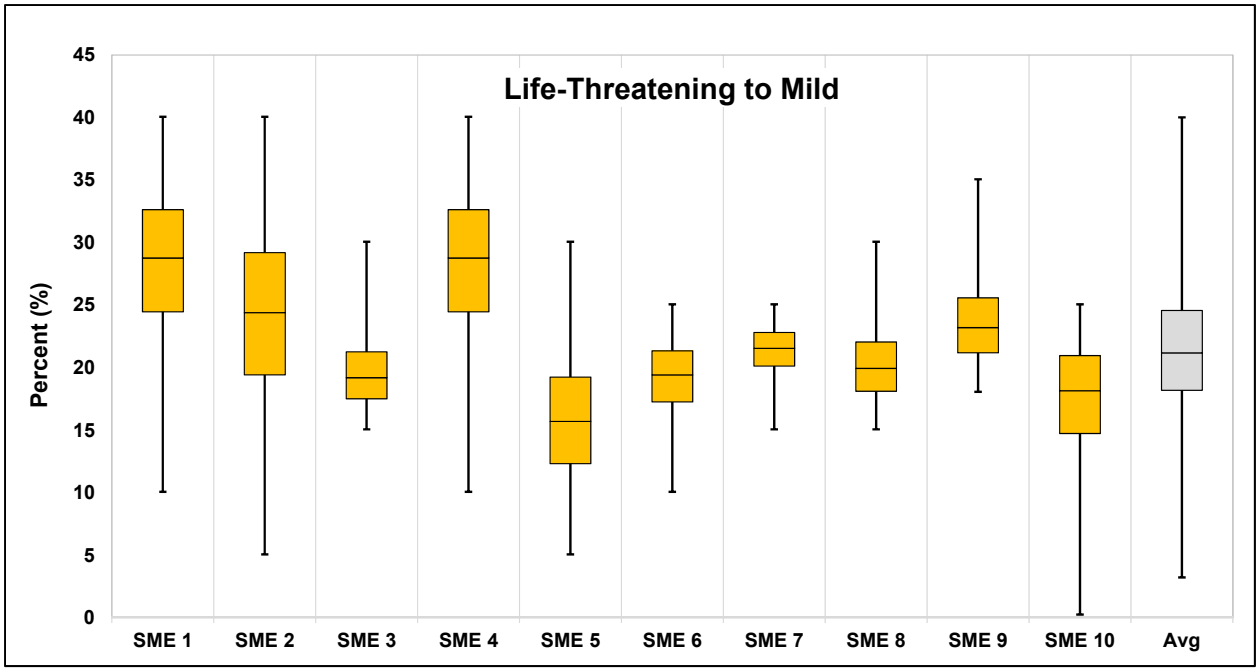

Figure B-4. Notional Representation of Individual SME Input and Resulting Combined Distribution

Individual SMEs will be permitted to update their individual contributions if desired. The goal of the review meeting is to reach a consensus on the combined distribution through an open discussion process among the Value SMEs. Feasibility study personnel will moderate/facilitate these discussions. The conclusion of this meeting will also conclude the involvement of the Value SMEs in the feasibility study process.

The final combined distributions can be applied to the chemical-specific dose-response data collected in Step 1 to produce long-term effect health curves. *Because the SME input is collected on a toxidrome (not a single chemical) basis, the resulting values can be applied to all chemicals within the toxidrome.* Conceptual illustrations of this step are provided on the Step 4 Preview tab of the "SME Input – Individual" Excel workbook. As discussed previously, existing dose-response estimates are not provided in this reference document or in SME materials. Only notional data are provided to prevent the feasibility study outputs (i.e., resulting long-term effect curves) from being used by SME participants to shape their likelihood estimates.

B-3 An Introduction to the Physiology of the Respiratory Tract and to Inhalation Toxicology

While the previous section maintained a more general description of the approach that is being implemented in this feasibility study, this section begins a more focused discussion on the toxidrome of interest – lower pulmonary (peripherally-acting) compounds. Any consideration of the acute and the long-term effects of inhalation exposures to chemicals acting predominantly on the respiratory tract presupposes a familiarity with certain basic concepts of respiratory physiology and toxicology. Thus, this section provides an overview of these concepts as preparation for participation in the feasibility study described in Section 2.

Chemicals with chiefly local effects on the respiratory tree are sometimes called "pulmonary irritants," although local irritation is characteristic of damage to the eyes, nose, mouth, throat, and large airways and may be completely absent even in fatal exposures to chemicals affecting the smaller airways.

It is common to refer to the respiratory tract as a single homogeneous organ system, but it is crucial to recognize that it in fact consists of two divisions, or compartments, to which inhaled chemicals may have differing affinities and which manifest distinctly separate responses to toxicants. In this document, these two divisions are referred to as the central and the peripheral compartments.

The oropharynx and the large airways exhibit similar although not identical responses to injury. For the purposes of this discussion, they can be grouped together as one compartment, the central compartment. Other names for this compartment (especially when considered distal to the glottis) are the upper airways, the large airways, the tracheobronchial region, and the conducting airways. It includes the trachea, the bronchi, and the bronchioles down to approximately the transition between the terminal bronchioles and the respiratory bronchioles. The other division of the respiratory tree is the peripheral compartment, also called the lower airways, the small airways, and the gas-exchange region. It comprises the respiratory bronchioles, the alveolar ducts, the alveolar sacs, and the alveoli.

The basic difference between the central and peripheral compartments is a physiological one: The conducting airways are the portion of the respiratory tree in which there is a back-and-forth bulk movement of a bolus of air with each breath. By the time one reaches about the 17th dichotomous bifurcation of the airways (at about the beginning of the respiratory bronchioles and thus the transition to the peripheral compartment), the total surface area of the airways has become so great that the velocity of air has decreased to essentially zero; thus, air flow in the peripheral compartment occurs primarily by diffusion, by Brownian motion.

One important implication of this physiological division is that one can to some degree predict where an inhaled vapor or gas will act in the respiratory tree (inhaled *particles* distribute in large measure according to aerodynamic size, but by the time that one gets down to the size of molecules in vapors or gases, size is no longer a discriminator), according to the following three rules:

1) Solubility: Compounds that exhibit high aqueous solubility tend to dissolve in the first fluid that they reach and act there. This rule is the typical textbook explanation of the fact that many water-soluble acids and bases affect chiefly the large airways, as well as the 'warning mucosal signs' occurring at the level of the eye, nose, and throat.
2) Reactivity: Compounds with high chemical reactivity tend to react with the first tissue that they encounter and therefore generally act in the central compartment, as well as extra-thoracic tissues. This rule is typically *not* in textbooks but explains the clinical effects of, say, sulfur mustard, which on the sole basis of its very low aqueous solubility would be predicted to be a peripherally-acting agent but which because of its extreme reactivity once it has dissolved shows predominantly central compartment effects at low to moderate doses.
3) Dose: Any target compartment selectivity observed at low to moderate doses tends to be lost at very high doses, at which both compartments are 'flooded' with the chemical.

Chemicals populate a spectrum from high to low aqueous solubility and chemical reactivity. Thus, even at low to moderate doses there may be overlap in the contribution of solubility and reactivity. Most acids, bases, and aldehydes (and sulfur mustard) are predominantly centrally-acting; most less water-soluble and more slowly reacting compounds such as carbon tetrachloride, perfluoroisobutylene, phosgene, oxides of nitrogen, and HC smoke (standard white military obscurant smoke) cause effects in the peripheral compartment. Chlorine and chloramines, which are intermediate in aqueous solubility and in chemical reactivity, tend to have approximately equal effects in both compartments even at low to moderate doses.

Another implication of, and rationale for, the division of the respiratory tract into two separate target systems is that their pathophysiologies are distinctly different. Centrally-acting chemicals cause denudation of respiratory epithelium, sometimes with tracheobronchial casts or pseudomembranes (both seen commonly with sulfur mustard), resulting in partial or total airway obstruction as well as local irritation that can lead in severe cases to irritative laryngospasm. Peripherally-acting compounds cause leakage of fluid first into alveolar septa and then into alveoli, with eventual filling of progressively larger airways; that is, they cause pulmonary edema, clinically recognizable as acute respiratory distress syndrome (ARDS).

The third implication is a clinical one and is particularly relevant to a symptom-based toxidromic approach. Partial airway obstruction converts smooth laminar flow to turbulent flow, and turbulence creates noise. Thus, *the clinical hallmark of damage to the central compartment is noise*: coughing, sneezing, inspiratory stridor, and wheezing. These effects, along with local irritation of the eyes and the oropharynx, constitute the central compartment toxidrome. Peripherally-acting agents begin damaging tissue soon after contact, but it takes time for fluid to build up to a degree that can cause symptoms. *The clinical hallmark of damage to the peripheral compartment is delayed-onset shortness of breath, or chest tightness*. This usually occurs after a latent period of several hours (because dose is usually inversely correlated with the duration of a latent period, shortness of breath beginning four hours or sooner after an exposure usually portends a grave outcome without therapy) and usually occurs well before the commonly looked-for signs or tests of dullness to percussion, radiographic changes (it usually takes an increase of six to eight times the normal amount of fluid in the lungs to show up as Kerley B lines on a chest radiograph), and blood-gas abnormalities. Thus, the clinical diagnosis of a patient exhibiting only symptoms but not the expected signs is easily missed by someone not familiar with the peripheral compartment toxidrome of delayed-onset shortness of breath, or chest tightness.

The aforementioned clinical hallmarks are critical to clinical diagnosis of an exposed patient and to a toxidromic approach to assessment and management. But any and all symptoms, signs, and tests can usefully be grouped according to compartment. The listing below identifies some of the clinical findings detailed in Section 4 of this document:

- *Ocular, nasal, and oropharyngeal irritation*: These are technically neither central nor peripheral (they are, rather, extrapulmonic) but are acute effects associated with centrally-acting agents or (transiently) high doses of peripherally-acting agents.
- *Drooling*: This effect is another extrapulmonic acute effect and associated primarily with agents that affect the central compartment.
- *Cough*: Acutely, cough is usually a classical central compartment (“upper pulmonary”) effect except when present transiently in a high-dose exposure to a

peripherally-acting agent or when associated with the production of the copious watery and sometimes frothy fluid characteristic of pulmonary edema. Chronic cough, with or without sputum production, is also referable to the central compartment.

- *Dyspnea*: This ambiguous term is best avoided altogether, although it is prevalent in the medical literature. To some, it means simply "difficulty in breathing," a very general term. To be more precise, "painful breathing" would usually be a central compartment effect, as would "inspiratory stridor". "Shortness of breath" and "chest tightness" would indicate peripheral compartment damage.
- *Wheezing*: This central compartment phenomenon involves partial obstruction of large airways, which leads to continuous coarse or whistling sounds. Obstruction high in the respiratory column, as in the larynx or trachea, can lead to a particularly high-pitched wheeze termed *stridor*.
- *Bronchospasm*: This condition of the large (conducting) airways indicates central compartment damage either from a centrally-acting toxicant or (transiently) from a high dose of a peripherally-acting agent. It can of course also indicate sensitization after a previous exposure under certain circumstances. This characteristic may be important in making a link between long-term effects such as the asthma-like bronchial hyperresponsiveness present in *reactive airways dysfunction syndrome (RADS)* (which may arise after a single high-level exposure in an individual with no pre-existing hyperreactivity) and similar entities (seen after repeated lower-level exposures). Note that bronchospasm is technically a process rather than a sign or symptom. A process can be a medical endpoint, but in many clinical reports it is inferred rather than directly observed.
- *Bronchitis and chemical pneumonia*: Bronchitis is both a process and a symptom: inflammation of the bronchi, usually manifested by coughing with sputum production. Bronchitis usually implies damage to the central compartment (most but not all bronchitis affects bronchi and bronchioles larger than the respiratory bronchioles), whereas pneumonia (or the more technical term pneumonitis) usually involves the peripheral compartment, although there can be overlap.
- *Reactive airways dysfunction syndrome (RADS)*: This central compartment process describes bronchial hyperresponsiveness arising after an acute exposure to a high dose of an inciting agent (often vapors or gases such as sulfur dioxide, acetic acid, chlorine, and ammonia) and leading to an asthma-like syndrome. It is now clear that related conditions can arise after acute or subchronic exposures to lower doses of agents.
- *Obstructive and restrictive pulmonary disease*: This term refers to two different kinds of long-term effects. Each is defined and characterized by findings on pulmonary function testing. Obstructive pulmonary disease refers to poor airflow primarily (except for emphysema) in the large airways (the central compartment) and often involves shortness of breath and chronic bronchitis (chronic cough with

the production of sputum). *Chronic obstructive pulmonary disease (COPD)* is a chronic airflow limitation that is not fully reversible. Its two major forms are *chronic bronchitis* (characterized by cough) and *emphysema* (in which there is an abnormal increase in the size of air spaces from tissue destruction). Restrictive pulmonary disease is characterized by a decrease in forced vital capacity on pulmonary function testing and may be extrapulmonic (extrinsic) in origin. Intrinsic causes include some conditions (such as hypersensitivity pneumonitis and ARDS) partially referable to the central compartment but also, and more seriously, pulmonary fibrosis affecting chiefly the peripheral compartment.

- *Bronchiolitis*: Bronchiolitis denotes an inflammatory process involving the bronchioles. *Constrictive bronchiolitis* indicates concentric narrowing of bronchioles by fibroconnective tissue in the bronchiolar wall; *proliferative bronchiolitis* refers to partial or total occlusion of the bronchiolar lumen by polyps of connective tissue. *Bronchiolitis obliterans (BO)* is an irreversible and frequently obstructive bronchiolar process described as a long-term effect after the inhalation of a variety of chemicals. BO has been used to refer to both constrictive bronchiolitis and also proliferative bronchiolitis, and the histological terms are more precise; however, BO is a very common term in the literature. *Bronchiolitis obliterans with organizing pneumonia (BOOP)* is a non-infectious process pathologically distinct from BO but also seen as a long-term effect after inhalation of certain chemicals. In BOOP, granulation tissue is present not only in the bronchiolar lumina but also in alveoli. Although the fibrous tissue obstructs alveoli and alveolar ducts, pulmonary function testing often shows a restrictive rather than an obstructive pattern. Note, however, that both BO and BOOP can co-exist with obstruction, restriction, or both. Many articles in the literature describe long-term effects less in terms of signs and symptoms and more in terms of the results of pulmonary function testing. Diagnosis can often be confirmed by high-resolution chest CT, although definitive diagnosis and assessment of degree of inflammatory activity requires biopsy and histologic assessment
- *Atelectasis*: Atelectasis refers not to a sign or a symptom but rather to collapse of part or all of a lung mainly because of collapse of alveoli. As such, it is primarily a condition of the peripheral compartment. It may be asymptomatic or associated with nonproductive cough, difficulty breathing, or chest pain.
- *Pulmonary edema*: This is a pathological diagnosis made at biopsy or autopsy or inferred radiologically. It is neither a sign nor a symptom but a process, the defining pathology of damage to the peripheral compartment. The clinical correlate is *acute respiratory distress syndrome (ARDS)*, which is defined on the basis of clinical appearance, radiographic abnormalities (bilateral infiltrates sparing the costophrenic angles), varying degrees of depression of the PaO_2/FiO_2 ratio, and a pulmonary arterial wedge pressure <18 mm Hg.

It is easier to grasp the acute and long-term effects from acute inhalational exposures to the many chemicals that have predominantly local effects on the respiratory tract if the following concepts are kept in mind:

- Signs, symptoms, and test findings, both acutely and long after exposure, are easier to assess if they are grouped by compartment when possible.
- The existence of a central compartment toxidrome (resulting in "noisy breathing" as described above) and a peripheral compartment toxidrome (delayed-onset shortness of breath, or chest tightness) can help in the clinical diagnosis of acute damage to one or both compartments in the respiratory tract.
- The presence of irritation and breathing noise acutely suggests damage to the central compartment. But these acute effects, especially if they are transient, may also result from high-level exposure to a peripherally-acting toxicant.
- In most cases, the determination of which compartment or compartments are damaged is clinically more important than the identification of the specific chemical to which an individual has been exposed.
- Signs and symptoms are often nonspecific. For example, difficulty breathing can reflect RADS, asthma, COPD, or extrapulmonic cardiac disease. It would likely be mechanistically easier to link underlying pathology to specific long-term effects than to try to link symptoms and signs. However, symptoms and signs comprise the majority of acute effects available for review in the literature described in Section 5.
- It is assumed that similar acute effects (injuries, symptoms, signs, and tests) caused by different chemicals in the same toxidrome (or subgroup) have the same probability of causing long-term health effects. However, although the identity of the specific chemical or chemical involved is less important in the initial clinical management than is a determination of the site or sites of the toxic insult, it has not yet been proven that acute effects as predictors of long-term effects are not chemical-specific. For example, exposure to certain chemicals such as nitrogen oxides and HC smoke (standard white military obscurant smoke) seems to confer a higher risk of bronchiolitis obliterans than does exposure to certain other chemicals.
- Acute effects comprise a subset of possible predictors of long-term effects. Other predictors may include, for example, whether an individual reported to a clinic or other medical facility for evaluation and treatment. Some of these "stand-in" measurements of presumed severity may prove useful when constructing guidelines for post-event assessment.

B-4 Focusing the Physiology and Toxicology Discussion onto the Lower Pulmonary (Peripherally-Acting) Toxidrome

As described in Section 3, inhaled chemicals can be broadly differentiated into those that have early (usually within seconds to minutes of exposure) mucous membrane and

upper (central) airway irritation, and those that lack early irritant warning properties and have a more delayed (hours-days) presentation with a predominance of lower (peripheral) airway-related symptoms. While water solubility is a key physical property differentiating these compounds, actual experience with large scale chemical releases or high concentration–time exposures in a closed setting has shown that presentations can be less dichotomous. Nonetheless, these clinical features are useful in differentiating likely agents across the spectrum of exposure, particularly in those patients presenting with moderate symptoms*. Our premise is that a population of exposed individuals with acute symptoms will have a quantifiable potential for progression to chronic health issues in the aftermath of the acute exposure.*

B-4.1 Literature Searches

The literature summary provided in Section 5 provides some evidence for aspects of the acute to long-term progression in reference to certain chemicals. Available literature was reviewed with an attempt to select those articles that provide both an assessment of acute symptoms and chronic health effects, focusing on pulmonary. A set of criteria for possible chemicals to include in this schema is listed below:

- Animal or human case studies describing long-term pulmonary health effects after acute exposure
- Existing literature regarding occupational exposure events with long-term follow-up (months-years)
- Previous mass chemical release with long-term follow-up (months-years)
- Non-carcinogenic long-term health effect studies of chemically-related compounds having similar acute toxidrome presentation

For the purposes of this feasibility study, the chemicals listed in **Table B-2** are considered “lower (peripheral) pulmonary chemicals” with the intent of investigating how well the existing literature and cumulative experience and expertise of the SMEs support the proposed criteria for this toxidrome class. Note that most of these chemicals are included in the “lower pulmonary toxidrome” as part of the CSAC Chemical Terrorism Risk Assessment (CTRA). Because of the toxidrome-based nature of the approach, the intent is for these chemicals to serve as representative of the lower pulmonary (peripherally-acting) toxidrome. Thus, the approach and resulting values would be applicable to other lower pulmonary (peripherally-acting) compounds not specifically listed in the table.

Table B-2. List of Lower Pulmonary (Peripherally-Acting) Chemicals Investigated in this Feasibility Study

Chemicals		
Bromine	Ethyl isocyanate	Perchloromethyl mercaptan
Chlorine	Hexachlorocyclopentadiene	Perfluoroisobutene
Chlorine dioxide	Hydrogen selenide	Phosgene
Chloropicrin	Methyl isocyanate	Thiophenol
Dimethyl sulfate	Oxides of nitrogen	HC Smoke (hexachloroethane)

The need for this feasibility study is predicated on the lack of existing data and studies describing the development of long-term health effects following acute exposures. Thus, the literature search strategy included multiple routes in an attempt to identify relevant references. An initial search was completed using only chemical names and more general terms: inhalation, toxicology, long-term, long-term health effect, chronic, and chronic health effect. This initial search covered several relevant science/toxicology databases accessed through Dialog and STN search services. Battelle identified potentially relevant titles/abstracts from this search for subsequent review by the Core SMEs. The Core SMEs developed a more focused strategy that included more specific long-term effects[8]. These follow-up searches were conducted through the following searching services:

- PubMed (http://www.ncbi.nlm.nih.gov/pubmed)
- Web of Science (https://webofknowledge.com/)
- TOXLINE (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm)
- SUMSearch2 (http://sumsearch.org/)

Potentially relevant titles/abstracts were identified from these searches by the Core SMEs. In addition to the online search tools, a review of toxicological overview documents was completed. These documents consisted of previously completed reviews that summarized literature relevant to a given compound. The documents reviewed by Core SMEs for potentially relevant articles/reports included the following:

[8] Specific long-term effects included in these searches included organizing pneumonia, fibrosis, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, asthma, tracheal stenosis, and restrictive lung disease. The terms “Graniteville” and “Bhopal” were also used to identify literature from those mass releases. Specific search logic can be provided upon request.

- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles (http://www.atsdr.cdc.gov/toxprofiles/index.asp) – chlorine, dimethyl sulfate, hexachlorocyclopentadiene, oxides of nitrogen, and phosgene.
- International Programme on Chemical Safety (IPCS) Environmental Health Criteria (EHC) Monographs (http://www.inchem.org/pages/ehc.html) – chlorine, dimethyl sulfate, hexachlorocyclopentadiene, oxides of nitrogen, and phosgene.
- IPCS Poisons Information Monographs (PIMs) (http://www.inchem.org/pages/pims.html) – bromine, chlorine, and oxides of nitrogen.

Finally, relevant chlorine literature from a previously mentioned task aimed at development of an analytical approach to this subject was also leveraged. All potentially relevant articles/reports were reviewed in their entirety by the Core SMEs (note that the literature was split among the SMEs). The references listed in the articles/reports were also obtained and reviewed where appropriate, as a number of clinically-relevant articles not identified in the search process were identified. The Core SMEs reviewed these second-generation articles and their reference lists as well, selecting additional articles for full-text review where appropriate. It is acknowledged that the lack of a reproducible search strategy raises the possibility of having missed relevant articles. However, the inability to find a sufficient literature through a more reproducible route is likely a reflection of the lack of available and relevant information on this subject. Furthermore, the consistency and recurrent notations of the selected articles/reports should provide an adequate basis for assessing the English literature.

Appendix C lists all of the articles reviewed; the findings from a sample of relevant articles (covering both experimental and human exposures with assessment of chronic pulmonary health impact) were summarized by the Core SMEs to facilitate review by the Value SMEs. As might be expected, the literature is limited in terms of pre-existing objective data of pulmonary function, adequacy of dose/time estimates for the actual exposure, consideration of confounders, and variability in the nature, duration, and specific endpoints of follow-up. Based on both available data for chlorine and phosgene, and accumulated clinical experience, it is posited that mild acute symptoms of rapidly resolving cough, dyspnea, and wheezing are less likely to progress to chronic fibrotic lung disease; while an acute exposure resulting in severe hypoxia and requiring prolonged invasive ventilatory support is more likely to result in chronic reactive and restrictive pulmonary disease.

B-4.2 Identification of Specific Health Effects

The tables below provides a “clinical thumbnail” of the various symptom categories, both acute exposure-related and long-term pulmonary effects (**Table B-3** and **Table B-4**, respectively). Note that these descriptions include a combination of symptoms,

clinical findings, test results, and therapy-related decisions and assessments. Note that the content of these tables has been previously presented in the mapping diagram in Section 2.2. As described in that section, Value SMEs are asked to make a quantitative estimate of likelihood for each connection (blue arrow) in the mapping figure (**Figure B-1**). A connection exists between from acute grouping to each long-term grouping. To reiterate a previous point, it is posited that mild acute symptoms of rapidly resolving cough, dyspnea, and wheezing are less likely to progress to chronic fibrotic lung disease; while an acute exposure resulting in severe hypoxia and requiring prolonged invasive ventilatory support is more likely to result in chronic reactive and restrictive pulmonary disease.

Table B-3. Acute Exposure Symptoms and Findings

Effect Category	Symptoms and Findings
Mild	• Cough that resolves with removal from exposure, although may recur with deep breathing or heavy exertion in first few hours • Dyspnea and/or wheezing that resolves with removal from exposure, without inhaled beta-agonist treatments • Laboratory and imaging studies are not indicated • Acute care evaluation is not necessary
Moderate	• Cough diminishing with rest within the day • Dyspnea and/or wheezing that resolve with one or two inhaled beta-agonist treatments • Laboratory and imaging studies, if obtained, are non-specific (e.g., mild hyperglycemia, hypokalemia, and leukocytosis consistent with “stress effect” and increased interstitial markings or small areas of atelectasis on CX-Ray) • Patients are likely to be discharged from the Emergency Department or Observation status within 24 hours
Severe	• Persistent or easily triggered cough, dyspnea, and wheezing that require continuous humidified oxygen delivery and multiple nebulized beta-agonist treatments. Intravenous corticosteroids are indicated • Room air oxygen saturation is decreased • Chest X-Ray may demonstrate increased interstitial markings or minor consolidation • Hospitalization is indicated
Life-Threatening	• Severe cough, dyspnea, and wheezing are present despite therapy as above • Decreased oxygen saturation is present, despite supplemental oxygenation

Effect Category	Symptoms and Findings
	• Decreased mental status is likely • Hypercarbia and metabolic acidosis are expected • Positive-pressure ventilatory support is required • Airway management is complicated by high peak airway pressures and decreased venous return, leading to peripheral edema and hypotension • Chest X-Ray (or Chest CT) demonstrates pulmonary edema. Atelectasis, cystic changes, and areas of consolidation may occur

Table B-4. Long-Term Symptoms and Findings

Effect Category	Symptoms and Findings
Mild	• Decreased exercise tolerance and conditioning may be described • Physical exam is likely normal • Mild obstructive findings (from baseline or in comparison to population norms) are present on formal pulmonary function testing (PFT)
Moderate	• Dyspnea on exertion, with or without wheezing is present • If wheezing is present, treatment with inhaled beta-agonists, or chronically with cromolyn sodium and/or inhaled corticosteroids is effective for symptom relief and improves obstructive pulmonary function test (PFT) results
Severe	• Debilitating shortness of breath with little exertion • May require use of ambulatory, supplemental oxygen to maintain oxygen saturation >90% • Imaging studies show cystic changes and fibrosis • PFTs demonstrate both obstructive and restrictive findings; either may predominate • PFT obstructive findings do not significantly reverse with inhaled beta-agonist

B-4.3 Additional Notes for Value SMEs

As a starting point for this effort, it is suggested that SMEs tasked with providing likelihood estimates list a pre-literature review estimate in **Table B-5** for progression from and to the following health effect categories, based on their own judgment and

using the descriptors above in **Table B-3** and **Table B-4** (as well as the mapping diagram in Section 2.2). This estimate can function as a starting point for the exercise, recognizing that everyone comes with his or her own experience and biases. Submission of these estimates as input to this feasibility study is optional (and may be useful as an internal check), and SMEs are cautioned against anchoring their final responses to these initial values.

Table B-5. SME a priori Assessment of Likelihood of Progression from Acute to Long-Term Health Effects

Acute Exposure Symptoms	=>	Long-Term Pulmonary Effect	Estimated Percent Likelihood of Progression (%)
Mild	=>	Mild	
Mild	=>	Moderate	
Mild	=>	Severe	
Moderate	=>	Mild	
Moderate	=>	Moderate	
Moderate	=>	Severe	
Severe	=>	Mild	
Severe	=>	Moderate	
Severe	=>	Severe	
Life-Threatening	=>	Mild	
Life-Threatening	=>	Moderate	
Life-Threatening	=>	Severe	

It must also be reiterated that this feasibility study represents the first implementation of an approach or model to estimate the long-term effects of acute exposures. As such, certain challenges can be expected. One such challenge encountered by the Core SMEs is that potential predictors of long-term effects may not easily map to the modeled acute effects. For example, decreases in forced expiratory volume in one second (FEV_1) or the extent and time course of treatment received may show potential in this regard. However, these factors are not easily mapped to the acute categories built into the model at this time. Thus, SMEs are asked to classify such predictors into the existing categories according to their best expert judgment.

One task likely to occur in the aftermath of a significant chemical event is ascertainment of causation in individuals presenting with pulmonary complaints at a later time following a documented or presumed chemical exposure. When reviewing the papers in Section B-5, consider the steps that would be necessary in an attempt to ascertain causation. For example, consideration of previous chronic medical conditions in terms of

susceptibility or diagnostic confounding (e.g., pre-existing asthma, chronic obstructive pulmonary disease, ischemic heart disease or cardiomyopathy), the potential for superimposed physiologic stress response as a confounder for acute symptom expression, and the subjective nature of some symptoms would all be potentially important in both forming a differential diagnosis and ascertaining medical endpoints.

Finally, when considering the task of determining the likelihood of a possible chronic outcome from a given acute presentation, it will be helpful for SMEs to rely on their own clinical experience (if/when applicable) and the culled literature estimates of a likelihood, based on the symptom/signs/testing described in the boxes in the mapping diagram shown in **Figure B-1**. This likelihood number would be a "gestalt" for an imaginary population of people who presented acutely with one of the symptom complexes on the left. Recognizing that there are individuals in that population who have vastly different risks for a chronic outcome (underlying chronic cardiopulmonary disease, smoking status, immunodeficiency states, access to follow-up care, finances, social support, etc.), SMEs should again use their own best estimate of the likelihood of all of these conditions – within a population – to derive the min and max estimates of a given likelihood. As an example, if you think the likelihood of a given progression is 50% (the outcome is as likely as it is unlikely), and there are 10% of individuals in a population that are at very high risk (perhaps all of them will have the selected chronic outcome), then the max for that particular progression might be somewhere between 50-60% in order to completely include that high-risk population. When these population parameters are applied to individual cases in the future, such an assessment would hopefully take all of these possible risk factors into consideration.

B-5 Long-Term Health Effects in the Literature

While the literature associated with long-term health effects resulting from acute exposures to lower pulmonary chemicals is limited, this section provides a summary of the most relevant articles/reports that were reviewed. This literature provides some insight on evidence of long-term effects from acute exposures, and is envisioned as helpful in allowing Value SMEs to make the necessary estimates for this feasibility study. As mentioned in the previous section, the literature includes mentions of putative predictors (such as odor, simple reporting of exposure or seeking care at a medical facility, the presence of obstruction rather than restriction as a possible marker of severity of exposure, and decreases of 10 to 15% in FEV_1) that may not fit easily into the mild, moderate, severe, or life-threatening categories shown in the mapping illustration in **Figure B-1**. Value SMEs are asked to use information from the literature as springboards to their thinking and to make their own individual decisions regarding the most appropriate assignments in the acute-findings columns for these potential predictors of long-term outcomes. For example, some but perhaps not all value SMEs may consider a 10-to-15% reduction in FEV_1 to be a moderate effect. Not all effects will be relevant to this project; for example, extrapulmonic effects such as post-traumatic

stress disorder (PTSD), although important, are beyond the scope of the model of this feasibility study. Please note that Tables or Figures referenced within the article summaries can be found within the specific articles, not within this report. All articles can be provided to Value SMEs upon request.

B-5.1 Human Studies

This section summarizes a series of relevant human studies. Again, this literature represents a subset of the available literature, with these studies being selected by Core SMEs as the best balance between providing relevant information and mitigating the burden on the Value SMEs. The summaries are presented chronologically, with the exception of a group of four methyl isocyanate (MIC)-specific references at the end of the list. Appendix A details abstracts for the studies listed here. Appendix C lists additional articles that were reviewed but not included in Appendix A.

Berghoff RS (1919) The more common gases; their effect on the respiratory tract: Observation on two thousand cases.

This article describes a follow-up assessment of approximately 2,000 World War I soldiers' exposures to gas attacks. Chlorine accounted for about one-fourth of the exposures, while mustard accounted for more than one-third; additional data is provided for phosgene, chloropicrin, and mixed exposures. The author reports clinical observations of long-term health complaints or findings at 3-4 months follow-up. Focusing on the 520 chlorine cases, the author notes that ~50% appear normal by "thorough exam" while having some complaints of cough and wonders about the difficulty of sorting through subjective complaints. Among a group with generally higher acute exposure (cloud/drift attack) requiring 4 months in hospital, 68% had cough while 8% had physical findings. Among a group with somewhat less exposure (high explosive gas shells) requiring 3 months in hospital, 25% had cough with 3% demonstrating physical findings. These exposures did not involve a lot of high tech testing, and current treatment would be very different (relied on oxygen by tent, sedatives such as barbiturates, and stimulants/venesection); however, this reference is a good example of a large scale exposure and outcomes, as well as historical relevance.

Kowitz TA et al. (1967) Effects of chlorine gas upon respiratory function.

This study investigated clinical observations and pulmonary function testing carried out over a 3-year period on a group of longshoremen exposed to chlorine gas. Acute findings in the 11 subjects were respiratory distress (11), rales (8), wheezes or rhonchi or both (6), hemoptysis (4), and edema or infiltrate on chest radiographs (4). At 4 to 6 weeks after exposure, symptoms included easy fatigability, dizziness on exertion, and vague paresthesia of the face and arms, all of which were judged compatible with psychosomatic illness. Lung volumes were reduced, arterial oxygen tension was

reduced at rest and fell significantly on mild exercise, and hyperventilation was present at rest and on exercise. Six months later, mean total lung capacity was still reduced, mean vital capacity was further reduced, and mean airway resistance had significantly increased. Arterial hypoxemia was present at rest and remained the same on exercise, and mean hematocrit had significantly increased. Subsequently, long volumes continued to return toward normal, although they were still low 2 to 3 years after the incident; and airway resistance remained elevated. Hyperventilation was still apparent 14 months after the incident. Arterial hypoxemia at rest appeared to secondary to abnormal ventilation-perfusion ratios and mild obstructive airway disease. Lung volumes continued to be decreased, and diffusing capacity and an increase elastic work of breathing suggested patchy atelectasis and a restrictive process associated with nodular scarring. There was a trend to higher airway resistance and lower total lung capacity in subjects who complained of dyspnea. The review-and-comment section also reports that in serial studies for up to 65 months of seven gold miners who had developed pulmonary edema from acute exposure to oxides of nitrogen, those who complained of residual dypsnea had a reduced maximal breathing capacity and an elevated expiratory total pulmonary resistance compatible with the residual effects of bronchiolitis fibrosa obliterans.

Harkonen H et al. (1983) Long-term effects of exposure to sulfur dioxide

This article examined the development of bronchial hyperresponsiveness (before the term RADS had been coined) as long-term sequelae of acute exposure to sulfur dioxide generated in a pyrite dust explosion. Although all seven individuals examined had evidence of bronchial hyperreactivity, the pattern of pulmonary impairment was obstructive in six cases and restrictive in one. Although the presumption that the initial exposure was less in the individual showing a restrictive pattern compared to those with obstructive patterns, this observation may nevertheless have relevance for Value SMEs.

Courteau J-P et al. (1994) Survey of construction workers repeatedly exposed to chlorine over a 3 to 6 month period in a pulpmill: I. Exposure and symptomatology

This study investigated 257 pulpmill workers reporting an average of 24 acute exposures to chlorine and chlorine derivatives over a 3- to 6-month period. Industrial-hygiene air-monitoring data were not useful in linking specific events reported by workers to environmental conditions in the bleach plant. Irritation of the throat (78%) and eyes (77%), cough (67%), and headache (63%) were the most frequently reported acute symptoms. Over 60% of the workers described a characteristic flu-like syndrome that lasted for an average of 11 to 20 days and was exacerbated by new bouts of exposure. Shortness of breath was reported by 54% of the participants and was not associated with agent, smoking state, or history of asthma or chronic bronchitis. Throat irritation and cough persisted for mean intervals of eight and 11 days, respectively, and 71% of subjects were considered to be at moderate to high risk of having persisting

respiratory symptoms. Workers were classified as high-risk for chronic lung disease if they had persisting shortness of breath or abnormal lung sounds and were enrolled in a prospective study, the results of that study are reported by Bherer L, et al. (q.v.). Subjects who consulted first-aid stations after a gassing incident were more likely to have persisting dyspnea, but several of those who had not reported ended up in the moderate- to high-risk groups. The authors concluded that "[t]here are no individual risk factors, nor are there are characteristics that can accurately predict which workers will develop serious symptoms after repeated exposure to chlorinated gases."

Bherer L et al. (1994) Survey of construction workers repeatedly exposed to chlorine over a 3 to 6 month period in a pulpmill: II. Follow up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended.

This prospective study was a follow-up to the study by Courteau JP, et al. (q.v) of 257 pulpmill workers repeatedly acutely exposed to chlorine gas. This follow-up study involved medical follow up 18 to 24 months after the initial investigation and followed 71 subjects classified as at either moderate risk [those with a) shortness of breath after the end of exposure but no longer present 1 month later, b) significant other medical conditions, or c) age 50 years or older] or high risk [those with a) persistent shortness of breath 1 month after exposure or b) abnormal breath sounds]. A questionnaire suggested a persistence of respiratory symptoms in 58 workers (72%), and 52 of these patients (the other six were unavailable) underwent spirometry and methacholine-challenge testing. A previous history of asthma was found more often among subjects with airway obstruction or bronchial hyperresponsiveness, and these subjects also tended to require more inhaled anti-inflammatory preparations. Those with a lower PC20 had significantly lower baseline FEV_1, and about half of these subjects had an FEV_1 <80% of predicted. (Only one subject with normal bronchial responsiveness had an FEV_1 <80% of predicted.) "The number of visits to a hospital emergency room was a significant predictor of the likelihood of being left with persistent bronchial hyperresponsiveness," and the authors concluded that "[t]he severity, therefore, of one or other of several episodes may be a more significant determinant of the likelihood of developing permanent functional sequelae than the number of episodes."

Gautrin D et al. (1995) Cross-sectional assessment of workers with repeated exposure to chlorine over a 3 year period.

This is a cross-sectional study that was the preliminary to the 1999 longitudinal assessment of the same workers by Gautrin D, et al. (q.v.) In this cross-sectional study, exposed workers filled out a questionnaire about symptoms dating back to the last three years and also underwent pulmonary function testing. The authors state the following: "Two conclusions can be drawn from our cross-sectional study, which explored respiratory symptoms, pulmonary function tests and airway responsiveness in workers

who experienced accidental inhalation of chlorine over a 3 year period. Firstly, persistent symptoms were not associated with exposure. Secondly, lung function tests and airway responsiveness are slightly but significantly different in workers who experienced immediate symptoms following acute chlorine exposure. In addition, a relationship was found between reported current respiratory symptoms and lower pulmonary function test values and a lower threshold in airway responsiveness."

Henneberger PK et al. (1996) Decrements in spirometry values associated with chlorine gassing events and pulp mill work.

Pulp and papermill workers previously enrolled in a prospective cohort study between 1961 and 1967 were reexamined approximately every 4 years. The current study was a cross-sectional reappraisal, conducted in 1992, of a subset of the original cohort. Approximately one third (105) of the 300 subjects reported having had an acute exposure to chlorine or chlorine dioxide, and 75% of the 55 subjects with at least 10 years of pulp-mill maintenance work reported having been gassed. Forty-seven subjects (45% of the 105) reported having been exposed once or twice, 37 (35%) reported three or more acute exposures, and 12 (20%) reported ten or more exposures. Seventeen (16%) had been hospitalized for a least one day and 43 (41%) had sought other medical care. The mean values for FEV_1/FVC and MMEF were somewhat less for those who had been gassed, but these contrasts were not statistically significant. An obstructive pattern on spirometry was seen for 8.6% of those reporting exposures vs. 2.6% of those reporting no exposures. The prevalence of obstruction increased with the amount of time since the last exposure. An incremental decline in FEV_1 associated with a history of acute exposures was limited to current smokers. The need for medical care after an acute exposure was predictive of more obstruction in those with 26 pack-years or less of cigarette smoking but not in heavier smokers. There was also a decrement in MMEF associated with each year of pulpmill work and suggestive of an additional effect of chronic low-level exposure.

Alberts WM and do Pico GA (1996) Reactive airways dysfunction syndrome.

This article is a good introduction to irritant-induced asthma and its subset, reactive airways dysfunction syndrome (RADS), which refers to new-onset asthma-like bronchial hyperreactivity (with a positive methacholine-challenge test) occurring within 24 hours from a single high-level acute inhalational exposure to a toxic substance and persisting for at least 3 months. RADS is considered to be the persistent and severe end of the spectrum of irritant responses in the airways. Because the induced bronchial hyperresponsiveness is nonspecific, subsequent bronchospastic responses can be elicited from many and varied environmental stimuli not limited to the original precipitating chemical. A variety of substances (many examples are given in the article) can precipitate the original episode. The article quotes the findings from Kern (full-text article was not available) that none of 7 individuals with low-level exposure to a spill of

glacial acetic acid developed RADS but that one of 30 with moderate-level exposure and three of 14 high-level exposure developed RADS, suggesting a dose-response effect. The article also refers to a study by Blanc et al. in which premorbid lung conditions and history of cigarette smoking but not the irritant potential of the exposure appeared to be risk factors for persistent health complaints. Suggested risk factors mentioned from a 1994 article (the full text of which is not yet available to this reviewer) by Demeter SL, et al. were age, sex, presenting PaO_2, premorbid smoking history, atopic status, and the concentration, toxicity, and duration of exposure to the irritant. This article also describes the related conditions "irritant-induced asthma" and "low-level RADS," which arise from repeated lower-level but not trivial acute exposures.

Gautrin D et al. (1999) Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine.

This 2-year-long longitudinal study was a follow up to the 1995 cross-sectional study by Gautrin D, et al. (q.v.). Its findings (which included a predictive value of the number of acute exposures and of accidents reported to the first-aid unit) suggested "(1) an effect on airway function related to the estimated number of puffs [acute exposures] with mild symptoms and gassing incidents, mostly among smokers; (2) a detectable increase in airway responsiveness associated with gassing incidents."

Leroyer C et al. (1999) Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine.

This was a cross-sectional study involving a questionnaire and pulmonary function testing to address the relationship of acute exposures to chlorine during a 2-year period to the development of chronic rhinitis and changes in lower-airways symptoms, airway function, and bronchial hyperresponsiveness. The proportion of workers reporting chronic rhinitis was 46.9% in 1992 and 42.2% in 1994. Chronic rhinitis reported in 1994 was significantly associated with acute exposure to chlorine (self reports, p=0.02; first aid reports, p=0.001). In a multivariate logistic regression analysis the presence of reported accidents at the first aid unit (one accident, odds ratio (OR) 3.1, 95% confidence interval (95% CI) 1.3 to 7.5; two or more accidents, OR 6.2, 1.1 to 35.8) and of personal atopy (OR 5.5, 2.2 to 10.8) were significant predictors of chronic rhinitis in 1994. Chronic lower airways symptoms were more frequent in 1994 among workers reporting chronic rhinitis on both assessments than in others (p=0.03) and changes in bronchial responsiveness were more pronounced in those with persistent rhinitis (p=0.09). The authors wrote, "Two conclusions can be drawn from this 2-year follow up study of 211 workers at risk for accidental acute exposure to chlorine. Firstly, chronic symptoms of rhinitis were often reported and significantly associated with accidental exposure to chlorine, also assessed by means of a questionnaire or through first aid reports. Secondly, chronic lower airways symptoms more often occurred in 1994 among those workers reporting the presence of chronic rhinitis on both assessments.

Also, workers with persistent rhinitis showed a tendency to a greater increase in bronchial hyperresponsiveness, as expressed by the slope of the dose-response curve."

Henneberger PK et al. (2005) The incidence of respiratory symptoms and diseases among pulp mill workers with peak exposures to ozone and other irritant gases.

This study used survey data from pulpmill workers with acute exposures to ozone, chlorine dioxide, or sulfur dioxide to calculate the incidence (rather than the prevalence) of three self-reported long-term health effects: a) physician-diagnosed asthma, b) attacks of wheezing, and c) chronic bronchitis (i.e., chronic cough with phlegm). Based on proportional hazards regression (controlling for gender, age, cigarette smoking, atopy, and peak irritant exposures that occurred before follow-up), workers who reported both ozone and ClO_2/SO_2 peak exposures had elevated hazard ratios (HRs) for all three outcomes. Those who reported only ozone peak exposures had elevated HRs of 6.5 (95% confidence interval [CI], 1.2 to 36.3) for asthma and 3.3 (95% CI, 1.1 to 10.2) for attacks of wheeze but no increase in risk for chronic bronchitis. Workers with only ClO_2/SO_2 peak exposures had elevated HRs for attacks of wheeze (HR, 7.5; 95% CI, 1.9 to 29.3) and chronic bronchitis (HR, 22.9; 95% CI, 4.5 to 118.2) but not for asthma. The reporting of acute exposures is itself an independent predictor of long-term effects in these cases.

Ghanei M et al (2008) An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients.

In this study, 15 patients with chronic respiratory disease from acute exposure to sulfur mustard (SM) were divided into those with severe acute exposure (6 cases) and mild exposure (9 cases). All had surgical (open or thoracoscopic) lung biopsy, pulmonary function tests (PFTs), and chest high-resolution computed tomography scan (HRCT). All patients had dyspnea and cough as the two main complaints. Most patients presented with sputum production (66%) and hemoptysis (53%), and "hemoptysis alone or in combination with air trapping in a non-smoker may be more common in patients with bronchiolitis than previously appreciated and in SM-exposed individuals might be a clue to SM-induced airway disease." Thirteen patients had normal PFTs, while one had obstruction and one had mild restriction. Six patients (66.6%) in the mild-exposure group and three (50%) with severe exposure showed greater than 25% air trapping on chest HRCT. Among the mild group, three had features of constrictive bronchiolitis and another had features (bronchiectasis and mucus stasis) suggestive of this condition. The next most common finding was mild-to-moderate chronic cellular bronchiolitis, seen in three patients. Two (33.3%) of those with severe exposure showed constrictive bronchiolitis, and one exhibited features suggestive of constrictive bronchiolitis. "The fact that there were no differences between the low- and high-dose groups suggests that effects of SM are not solely dependent on the severity of exposure."

Shakeri MS et al. (2008) Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review.

In this systematic review, the most common agents associated with RADS were chlorine (9 patients), toluene diisocyanate (TDI, 6 patients), oxides of nitrogen (5), acetic acid (4), sulfur dioxide (4), and paint (4). The most common initial signs and symptoms were dyspnea (71%), cough (65%), wheezing (43%), chest tightness (43%), upper respiratory irritation (29%), eye irritation (25%), mucus production (16%), and cyanosis (6%). Although this is cross-sectional data, it is one of the few articles that attempts to quantify initial signs and symptoms in patients who develop a specific long-term effect (i.e., bronchiolitis obliterans).

Kreiss K (2013) Occupational causes of constrictive bronchiolitis.

This is an excellent review article on obstructive bronchiolitis and is one of the rare articles to address predictions of risk even in a general way. It summarizes results of a 2010 study by Chaisson NK, Kreiss K, et al. that showed that longitudinal limits of decline in FEV_1 were superior to relative percentage decline among flavoring-exposed workers and refers to the American College of Occupational and Environment Medicine (ACOEM) guidance statement that recommends medical referral for workers with declines of 10-15% in FEV_1, after allowing for expected loss from aging. There is also a section that suggests that exposure to higher doses of flavoring was associated with an excessive decline in FEV_1 over a 1-year period and 9.2-fold risk of airway obstruction.

Meza F et al. (2013) Evaluation of health effects of a chlorine gas release in a poultry processing plant – Arkansas.

A NIOSH Health Hazard Evaluation examined a June 2011 chlorine release resulting in 195 individuals who sought medical care, 152 who were hospitalized, and five who were admitted to intensive-care units immediately after the incident. Questionnaires were administered during a site visit in June 2011, and 4 months later a second site visit was conducted to evaluate participants for asthma symptoms and for PTSD. On a third site visit, in January 2012, spirometry and methacholine-challenge tests were administered to participants who reported asthma symptoms on the second site visit but who had had no asthma symptoms prior to the release. The most commonly reported symptoms within 24 hours of the release were burning throat, headache, burning eyes, and cough; headache, burning throat, and cough were the most commonly reported symptoms three to five days after release by those reporting a strong chlorine odor. Lower-respiratory-tract symptoms (cough, shortness of breath, chest tightness, or wheezing) were reported by 47% of participants at the first site visit, 48% had one or more asthma symptoms in the 2 weeks prior to that site visit, and 22% reported symptoms consistent with PTSD 4 months after release; the prevalence of PTSD symptoms increased with increasing strength of reported chlorine odor. At the third site visit, three individuals had

bronchial hyperreactivity consistent with reactive airway dysfunction syndrome (RADS). This study is important mainly for its consideration of PTSD as an effect evident 4 months after exposure and for its linkage of the strength of the odor of chlorine with the degree of PTSD.

Cummings KJ and Kreiss K (2015) Occupational and environmental bronchiolar disorders.

This is an excellent review article that defines confusing terms relating to the various kinds of bronchiolitis, discusses known precipitants (including oxides of nitrogen, sulfur dioxide, methyl isocyanate, and sulfur mustard), and also points out that not only can cases develop after symptomatic acute exposures but also after acute exposures following which initial symptoms are delayed for 10 days to a month. The research-needs section of the article discusses biomarkers that might be used for early detection of late-onset bronchiolitis, although it is unclear how early after exposure such biomarker abnormalities might occur.

Kamat SR et al. (1992) Sequential respiratory, psychologic, and immunologic studies in relation to methyl isocyanate exposure over 2 years with model development.

This study is a 2 year follow-up of 113 individuals from a geographic cohort of 10,000 exposed (135 dying within the month, 1640 treated medically, 872 admitted) following the MIC release in Bhopal. As noted in the abstract, 87 of the 113 were assessed at 2 years. The initial exposure in this cohort was mild, moderate, or severe for 27%, 50%, and 23%, respectively. A portion of this cohort had bronchodilator responsiveness, but this did not increase (11% initially to 8% at 3 months); 10 individuals tested at 3 or 6 months with methacholine challenge did not demonstrate hyper-responsiveness (the authors do not indicate in this paper why those individuals were selected). Evidence of improvement in respiratory symptoms and PFTs (particularly peak expiratory flow rate, PEFR) was tempered by some worsening at the last follow-up point (although note that there was an increase from 68 to 87 individuals tested). These results are depicted for symptoms (Table 3), X-Ray abnormalities (Table 5), and PFT/lung function assessment (Table 6). The authors also attempted to model their results for the larger Bhopal exposed population (Table 20).

Vijayan VK (1998) Long-term clinical, radiological and pulmonary function studies in victims of the Bhopal tragedy.

The 89 subjects of this study were selected from those attending the Hamidia Hospital approximately 5 years after the Bhopal MIC exposure, and screened for pre-existing “cardiorespiratory diseases” (but not prior smoking; 20% were current smokers). All had cough and breathlessness on exertion, while 1/4 had rhonchi/rales on exam and 1/2 had irregular linear opacities on X-Ray. Formal PFTs used the best parameter from any

of 3 trials and abnormal function was defined as more than 20% below predicted, with a mean FEV_1/FVC of 2.31L/3.1L (+/- 0.8 L; these means were 20% below predicted). The majority (72 of 89) had DLCO and KCO determined, with 1/5 having abnormal diffusing capacity. Using previously described criteria for both the severity of the acute exposure and American Thoracic Society/International Labor Organization criteria for respiratory impairment/pneumoconiosis-attributed small opacities on chest X-Ray [variability in profusion across zones not described] respectively, these authors report that mildly exposed subjects (n=9) had normal pulmonary function (compared to literature Indian population-based controls), while more than 1/3 (39%) of those with moderate and nearly 2/3 (63%) of those with severe initial exposure had impairment in pulmonary function; obstructive findings predominated, with most restrictive deficits identified in those with severe exposure (12 of 49 vs. 2 of 31). Looking only at the subjects with abnormal pulmonary function (n=43), ATS-consistent “mild impairment” was exhibited by 25%, “moderate” in 16% and “severe” in 8%.

Dhara VR (2002) Personal exposure and long-term health effects in survivors of the Union Carbide disaster at Bhopal.

This study attempted to develop a personal exposure index and correlate it with symptoms and PFTs 9 years after the Bhopal release using households (representatives from 1,618 randomly chosen individuals) from small electoral wards spaced at 2km intervals from 0 to >6km from the plant along an “exposure line.” Overall, interviews of 452 people (including 130 non-exposed) and PFTs of every 4th interviewee [86 (12 non-exposed)] were obtained in those above the age of 18 (9 y.o. at the time of exposure). Hospital records were used to find an additional 100 subjects with severe, acute symptoms (average distance 0.6km from the plant) at the release; a random sampling of 22 of these individuals had questionnaires/PFTs performed for the study. Care was taken to ascertain presence at the time of the gas release and a number of questions were used to estimate extent of exposure, including location- and response-related variables (time, activities increasing minute ventilation, protective steps). Missing data elements were imputed from other interview information when possible (<10% overall, with seemingly <1% un-interpretable, and subsequently, excluded data). There were a large number of “ever-smokers” in the study that varied across exposure levels (15-100%), but fewer current smokers; current smoking was not identified as an independent variable for symptoms or PFT abnormalities. Exposure severity correlated with current chest pain, taste abnormalities, and fever in previous year, although statistical significance varied with the definition of exposure index (distance alone, weighted distance with activity, etc.). Current symptom prevalence ratio (PR) for exposed vs non-exposed is shown in Table 4, with highest PR for self-reported asthma diagnosis. Distance from the plant was most correlated with subjective symptoms in this sample (community-dwelling individuals), while strength of association of FEF25-75% (taken as a small airways dysfunction indicator) was greatest with estimate of total exposure. Correlation between estimated exposure severity and

symptoms or PFT abnormalities is shown in Tables 6 and 8, respectively. An α of 0.1 was taken as significant (it is unclear if adjustment was made for multiple or serial comparisons).

Cullinan P et al. (1997) Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: A cross sectional survey.

NOTE: A previous study by same authors (published in 1996 in the National Medical Journal of India) was a survey of 474 persons (with a control group of unexposed Bhopal residents). A random sample of 76 persons had respiratory and neurologic testing: 70% had cough; 43% had phlegm (cf 38% and 22% unexposed) 2-fold increase in number of problems: "general" 94% v 52%; fever 7.5 v 2.4/yr; miscarriage 9% v 4%; respiratory symptoms 81% v 38% - with stated gradation by ward exposure rating (e.g. 99% DOE v 83% v 50% in "unexp.").

In the 1997 study, the description of random selection and testing seems to be the same group as in the Dhara 2002 paper, with the additional notation that the PFTs were performed before and after administration of inhaled β-agonist; they note that only 2 patients (MIC exposed, but no indication of proximity) had significant responses. When stratified by severity of PFT abnormality, 35% within 0-2km had FEF25-75 in the lowest quartile (<67%predicted); while 29%, 18%, and 0% had these findings in the 2-6km, 6-10km, and >10km categories. Several tables and figures focus on prevalence of symptoms and PFT abnormalities.

B-5.2 Animal Studies

In general, the reviewed animal studies were complementary to the human data. For example, the severity of the acute effects of chemicals such as methyl isocyanate and chlorine were time- and dose-dependent. The observed acute pulmonary effects, relevant to this project, included decrements in pulmonary function, pulmonary edema, and mortality. These acute effects resulted in long-term lower pulmonary effects in some but not all test animals. Thus, as in the human exposure scenarios, both the acute and long-term responses of the test animals were variable even in the case of inbred mouse strains. Despite these animal-to-man similarities, the number of studies examining the target chemicals for the long-term effects of acute exposures was relatively small, and the usefulness of the acute animal data in evaluating predictive values for long-term sequelae was limited by the small number of animals used in each exposure group. One exception would be the post-World War I study by Winternitz (1920) in which 326 dogs were acutely exposed to 50 to 2000 ppm chlorine. Overall, 56 of the 326 chlorine-exposed dogs survived from 30 to 193 days after the acute chlorine exposure at the different concentrations and 51% of the ‘survivors’ had some type of pneumonia and 34% had bronchitis or bronchiolitis. Appendix B shows abstracts for

this and a select number of additional relevant studies. Appendix C lists additional articles that were reviewed but not included in Appendix B.

B-6 Summary

In summary, Value SMEs have been asked by APHC and the CSAC to participate in a feasibility study that implements a toxidrome-based, SME-informed approach to estimating acute exposures that lead to chronic effects. APHC and the CSAC are grateful to those that are participating.

This reference document provides the Value SMEs with instructions on the process, a primer on physiology and toxicology, and a summary of relevant literature. Value SMEs are asked to use these resources and the accompanying Excel workbook to provide the requested quantitative input by noon Eastern Standard Time on 29 August. Following the submission of input, SMEs will participate in a group review to continue the steps of the study.

Following completion of the study, APHC and the CSAC welcome any comments, recommendations, or lessons learned in regards to SME participation in the study. Future applications of the approach may be implemented and this feedback is welcome and encouraged to improve the process.

B-7 Abstracts for Human Studies

Kowitz TA et al. (1967) Effects of chlorine gas upon respiratory function. Archives of Environmental Health: An International Journal 14(4): 545-558.

[There is no published abstract for this article.]

Harkonen H et al. (1983) Long-term effects of exposure to sulfur dioxide. The American Review of Respiratory Disease 128(5): 890-893.

The lung function of seven men accidentally exposed to sulfur dioxide (SO2) in a pyrite dust explosion was followed for 4 yr. The greatest decrease in forced vital capacity, forced expiratory volume in one second, and maximal midexpiratory flow was observed 1 week after the accident. After about 3 months no further decrement occurred. The pattern of spirometric findings was obstructive in 6 and restrictive in 1 of the patients. Four years after the accident a reversible obstruction of the bronchi was still observable in 3. Four patients reacted positively to the histamine challenge test. Two patients either did not respond to bronchodilator or did not react to histamine. The results suggest that bronchial hyperreactivity is a frequent sequela after exposure to high concentrations of SO2. The hyperreactivity may persist for several years. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/6638677).

Courteau J-P et al. (1994) Survey of construction workers repeatedly exposed to chlorine over a 3 to 6 month period in a pulpmill: I. Exposure and symptomatology. Occupational and environmental medicine 51(4): 219-224.

OBJECTIVE: The admission to hospital of three construction workers with acute respiratory distress caused by inhalation of chlorine gas prompted the inspection of a building site located in a kraft pulpmill. The accidental emissions had taken place in the bleach plant and the construction workers assigned there were surveyed to uncover possible large scale health effects.

DESIGN AND PARTICIPANTS: A questionnaire was presented to 281 workers (participation rate = 97%); 257 workers reported an average of 24 exposure episodes to chlorine and derivatives over a 3- to 6-month period. The air monitoring data available from the pulpmill's industrial hygienist were not useful in linking specific events reported by the workers to environmental conditions in the bleach plant.

RESULTS: Over 60% of the workers described a characteristic flu like syndrome that lasted for an average of 11 days and was exacerbated by new bouts of exposure. Irritation of the throat (78%) and eyes (77%), cough (67%), and headache (63%) were the most often reported symptoms. Shortness of breath was reported by 54% of the participants and was not associated with age, smoking state, or history of asthma or chronic bronchitis. First aid self-referral was associated with significantly greater reporting of most symptoms, including dyspnoea and cough. A significantly greater proportion of workers in the dyspnoea group had gone at least once for first aid care after a gassing incident (64% as opposed to 48%, p = 0.008). Throat irritation and cough persisted for mean intervals of eight and 11 days respectively. A flu like syndrome lasted for an average of 20 days. Seventy one subjects were considered to be a moderate to high risk of having persisting respiratory symptoms.

CONCLUSION: Throat and eye irritation as well as cough and flu like symptoms are frequent occurrences after repeated accidental inhalation of chlorine. Subjects who consulted first aid care stations after a gassing incident are more likely to have persisting dyspnoea. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/8199661).

Bherer L et al. (1994) Survey of construction workers repeatedly exposed to chlorine over a 3- to 6-month period in a pulpmill: II. Follow up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended. Occupational and environmental medicine 51(4): 225-228.

OBJECTIVE: The aim was to determine the prevalence of persistent respiratory symptoms and bronchial hyper-responsiveness due to reactive airways dysfunction syndrome in a population of construction workers at moderate to high risk of developing the syndrome, at an interval of 18 to 24 months after multiple exposures to chlorine gas during renovations to a pulp and paper mill.

DESIGN AND PARTICIPANTS: 71 of 289 exposed workers (25%) were identified on the basis of an exposure and the onset of respiratory symptoms shortly after this event (moderate to high risk). A standardized respiratory questionnaire was first presented, followed by spirometry and a methacholine inhalation test on those whose questionnaire suggested the persistence of respiratory symptoms.

RESULTS: 64 of 71 (90%) subjects completed the respiratory questionnaire at the time of the follow up. The questionnaire suggested a persistence of respiratory symptoms in 58 of the 64 workers (91%). Of the 58 subjects, 51 underwent spirometry and assessment of bronchial responsiveness. All of them used bronchodilators as required (not regularly) and four required inhaled anti-inflammatory preparations. Sixteen had bronchial obstruction (forced expiratory volume in one second) (FEV1 < 80% predicted) and 29 showed significant bronchial hyper-responsiveness.

CONCLUSION: Of the subjects (n = 71) who were at moderate to high risk of developing reactive airways dysfunction syndrome after being exposed to chlorine and were seen 18 to 24 months after exposure ended, 58 (82%) still had respiratory symptoms, 16 (23%) had evidence of bronchial obstruction, and 29 (41%) had bronchial hyper-responsiveness. (Abstract available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1127951/).

Gautrin D et al. (1995) Cross-sectional assessment of workers with repeated exposure to chlorine over a 3-year period. The European Respiratory Journal 8(12): 2046-2054.

Airflow obstruction has been described in workers who experienced symptoms after acute exposure to chlorine. Persistent bronchial hyperresponsiveness has also been assessed, but mainly in case studies. In this cross-sectional study, we have assessed the relationship between inhalational accidents ("puffs") involving chlorine and persistent symptoms as well as hyperresponsiveness in 239 out of 255 at-risk workers (94%). No relationship was found between persistent symptoms and the exposure variables studied. Forced vital capacity (FVC) was higher in subjects who had had no symptoms after a "puff," compared with those who had experienced mild symptoms. Forced expiratory volume in one second (FEV1) and FVC were significantly lower in subjects who experienced more than 10 puffs with mild symptoms than in subjects who reported no symptomatic puff. The presence of bronchial hyperresponsiveness was not related to exposure, but the methacholine dose-response slope showed a tendency to increased bronchial responsiveness with increased exposure. A significant difference

was shown in subjects who experienced more than 10 puffs with mild symptoms. In this group of workers, repeated exposure to chlorine with acute respiratory symptoms was associated with a slight but significant reduction in expiratory flow rates, together with an increase in bronchial responsiveness, without long-term symptoms. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/8666099).

Henneberger PK et al. (1996) Decrements in spirometry values associated with chlorine gassing events and pulp mill work. American Journal of Respiratory and Critical Care Medicine 153(1): 225-231.

In a previous study of older pulp and paper workers in Berlin, New Hampshire, decrements in spirometry results associated with accidental exposures to high levels of irritant gases depended on cumulative levels of pulp mill exposure and cigarette smoking. Many of those subjects were older and retired. A new study was initiated to assess whether gassing events were a problem among current workers. Three hundred white male pulp and paper workers from the mill in Berlin, New Hampshire, were surveyed in 1992. Testing included spirometry and questionnaires. The mean age was 40.4 yr, and the mean tenure with the company was 18.5 yr. A total of 105 of the 300 subjects (35%) reported ever having an episode of high exposure to chlorine gases (i.e., being gassed). The percentage gassed was 51% for pulp mill workers and only 13% for other employees. For subjects with no more than 26 pack-years of cigarette smoking, obstruction (i.e., abnormally low FEV1 and FEV1/FVC) was observed only among those with a history of gassing. Also, the combination of high cigarette smoking (i.e., > 26 pack-years) and gassing had a greater than additive effect on obstruction. These findings suggest that additional controls are needed to minimize the number of gassing events in this and other chemical pulp mills. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/8542120).

Alberts WM and do Pico GA (1996) Reactive airways dysfunction syndrome. Chest 109(6): 1618-1626.

[There is no published abstract for this article.]

Gautrin D et al. (1999) Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine. American Journal of Respiratory and Critical Care Medicine 160(4): 1232-1237.

This longitudinal study (1992-1994) was performed to determine the relation between accidental chlorine exposure and changes in lung function and airway responsiveness in 239 workers in a metal production plant. These workers had taken part in a cross-sectional survey in 1992. In both the initial and the follow-up surveys, history of exposure to chlorine ("puffs"), accidental chlorine inhalation reported to the first-aid unit (gassing incidents), and of chronic symptoms were documented; spirometry and

methacholine challenge tests were performed. At follow-up, 211 workers (88.3%) were seen. In workers with 20 pack-years or more of cigarette smoking, the fall in FEV(1) was associated with having had a gassing incident during the follow-up period; the fall in FEV(1)/FVC (%) was predicted by the number of puffs causing mild symptoms between the two assessments. An increase in airway responsiveness (PC(20) decrease > 1.5-fold) was present in 19 workers; it was associated with accidents reported to the first-aid unit during the previous 2 yr (OR: 5.9, 95% CI: 1.1 to 32.3). These findings suggest: (1) an effect on airway function related to the estimated number of puffs with mild symptoms and gassing incidents, mostly among smokers; (2) a detectable increase in airway responsiveness associated with gassing incidents. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/10508812).

Leroyer C et al. (1999) Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. Occupational and Environmental Medicine 56(5): 334-338.

BACKGROUND: To assess the frequency of chronic upper airways symptoms and to relate the presence of these symptoms to accidental exposure to chlorine and changes in lower airways symptoms, airway function, and bronchial responsiveness in a cohort of workers at risk of sporadic occupational exposure to high concentrations of chlorine.

METHODS: Data were collected on symptom assessment, spirometry, and methacholine challenge tests from 211 workers seen twice at a 2-year interval (1992-4).

RESULTS: The proportion of workers reporting chronic rhinitis was 46.9% in 1992 and 42.2% in 1994. Chronic rhinitis reported in 1994 was significantly associated with acute exposure to chlorine (self-reports, p = 0.02; first aid reports, p = 0.001). In a multivariate logistic regression analysis the presence of reported accidents at the first aid unit (one accident, odds ratio (OR) 3.1, 95% confidence interval (95% CI) 1.3 to 7.5; two or more accidents, OR 6.2, 1.1 to 35.8) and of personal atopy (OR 5.5, 2.2 to 10.8) were significant predictors of chronic rhinitis in 1994. Chronic lower airways symptoms were more frequent in 1994 among workers reporting chronic rhinitis on both assessments than in others (p = 0.03) and changes in bronchial responsiveness were more pronounced in those with persistent rhinitis (p = 0.09).

CONCLUSIONS: These results suggest that persistent nasal symptoms in workers at risk of reactive airways dysfunction syndrome could be a useful marker of lower respiratory tract abnormalities. (Abstract available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1757733/).

Henneberger PK et al. (2005) The incidence of respiratory symptoms and diseases among pulp mill workers with peak exposures to ozone and other irritant gases. Chest 128(4): 3028-3037.

OBJECTIVES: Pulp mills in Sweden started to use ozone as a bleaching agent in the early 1990s. The goal of this study was to investigate whether the incidence of selected respiratory outcomes was associated with peak exposures to ozone or other irritant gases (ie, chlorine dioxide [ClO2] or sulfur dioxide [SO2]) used in these mills.

METHODS: Bleachery workers (n = 245) from three pulp mills where ozone was used participated in surveys in the mid- to late-1990s. Comparison workers (n = 80) were from two adjacent paper mills. The person-time at risk was calculated for each participant, covering the period of employment when ozone was used. Data were collected by questionnaire, and a peak exposure was defined as a self-reported exposure to an irritant gas resulting in acute respiratory symptoms. The outcomes analyzed were self-reports of physician-diagnosed asthma, attacks of wheeze, and chronic bronchitis (i.e., chronic cough with phlegm). Participants also reported when the peak exposures and outcomes occurred.

RESULTS: Based on proportional hazards regression (controlling for gender, age, cigarette smoking, atopy, and peak irritant exposures that occurred before follow-up), workers who reported both ozone and ClO2/SO2 peak exposures had elevated hazard ratios (HRs) for all three outcomes. Those who reported only ozone peak exposures had elevated HRs of 6.5 (95% confidence interval [CI], 1.2 to 36.3) for asthma and 3.3 (95% CI, 1.1 to 10.2) for attacks of wheeze but no increase in risk for chronic bronchitis. Workers with only ClO2/SO2 peak exposures had elevated HRs for attacks of wheeze (HR, 7.5; 95% CI, 1.9 to 29.3) and chronic bronchitis (HR, 22.9; 95% CI, 4.5 to 118.2) but not for asthma.

CONCLUSIONS: These findings suggest the need for additional efforts to prevent peak exposures in pulp-bleaching operations. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/16236983).

Ghanei M et al (2008) An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. Respiratory Medicine 102(6): 825-830.

BACKGROUND: Recent studies have shown strong evidence that bronchiolitis obliterans is the major long-term sequelae of exposure to sulfur mustard (SM). This study is the first to examine the histopathologic spectrum of changes in a large number of surgical lung biopsies from patients exposed to SM.

METHOD: Fifteen patients with chronic respiratory disease from mustard gas exposure were divided into severe (6 cases) and mild exposure (9 cases). All had surgical (open

or thoracoscopic) lung biopsy, pulmonary function tests (PFTs) and chest high-resolution computed tomography scan (HRCT).

RESULT: The mean age of the cases was 43.8+/-9.6 (range 33-65). All patients had dyspnea and cough as the two main complaints. Only one patient was a smoker. Thirteen patients had normal PFTs, while one had obstruction and one had mild restriction. Six (66.6%) patients in the mild exposure and 3 (50%) in the severe exposure group showed evidence of more than 25% air trapping on chest HRCT. Among the mild group, 3 had features of constrictive bronchiolitis and another had features suggestive of this (bronchiolectasis and mucus stasis). The next most common finding was a mild-to-moderate chronic cellular bronchiolitis (3 patients). Two among the 6 in the severe group showed constrictive bronchiolitis and one showed features suggestive of constrictive bronchiolitis.

CONCLUSION: We conclude that about half of patients had diagnostic constrictive bronchiolitis, or bronchiolectasis and mucus stasis consistent with more proximal luminal compromise. The fact that there were no differences between the low- and high-dose groups suggests that effects of SM are not solely dependent on the severity of exposure. The results also indicate that the diagnosis of chronic lung disease due to SM may be difficult. Surgical lung biopsy may be helpful in difficult cases, as constrictive (obliterative) bronchiolitis can be present in symptomatic patients with normal PFTs and chest HRCT. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/18339530).

Shakeri MS et al. (2008) Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review. Occupational Medicine (Oxford, England) 58(3): 205-211.

AIM: To identify those agents reported as being associated with reactive airways dysfunction syndrome (RADS).

METHODS: A systematic review was undertaken. Abstracts were screened and those selected reviewed against pre-determined diagnostic criteria for RADS. RESULTS: Significant information gaps were identified for all measures of interest. In some articles, even the causative agent was not reported. The most commonly reported agents were chlorine (nine subjects), toluene di-isocyanate (TDI) (n = 6) and oxides of nitrogen (n = 5). Most exposures occurred in the workplace (n = 51) and affected men (60%). Dyspnoea (71%) and cough (65%) were the commonest symptoms. Median symptom duration was 13 months (interquartile range = 6.5-43.5) for RADS.

CONCLUSIONS: Although the most commonly reported agent associated with RADS was chlorine, the main finding of a general lack of adequate information on exposure, investigation and outcome suggests that to better explore RADS a more structured

approach to gathering information is required. A minimum data set for reporting RADS cases is proposed. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/18308694).

Kreiss K (2013) Occupational causes of constrictive bronchiolitis. Current Opinion in Allergy and Clinical Immunology 13(2): 167-172.

Purpose of review: New literature from 2009 to 2012 regarding occupational constrictive bronchiolitis challenges textbook descriptions of this disease, formerly thought to be limited to fixed airflow limitation arising in the wake of accidental overexposure to noxious chemicals. Indolent evolution of dyspnea without a recognized hazardous exposure is a more common presentation. Recent findings: Biopsy-confirmed case series of constrictive bronchiolitis from U.S. soldiers, Iranian survivors of sulfur mustard gassing, hospital-based studies, and flavoring-related cases document that indolent constrictive bronchiolitis cases can have normal spirometry or either restrictive or obstructive abnormalities. High-resolution computerized tomography studies can be normal or reflect air-trapping and mosaic attenuation on expiratory films. Thus, in the absence of noninvasive abnormalities, the diagnosis in dyspneic patients may require thoracoscopic biopsy in settings in which exposure risk has not been recognized. Many workers with occupational constrictive bronchiolitis stabilize with cessation of exposures causing bronchiolar epithelial necrosis. Summary: Clinicians need a high index of suspicion for constrictive bronchiolitis in young patients with rapidly progressing exertional dyspnea, regardless of spirometric and radiologic findings. Identification of novel causes and exposure-response relations for known causes are needed to provide guidance for protecting workers at risk for this largely irreversible lung disease. (Abstract available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522912/).

Meza F et al. (2013) Evaluation of health effects of a chlorine gas release in a poultry processing plant – Arkansas. CDC/NIOSH Health Hazard Evaluation Report. HETA 2011-0128-3166.

[There is no published abstract for this report.]

Cummings KJ and Kreiss K (2015) Occupational and environmental bronchiolar disorders. Seminars in Respiratory and Critical Care Medicine 36(3): 366-378.

Occupational and environmental causes of bronchiolar disorders are recognized on the basis of case reports, case series, and, less commonly, epidemiologic investigations. Pathology may be limited to the bronchioles or also involve other components of the respiratory tract, including the alveoli. A range of clinical, functional, and radiographic findings, including symptomatic disease lacking abnormalities on noninvasive testing, poses a diagnostic challenge and highlights the value of surgical biopsy. Disease clusters in workplaces and communities have identified new etiologies, drawn attention to indolent disease that may otherwise have been categorized as idiopathic, and

expanded the spectrum of histopathologic responses to an exposure. More sensitive noninvasive diagnostic tools, evidence-based therapies, and ongoing epidemiologic investigation of at-risk populations are needed to identify, treat, and prevent exposure-related bronchiolar disorders. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/26024345).

Kamat SR et al. (1992) Sequential respiratory, psychologic, and immunologic studies in relation to methyl isocyanate exposure over 2 years with model development. Environmental Health Perspectives 97: 241-253.

Of 113 methyl isocyanate (MIC)-exposed subjects studied initially at Bhopal, India, 79, 56, 68, and 87 were followed with clinical, lung function, radiographic, and immunologic tests at 3, 6, 12, 18, and 24 months. Though our cohort consisted of subjects at all ages showing a varied severity of initial illness, fewer females and young subjects were seen. Initially all had eye problems, but dominant symptoms were exertional dyspnea, cough, chest pain, sputum, and muscle weakness. A large number showed persistent depression mixed with anxiety, with disturbances of personality parameters. The early radiographic changes were lung edema, overinflation, enlarged heart, pleural scars, and consolidation. The persistent changes seen were interstitial deposits. Lung functions showed mainly restrictive changes with small airway obstruction; there was impairment of oxygen exchange. Oxygen exchange improved at 3-6 months, and spirometry improved at 12 months, only to decline later. The expiratory flow rates pertaining to large and medium airway function improved, but those for small airways remained low. There were changes of alveolitis in bronchoalveolar lavage fluid on fiber optic bronchoscopy, and in 11 cases positive MIC-specific antibodies to IgM, IgG, and IgE were demonstrated. On follow up, only 48% of the subjects were clinically stable, while 50% showed fluctuations. Thirty-two percent of the subjects had lung function fluctuations. Detailed sequential behavior over 2-4 years was predicted for dyspnea, forced vital capacity, maximum expiratory flow rate (0.25-0.75), peak expiratory flow rate, VO2, and depression score. A model for clinical behavior explained a total variance of 52.4% by using the factors of cough, PCO2 and X-ray zones in addition to above five parameters. The behavior of the railway colony group (1640 patients) revealed a similar pattern of illness. When this observed pattern of changes was transferred to the affected Bhopal city sections (with an equitable age-sex distribution), our model results were again validated. Thus, the picture of MIC-induced disease seems similar despite the differences for age-sex and initial severity of illness in our cohort and in the population of Bhopal city as predicted by our model. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/1396463).

Vijayan VK (1998) Long-term clinical, radiological and pulmonary function studies in victims of the Bhopal tragedy. Advances in the Prevention of Occupational Respiratory Diseases. 1st Edition. Proceedings of the 9th International Conference, Tokyo, Japan. K. Chiyotani, Y. Hosoda, and Y. Aizawa, editors.

The clinical, radiological and pulmonary function studies were carried out in 89 symptomatic methyl isocyanate (MIC) gas-exposed subjects at Bhopal 4.7 ± 1.4 years (range 3-7 years) after exposure to evaluate the long-term effects of toxic gas on the respiratory system. Pulmonary function tests included spirometry, static lung volumes and diffusing capacity measurements. Chest radiographs were assessed using the International Labour Organisation (ILO) classification. Lung signs were present in 24 subjects (27%) and radiographic abnormalities were persistent in 50 (56%). The mean forced vital capacity ($p<0.001$), forced expiratory volume in 1 s ($p<0.001$), and total lung capacity ($p<0.05$) were significantly lower and residual volume ($p = 0.01$) was significantly higher in gas-exposed subjects compared to predict values. However, the mean functional residual capacity ($p>0.2$), diffusing capacity ($p>0.1$), and transfer coefficient ($p>0.2$) were not significantly different. Pulmonary function abnormalities were noticed in 43 subjects (48%); 22 (25%) had mild, 14 (16%) had moderate and seven (8%) had severe respiratory impairment. Obstructive ventilatory defect was seen in 29 subjects (33%) and restrictive defect in 14 (16%). Reduced diffusing capacity (<80% of the predicted values) was seen in 16 of the 72 (22.2%) patients. Pulmonary function abnormalities were predominantly seen in subjects severely exposed to the gas. Thus, single massive exposure to toxic gas at Bhopal had resulted in permanent lung damage, especially obstructive airway disease.

Dhara VR (2002) Personal exposure and long-term health effects in survivors of the Union Carbide disaster at Bhopal. Environmental Health Perspectives 110(5): 487-500.

Nine years after the Bhopal methyl isocyanate disaster, we examined the effects of exposures among a cross-section of current residents and a subset of those with persistent symptoms. We estimated individual exposures by developing exposure indices based on activity, exposure duration, and distance of residence from the plant. Most people left home after the gas leak by walking and running. About 60% used some form of protection (wet cloth on face, splashing water). Mean and median values of the exposure indices showed a declining trend with increasing distance from the plant. For those subjects reporting any versus no exposure, prevalence ratios were elevated for most respiratory and nonrespiratory symptoms. We examined exposure-response relationships using exposure indices to determine which were associated with health outcomes. The index total exposure weighted for distance was associated with most respiratory symptoms, one measure of pulmonary function in the cross-sectional sample [mid-expiratory flow (FEF)(25-75), $p = 0.02$], and two measures of pulmonary function in the hospitalized subset [forced expiratory volume (FEV)(1), $p = 0.02$; FEF(25-75), $p = 0.08$). Indices that correlated with FEV(1) and forced vital capacity in the hospitalized subset did not correlate with the cross-sectional sample, and most indices (except total exposure) that correlated with the hospitalized subset did not correlate with the cross-sectional sample. Incorporation of distance into every index increased the number of symptoms associated; an improvement was also noted in the

strength of the association for respiratory symptoms, but not for pulmonary function. The sum of duration (p = 0.02) and total exposure (p = 0.03) indices independently demonstrated stronger associations with percent predicted FEF(25-75) than the distance variable (p = 0.04). The results show that total exposure weighted for distance has met the criteria for a successful index by being associated with most respiratory symptoms as well as FEF(25-75), features of obstructive airways disease. (Abstract available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240837/).

Cullinan P et al. (1997) Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: A cross sectional survey. The BMJ 314(7077) 338-342.

OBJECTIVE: To examine the role of exposure to the 1984 Bhopal gas leak in the development of persistent obstructive airways disease.

DESIGN: Cross sectional survey.
SETTING: Bhopal, India.

SUBJECTS: Random sample of 454 adults stratified by distance of residence from the Union Carbide plant.

MAIN OUTCOME MEASURES: Self-reported respiratory symptoms; indices of lung function measured by simple spirometry and adjusted for age, sex, and height according to Indian derived regression equations.

RESULTS: Respiratory symptoms were significantly more common and lung function (percentage predicted forced expiratory volume in one second (FEV1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF25-75), and FEV1/FVC ratio) was reduced among those reporting exposure to the gas leak. The frequency of symptoms fell as exposure decreased (as estimated by distance lived from the plant), and lung function measurements displayed similar trends. These findings were not wholly accounted for by confounding by smoking or literacy, a measure of socioeconomic status. Lung function measurements were consistently lower in those reporting symptoms.

CONCLUSION: Our results suggest that persistent small airways obstruction among survivors of the 1984 disaster may be attributed to gas exposure. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/9040323)

B-8 Abstracts for Animal Studies

Demnati R et al. (1998) Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats. The European Respiratory Journal 11(4): 922-928.

Reactive airways dysfunction syndrome (RADS) is an asthma-like condition that follows exposure to very high concentrations of an irritant material. We assessed the time-course of pathophysiological alterations in a model of RADS. Sprague-Dawley rats were exposed to 1,500 parts per million (ppm) of chlorine for 5 min. Lung resistance (RL), responsiveness to inhaled methacholine (MCh), the airway epithelium and bronchoalveolar lavage (BAL) were assessed over a 3 month period after exposure. RL increased significantly up to 3 days after exposure, reaching a maximal change of 110+/-16% from baseline. There was a significant decrease in the concentration of MCh required to increase RL by 0.20 cmH2O x mL(-1) x s from days 1-7 after exposure. In some rats, MCh hyperresponsiveness and RL changes persisted after exposure for as long as 1 and 3 months, respectively. Histological evaluation with morphometric evaluation revealed epithelial flattening, necrosis, increase in smooth muscle mass and evidence of epithelial regeneration. BAL showed an increased number of neutrophils. The timing of maximal abnormality in the appearance of the epithelium (days 1-3) corresponded to that of the maximal functional changes. Acute high chlorine exposure results in functional and pathological abnormalities that resolve in the majority of animals after a variable period; however, these changes can persist in some animals. Functional abnormalities in the initial stages may be related to airway epithelial damage. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/9623698).

Tepper JS et al. (1987) Cardiopulmonary effects in awake rats 4 and 6 months after exposure to methyl isocyanate. Environmental Health Perspectives 72: 95-103.

Cardiopulmonary function was assessed 4 and 6 months after Fischer 344 rats were exposed to 2 hr to 0, 3, or 10 ppm methyl isocyanate (MIC). During assessment, the rats were challenged with 4 and 8% carbon dioxide (CO2) to stimulate ventilatory drive. Minute ventilation (VE) during CO2 challenge was increased in MIC-treated rats compared to controls when examined 4 months after exposure to 10 ppm MIC, suggesting a ventilation/perfusion inequality. An increase in maximum expiratory flow and a decrease in expiratory time indicated increased lung recoil in these rats. Evidence of pulmonary hypertension was observed in electrocardiograms (ECGs) and supported by postmortem analysis that showed a positive association between increased ECG abnormalities and increased right ventricular weights in the rats treated with 10 ppm MIC. At 6 months, forced expiratory flow-volume curves indicated persistent airway obstruction; however, no changes in inspiratory or expiratory resistance were evident. Decreased dynamic compliance and changes in two new measures of lung function (volume and time at zero expiratory intrapleural pressure) suggest that MIC-induced lung dysfunction also exhibited elements of a restrictive disease. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/2957196).

Ferguson JS and Alarie Y (1991) Long term pulmonary impairment following a single exposure to methyl isocyanate. Toxicology and Applied Pharmacology 107(2): 253-268.

Groups of guinea pigs were exposed for 3 hr to 6, 13, 19, 27, or 37 ppm of methyl isocyanate (MIC). Pulmonary performance was evaluated immediately postexposure and for a period of 1 year in the animals surviving 19 or 37 ppm of MIC. At 6 and 13 ppm deterioration of pulmonary performance was observed but complete recovery occurred within a few weeks. In those animals surviving 19 or 37 ppm some recovery occurred but a long lasting impairment of pulmonary performance was observed. One year after a single exposure to MIC these animals presented a condition best described as chronic obstructive lung disease. Using flow-volume measurements during air breathing and during CO2 challenge, animals surviving at 19 or 37 ppm presented typical abnormalities associated with airflow limitation along the conducting airways. One year after exposure lung hyperinflation was also present. At this time the poor ventilatory response to CO2 was due to mechanical limitation of lung expansion during inspiration and airflow limitation during expiration. The findings were similar to humans with severe obstructive lung disease. Microscopic examination substantiated the flow-volume measurements in that the main bronchi, small bronchi, and bronchioles were found to have an increase in dense fibrous tissue, while the alveolar level was characterized by destruction of alveolar walls and an increase in septal thickness. Thus a single exposure to MIC, if the concentration is high enough, is sufficient to induce permanent pulmonary toxicity. (Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/1704645).

Winternitz MC (1920) Collected studies on the pathology of war gas poisoning. From the Department of Pathology and Bacteriology, Medical Science Section, Chemical Warfare Service. New Haven, Yale University Press.

[There is no published abstract for this report.]

B-9 List of Reviewed Articles

First Author	Title	Year
Berghoff RS	The more common gases; their effect on the respiratory tract – observation on two thousand cases	1919
Meakins JC	The after-effects of chlorine gas poisoning	1919
Nichols BH	The clinical effects of the inhalation of nitrogen dioxide	1930
Gilchrist HL	The residual effects of war gases: the use of phosgene gas, with report of cases	1933

First Author	Title	Year
Galdston M	A study of the residual effects of phosgene poisoning in human subjects. I. After acute exposure	1947
Hoveid P	The chlorine accident in Mjøndalen 26 January 1940; follow-up	1956
Becklake MR	The long-term effects of exposure to nitrous fumes	1957
Dalhamn T	Chlorine dioxide: toxicity in animal experiments and industrial risks	1957
Gross P	Chronic pneumonitis caused by phosgene. An experimental study.	1965
Kowitz TA	Effects of chlorine gas upon respiratory function	1967
Beach FXM	Respiratory effects of chlorine gas	1969
Milne JEH	Nitrogen dioxide inhalation and bronchiolitis obliterans: a review of the literature and report of a case	1969
Weill H	Late evaluation of pulmonary function after acute exposure to chlorine gas.	1969
Glass WI	Phosgene poisoning: case report.	1971
Kaufman J	Clinical, roentgenologic, and physiologic effects of acute chlorine exposure	1971
Ramirez J	Silo-Filler's Disease: nitrogen dioxide-induced lung injury; long-term follow-up and review of the literature	1971
Jones GR	Pulmonary effects of acute exposure to nitrous fumes	1973
Paulet G	Action of a discontinuous exposure to chlorine dioxide (ClO2) on the rat (summary)	1974
Williams N	Polymer-fume fever: not so benign	1974
Barrow RE	Chlorine-induced pulmonary function changes in rabbits	1975
Pham Q	Methodology of an epidemiological survey in the iron ore mines of Lorraine. Research into the long-term effect of potentially irritant gases on the pulmonary system.	1976
Chester EH	Pulmonary injury following exposure to chlorine gas. Possible beneficial effects of steroid treatment	1977
Horvath EP	Nitrogen dioxide-induced pulmonary disease	1978
Barrow CS	An inhalation toxicity study of chlorine in Fischer 344 rats following 30 days of exposure	1979
Morse DL	Occupational exposure to hexachlorocyclopentadiene	1979
Mustchin CP	"Coughing water": bronchial hyperreactivity induced by swimming in a chlorinated pool	1979
Woodford DM	Obstructive lung disease from acute sulfur dioxide exposure	1979
Dodd DE	Lung sulfhydryl changes in rats following chlorine inhalation	1980

First Author	Title	Year
Kominsky	Hexachlorocyclopentadiene contamination of a municipal wastewater treatment plant	1980
Wilber CG	Toxicology of selenium: a review	1980
Barrow CS	Sensory irritation tolerance development to chlorine in F-344 rats following repeated inhalation	1982
Rand GM	The clara cell: an electron microscopy examination of the terminal bronchioles of rats and monkeys following inhalation of hexachlorocyclopentadiene	1982
Schlueter DP	Infiltrative lung disease hypersensitivity pneumonitis	1982
Harkonen H	Long-term effects of exposure to sulfur dioxide: lung function 4 years after a pyrite dust explosion	1983
Hasan FM	Resolution of pulmonary dysfunction following acute chlorine exposure	1983
Lam C	Long-term sequelae of bronchiolitis induced by nitrogen dioxide in hamsters	1983
Brooks SM	Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures	1985
Charan NB	Effects of accidental chlorine inhalation on pulmonary function	1985
Diller WF	Late sequelae after phosgene poisoning: a literature review	1985
Withers RMJ	The assessment of major hazards: the lethal toxicity of chlorine. Part 2. Model of toxicity to man	1985
Alderman LC	Hydrogen selenide poisoning: an illustrative case with review of the literature	1986
Gassert T	Long term pathology of lung, eye, and other organs following acute exposure of rats to methyl isocyanate	1986
Irani SF	A survey of Bhopal children affected by methyl isocyanate gas.	1986
Jones RN	Lung function after acute chlorine exposure	1986
Naik SR	Medical survey of methyl isocyanate gas affected population of Bhopal. Part I. General medical observations 15 weeks following exposure	1986
Naik SR	Medical survey of methyl isocyanate gas affected population of Bhopal. Part II. Pulmonary effects in Bhopal victims as seen 15 weeks after MIC exposure.	1986
Alarie Y	Sensory and pulmonary irritation of methyl isocyanate in mice and pulmonary irritation and possible cyanide-like effects of methyl isocyanate in guinea pigs	1987
Boorman GA	Two-hour methyl isocyanate inhalation and 90-day recovery study in B6C3F1 mice	1987

First Author	Title	Year
Bucher JR	Two-hour methyl isocyanate inhalation exposure and 91-day recovery: a preliminary description of pathologic changes in F344 rats	1987
Bucher JR	Toxicity of inhaled methyl isocyanate in F344/N Rats and B6C3F1 mice. I. Acute exposure and recovery studies	1987
Stevens MA	Functional evidence of persistent airway obstruction in rats following a two-hour inhalation exposure to methyl isocyanate	1987
Tepper JS	Cardiopulmonary effects in awake rats 4 and 6 months after exposure to methyl isocyanate	1987
Andersson N	Exposure and response to methyl isocyanate: results of a community based survey in Bhopal	1988
Kraut A	Chemical pneumonitis due to exposure to bromine compounds	1988
Rastogi SK	Effect of exposure to toxic gas on the population of Bhopal: Part II – respiratory impairment	1988
Shroff CP	Respiratory cytopathology in chlorine gas toxicity: a study in 28 subjects	1988
Weill H	Disaster at Bhopal: the accident, early findings and respiratory health outlook in those injured	1988
Ying W	Clinical report on 62 cases of acute dimethyl sulfate intoxication	1988
Abhyankar A	Six month follow-up of fourteen victims with short-term exposure to chlorine gas.	1989
Bucher JR	Carcinogenicity and pulmonary pathology associated with a single 2-hour inhalation exposure of laboratory rodents to methyl isocyanate	1989
Epler GR	Silo-Filler's Disease: a new perspective	1989
Givan DC	Longitudinal evaluation of pulmonary function in an infant following chlorine gas exposure	1989
Ip M	Lung injury in dimethyl sulfate poisoning.	1989
Donnelly SC	Reactive airways dysfunction syndrome (RADS) due to chlorine gas exposure.	1990
Schwartz DA	The pulmonary sequelae associated with accidental inhalation of chlorine gas	1990
Ferguson JS	Long term pulmonary impairment following a single exposure to methyl isocyanate.	1991
Kennedy SM	Lung health consequences of reported accidental chlorine gas exposures among pulpmill workers.	1991

First Author	Title	Year
Moore BB	Chronic reactive airway disease following acute chlorine gas exposure in an asymptomatic atopic patient	1991
Salisbury DA	First-aid reports of acute chlorine gassing among pulpmill workers as predictors of lung health consequences	1991
Carel RS	Delayed health sequelae of accidental exposure to bromine gas	1992
Kamat SR	Sequential respiratory, psychologic, and immunologic studies in relation to methyl isocyanate exposure over 2 years with model development	1992
Moulick ND	Acute accidental exposure to chlorine fumes: a study of 82 cases	1992
Das R	Chlorine gas exposure and the lung: a review	1993
Henneberger PK	Accidental gassing incidents and the pulmonary function of pulp mill workers	1993
Konichezky S	Thionyl-chloride-induced lung injury and bronchiolitis obliterans	1993
Mrvos R	Home exposures to chlorine/chloramine gas: review of 216 cases	1993
Bherer L	Survey of construction workers repeatedly exposed to chlorine over a 3- to 6-month period in a pulpmill: II. Follow up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended	1994
Courteau JP	Survey of construction workers repeatedly exposed to chlorine over a 3- to 6-month period in a pulpmill: I. Exposure and symptomatology	1994
Deschamps D	Persistent asthma after inhalation of a mixture of sodium hypochlorite and hydrochloric acid	1994
Malo J-L	Bronchial hyperresponsiveness can improve while spirometry plateaus 2 to 3 years after repeated exposure to chlorine causing respiratory symptoms	1994
Malo J-L	Bronchial hyperresponsiveness can improve while spirometry plateaus 2 to 3 years after repeated exposure to chlorine causing respiratory symptoms	1994
Meggs WJ	RADS and RUDS: the toxic induction of asthma and rhinitis	1994
Mohsenin V	Human exposure to oxides of nitrogen at ambient and supra-ambient concentrations	1994
National Toxicology Program	NTP toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 77-47-4) in F344/N rats and B6C3F1 mice (inhalation studies)	1994

First Author	Title	Year
Sriramachari S	Comparative toxicity of methyl isocyanate and its hydrolytic derivatives in rats. II. Pulmonary histopathology in the subacute and chronic phases.	1994
Weiss SM	Acute inhalation injury	1994
Gautrin D	Cross-sectional assessment of workers with repeated exposure to chlorine over a 3-year period	1995
Rivoire B	Chronic course of reactive bronchial dysfunction syndrome. Apropos of 6 further cases	1995
Wolf	Two-year inhalation exposure of female and male B6C3F1 mice and F344 rats to chlorine gas induces lesions confined to the nose	1995
Alberts WM	Reactive airways dysfunction syndrome	1996
Cullinan P	Long term morbidity in survivors of the 1984 Bhopal gas leak	1996
Henneberger PK	Decrements in spirometry values associated with chlorine gassing events and pulp mill work	1996
Ibanes JD	Reexamination of respiratory tract responses in rats, mice, and rhesus monkeys chronically exposed to inhaled chlorine	1996
Meggs WJ	Nasal pathology and ultrastructure in patients with chronic airway inflammation (RADS and RUDS) following an irritant exposure	1996
Nemery B	Late consequences of accidental exposure to inhaled irritants: RADS and the Bhopal disaster	1996
Schonhofer B	Long-term lung sequelae following accidental chlorine gas exposure	1996
Taylor AJN	Respiratory irritants encountered at work	1996
Vijayan VK	Relationship between lung inflammation, changes in lung function and severity of exposure in victims of the Bhopal tragedy	1996
Cullinan P	Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: a cross sectional survey. The International Medical Commission on Bhopal.	1997
Lemiere C	Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment	1997
Misra UK	A study of cognitive functions in methyl-iso-cyanate victims 1 year after bhopal accident	1997
Williams JG	Inhalation of chlorine gas	1997
Bonin AM	P2G215 - Micronucleus induction following phosphine inhalation in rodents: Short term and subchronic	1998
Demnati R	Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats	1998

First Author	Title	Year
Sexton JD	Chlorine inhalation	1998
Vijayan VK	Long-term clinical, radiological and pulmonary function studies in victims of the Bhopal tragedy	1998
Gautrin D	Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine	1999
Hyback B	A long-term study of pulmonary function at low exposures to chlorine	1999
Leroyer C	Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine	1999
Leroyer C	Changes in airway function and bronchial responsiveness after acute occupational exposure to chlorine leading to treatment in a first aid unit	1999
Leininger JR	Comparison of nasal mucous cell response following chronic inhalation of chlorine in rodents and monkeys	2000
Ueno H	Hematological effects of chlorine dioxide on in vitro exposure in mouse, rat and human blood and on subchronic exposure in mice	2000
Gilbert NL	A 5-year follow-up of airway function and bronchial responsiveness in workers acutely exposed to chlorine in a metal production plant	2001
Hatch G	An ‘injury-time integral’ model for extrapolating from acute to chronic effects of phosgene	2001
Dhara VR	The Union Carbide disaster in Bhopal: a review of health effects	2002
Dhara VR	Personal exposure and long-term health effects in survivors of the union carbide disaster at Bhopal	2002
Di Napoli A	Respiratory effects of exposure to chlorine vapors during a swimming pool accident in a recreational center in Rome	2002
Health Council of the Netherlands	Perchloromethyl Mercaptan. Health-based reassessment of administrative occupational exposure limits	2002
Olin AC	Respiratory health among bleachery workers exposed to ozone and chlorine dioxide	2002
Traub SJ	Case report and literature review of chlorine gas toxicity	2002
Dompeling E	Chronic bronchiolitis in a 5-yr-old child after exposure to sulphur mustard gas	2003
Kilburn KH	Brain but not lung functions impaired after a chlorine incident	2003
King TE	Miscellaneous causes of bronchiolitis: inhalational, infectious, drug-induced, and idiopathic	2003
Martin JG	Chlorine-induced injury to the airways in mice	2003

First Author	Title	Year
Thomason JWW	Bronchiolitis obliterans in a survivor of a chemical weapons attack	2003
Yang CY	Adverse respiratory and irritant health effects in airport workers in Taiwan.	2003
Bjarnason SG	Long-term sequelae from acute exposure to chlorine gas: a review	2004
Ghanei M	Bronchiolitis obliterans following exposure to sulfur mustard: chest high resolution computed tomography	2004
Gorguner M	Reactive airways dysfunction syndrome in housewives due to a bleach-hydrochloric acid mixture	2004
Yildirim C	Long-term pulmonary histopathologic changes in rats following acute experimental exposure to chlorine gas	2004
Evans RB	Chlorine: state of the art	2005
Henneberger PK	The incidence of respiratory symptoms and diseases among pulp mill workers with peak exposures to ozone and other irritant gases	2005
Medina-Ramon R	Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study	2005
Mehta AJ	Airflow limitation and changes in pulmonary function among bleachery workers	2005
Beheshti J	Mustard lung secrets: long term clinicopathological study following mustard gas exposure	2006
Bonetto G	Longitudinal monitoring of lung injury in children after acute chlorine exposure in a swimming Pool	2006
Nemery B	Chemical-induced lung injury and its long-term sequelae	2006
Pauluhn J	Acute nose-only exposure of rats to phosgene. Part I: concentration x time dependence of LC50s, nonlethal-threshold concentrations, and analysis of breathing patterns	2006
Vohra R	Chlorine-related inhalation injury from a swimming pool disinfectant in a 9-year-old girl	2006
Brent J	Of paradigms and paradoxes: unraveling the basis of chlorine poisoning	2008
Ghanei M	An International collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients	2008
Neghab M	Inhalation exposure to low levels of chlorine gas induces reversible impairment of the lung function	2008
Shakeri MS	Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review	2008
Tuck SA	Time course of airway remodelling after an acute chlorine gas exposure in mice	2008

First Author	Title	Year
Anduja P	Acute and subacute chemical pneumonitis	2009
Malo J-L	Long-term outcomes of acute irritant-induced asthma	2009
Malo J-L	Long-term outcomes of acute irritant-induced asthma	2009
Mishra PK	Bhopal gas tragedy: review of clinical and experimental findings after 25 years	2009
Takeda N	Long-term pathologic consequences of acute irritant-induced asthma	2009
Al B	Histopathological study of short and long-term pulmonary effects of nebulized sodium bicarbonate treatment in chlorine gas exposed rats	2010
Bhopal Gas Disaster Research Centre	Health effects of the toxic gas leak from union carbide methyl isocyanate plant in Bhopal	2010
Clark K	Millworker lung function decline following a large chlorine spill event	2010
Mohan A	Acute accidental exposure to chlorine gas: clinical presentation, pulmonary functions and outcomes	2010
Pesonen M	Capsaicinoids, chloropicrin and sulfur mustard: possibilities for exposure biomarkers.	2010
Samal A	Potential for chlorine gas-induced injury in the extrapulmonary vasculature	2010
White CW	Chlorine gas inhalation: human clinical evidence of toxicity and experience in animal models	2010
Collins JJ	Results from the US industry-wide phosgene surveillance: the Diller Registry	2011
Duncan MA	Follow-up assessment of health consequences after a chlorine release from a train derailment – Graniteville, SC, 2005.	2011
King MS	Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan	2011
McGovern T	AEOL10150: a novel therapeutic for rescue treatment after toxic gas lung injury	2011
Meng G	Long-term effect of a single perfluoroisobutylene exposure induced acute lung injury in mice	2011
Senthilkumar CS	Cancer morbidity among methyl isocyanate exposed long-term survivors and their offspring: a hospital-based 5 year descriptive study (2006 - 2011) and future directions to predict cancer risk in the affected population	2011
Song W	Postexposure administration of a beta(2)-agonist decreases chlorine-induced airway hyperreactivity in mice	2011

First Author	Title	Year
Akamatsu A	Six-month low level chlorine dioxide gas inhalation toxicity study with 2-week recovery period in rats	2012
De S	Retrospective analysis of lung function abnormalities of Bhopal gas tragedy affected population	2012
Mishra PK	A pragmatic and translational approach of human biomonitoring to methyl isocyanate exposure in Bhopal	2012
Chen J	Inhibition of chlorine-induced pulmonary inflammation and edema by mometasone and budesonide	2013
Chierakul N	Respiratory health effect of persons accidentally expose to high concentration of chlorine gas	2013
Jonasson S	Inhalation of chlorine causes long-standing lung inflammation and airway hyperresponsiveness in a murine model of chemical-induced lung injury	2013
Jonasson S	Early treatment of chlorine-induced airway hyperresponsiveness and inflammation with corticosteroids	2013
Kreiss K	Occupational causes of constrictive bronchiolitis	2013
Meza F	Evaluation of health effects of a chlorine gas release in a poultry processing plant - Arkansas	2013
Mo Y	Differential susceptibility of inbred mouse strains to chlorine-induced airway fibrosis	2013
O'Koren EG	Loss of basal cells precedes bronchiolitis obliterans-like pathological changes in a murine model of chlorine gas inhalation	2013
Guidotti TL	Bronchiolitis obliterans	2014
Mackie E	Management of chlorine gas-related injuries from the Graniteville, South Carolina, train derailment	2014
Massa CB	Acute chlorine gas exposure produces transient inflammation and a progressive alteration in surfactant composition with accompanying mechanical dysfunction	2014
Cummings KJ	Occupational and environmental bronchiolar disorders	2015
Jurkuvenaite A	Upregulation of autophagy decreases chlorine-induced mitochondrial injury and lung inflammation	2015
Kerger BD	Pathology, toxicology, and latency of irritant gases known to cause bronchiolitis obliterans	2015
Mishra PK	Molecular bio-dosimetry for carcinogenic risk assessment in survivors of bhopal gas tragedy	2015
Mo Y	Abnormal epithelial structure and chronic lung inflammation after repair of chlorine-induced airway injury	2015
Mo YQ	Abnormal epithelial structure and chronic lung inflammation after repair of chlorine-induced airway injury	2015

First Author	Title	Year
Senthilkumar CS	Increased micronucleus frequency in peripheral blood lymphocytes contributes to cancer risk in the methyl isocyanate-affected population of Bhopal	2015
Wigenstam E	N-acetyl cysteine improves the effects of corticosteroids in a mouse model of chlorine-induced acute lung injury	2015
Zholos AV	TRP channels in respiratory pathophysiology: the role of oxidative, chemical irritant and temperature stimuli	2015

APPENDIX C

FEASIBILITY STUDY SUBJECT MATTER EXPERTS

Listed below are the 10 SMEs who particpated in the lower pulmonary toxidrome feasibility study.

Table C-1. List of Feasibility Study Core and Value SMEs

SME Type	Name	Affiliation	Qualifications
Core and Value	Terry Gordon	New York University School of Medicine	PhD in toxicology with expertise in inhalation toxicology, air pollution, genetic susceptibility, and occupational health.
Core and Value	James Madsen	US Army Medical Research Institute of Chemical Defense	Board-certified in anatomic pathology, clinical pathology, occupational medicine, and medical toxicology. Extensive teaching and publishing in the medical management of chemical-warfare-agent casualties.
Core and Value	Charles McKay	American College of Medical Toxicology (ACMT)	Board-certified in medical toxicology, emergency medicine, and internal medicine with training in anatomic pathology. Medical Director of a regional poison center.
Value	Michael Beuhler	ACMT	Board-certified in medical toxicology and emergency medicine.
Value	Adolph Januszkiewicz	APHC	PhD in pharmacology and toxicology with expertise in human and animal physiology and pulmonary toxicology.
Value	Charles McCannon	APHC	Board-certified in public health and preventive medicine.
Value	Arthur O'Neill	APHC	BS in biology with over 25 years of experience in inhalation toxicology.
Value	Andrew Stolbach	ACMT	Board-certified in medical toxicology and emergency medicine.
Value	Paul Wax	ACMT	Board-certified in medical toxicology and emergency medicine.
Value	George Woodall	U.S. Environmental Protection Agency	PhD in toxicology, with specialties including assessment of health risks posed by toxic chemicals and acute inhalation risk assessment.

APPENDIX D

INDIVIDUAL SME INPUTS TO THE FEASIBILITY STUDY

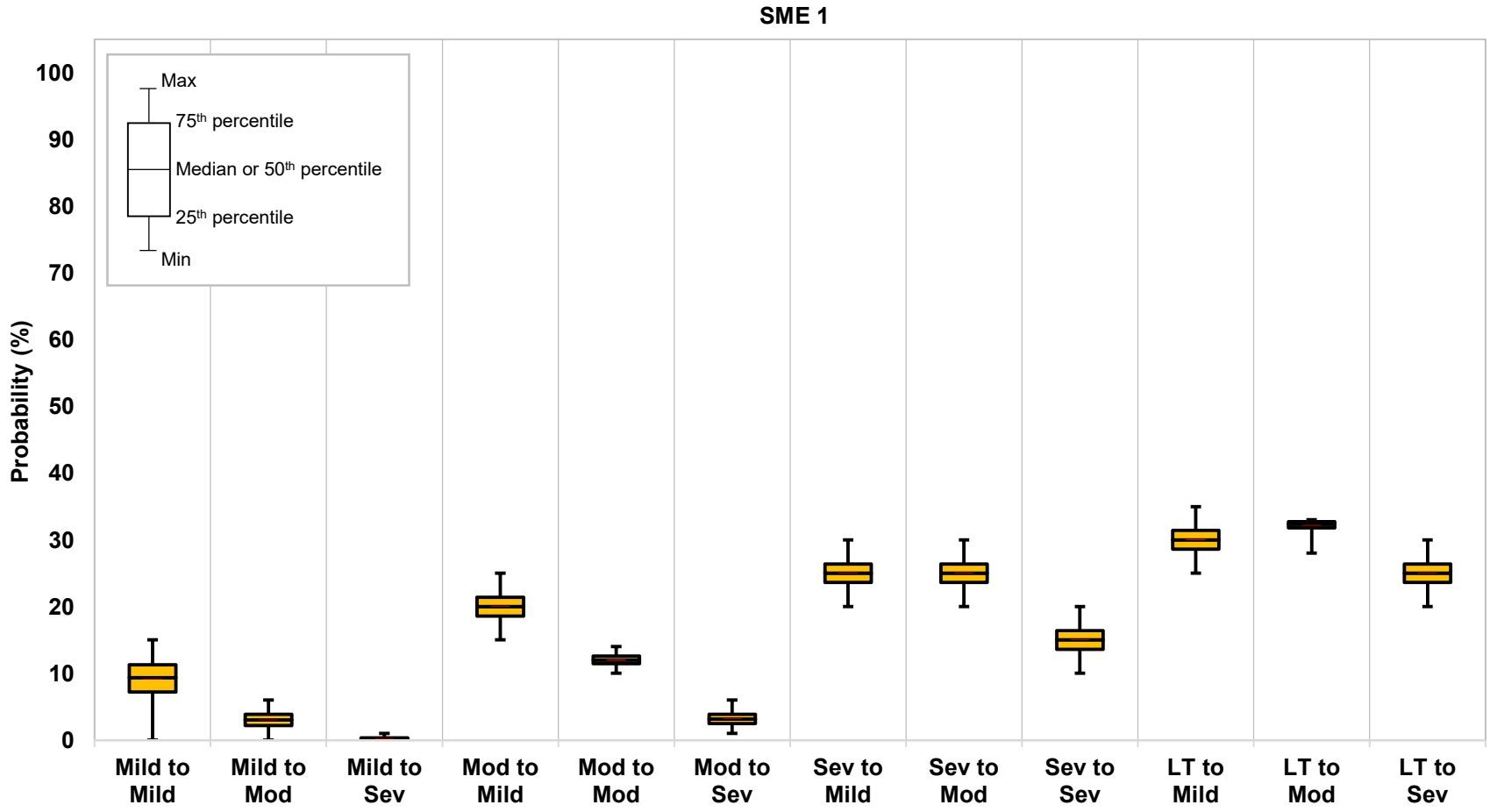

Figure D-1. SME1 Input to the Feasibility Study

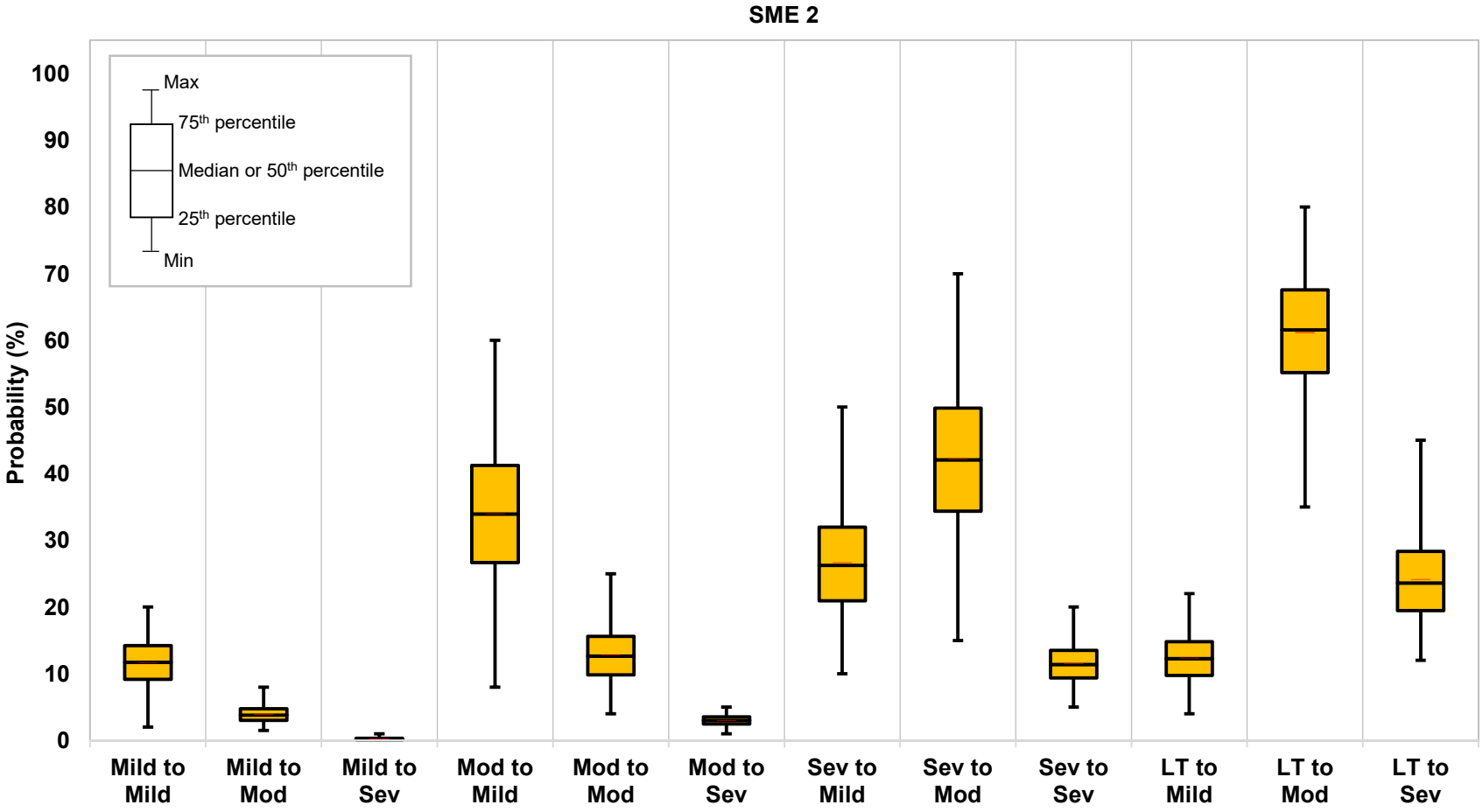

Figure D-2. SME2 Input to the Feasibility Study

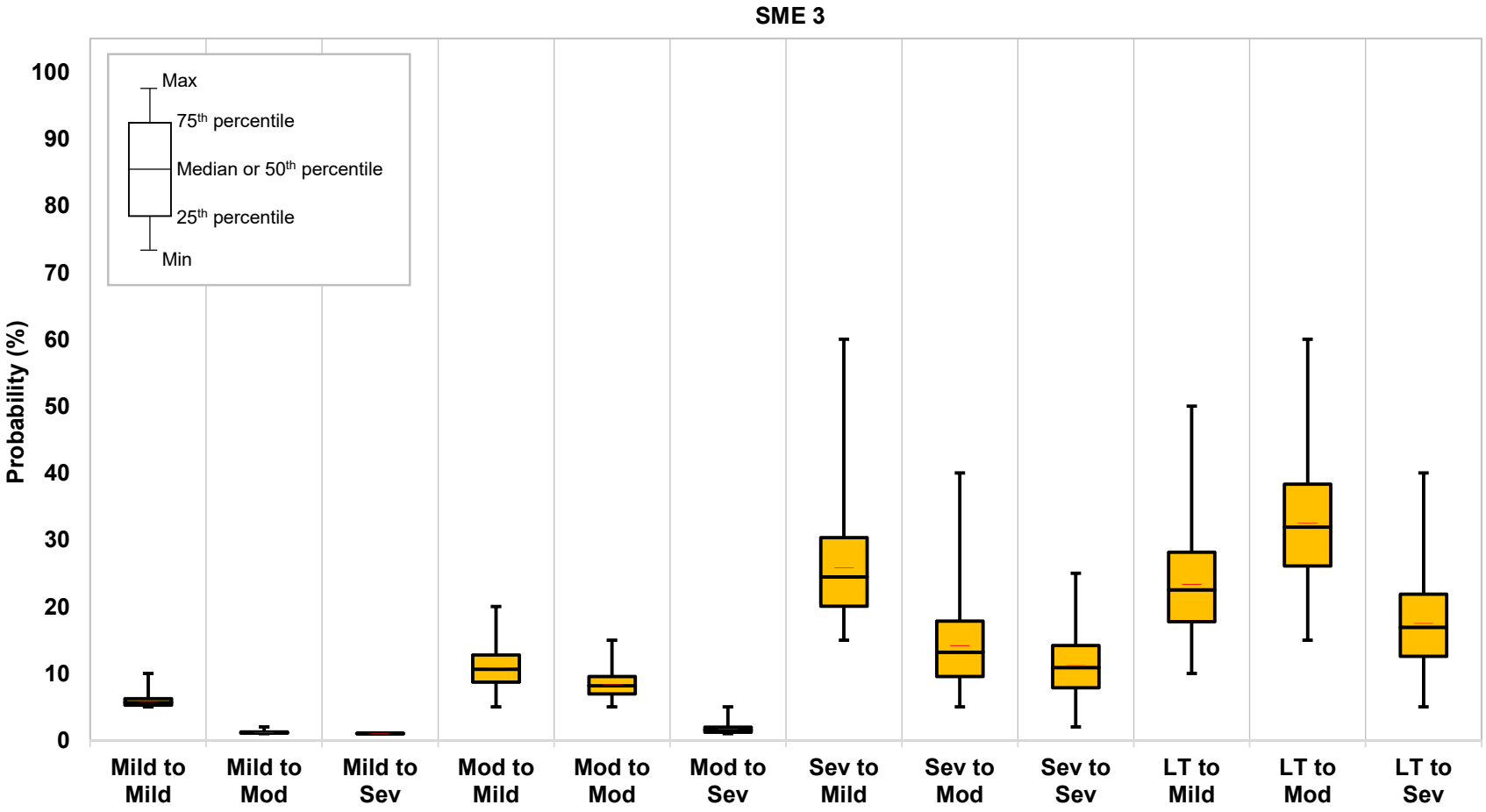

Figure D-3. SME3 Input to the Feasibility Study

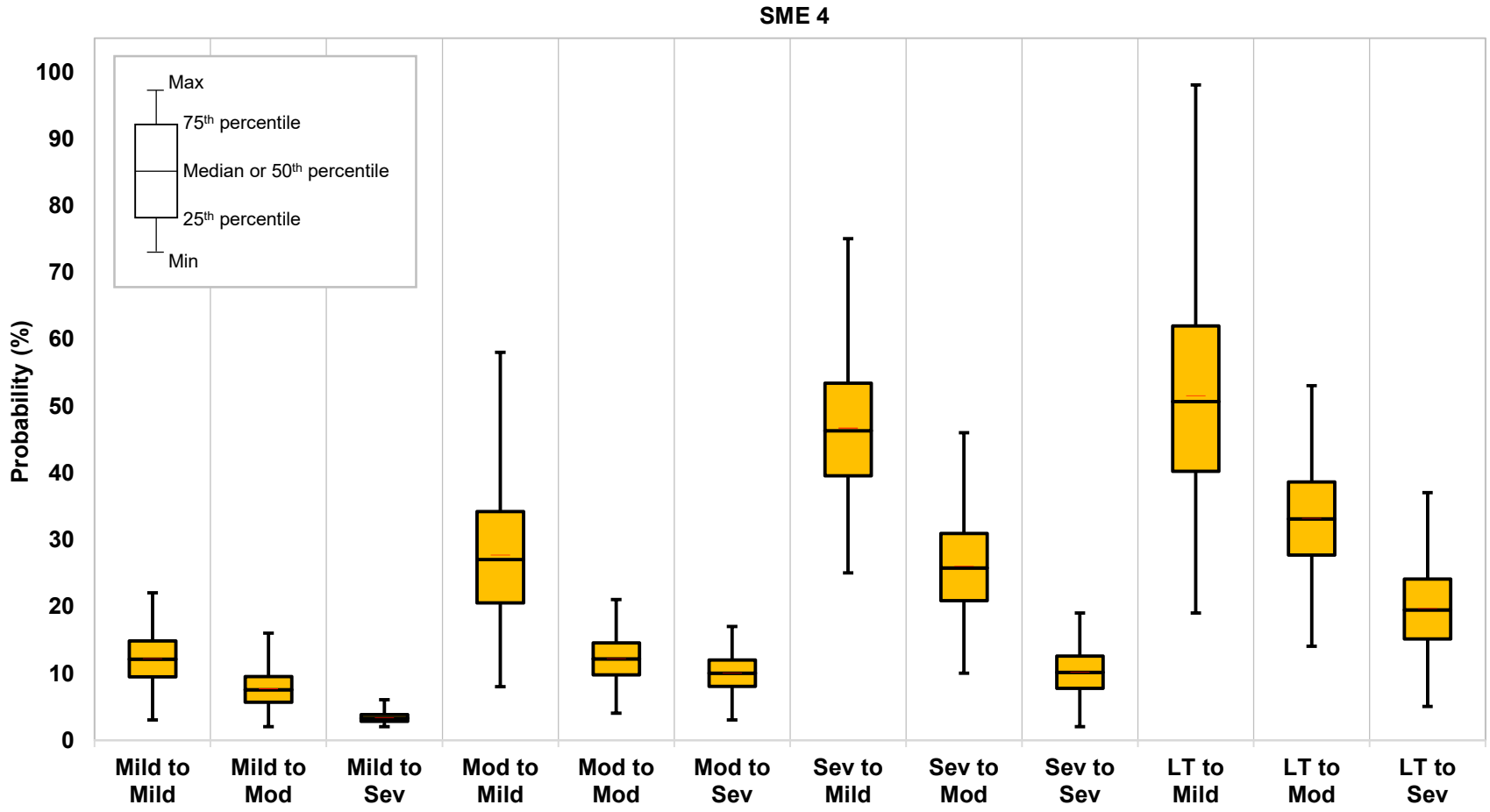

Figure D-4. SME4 Input to the Feasibility Study

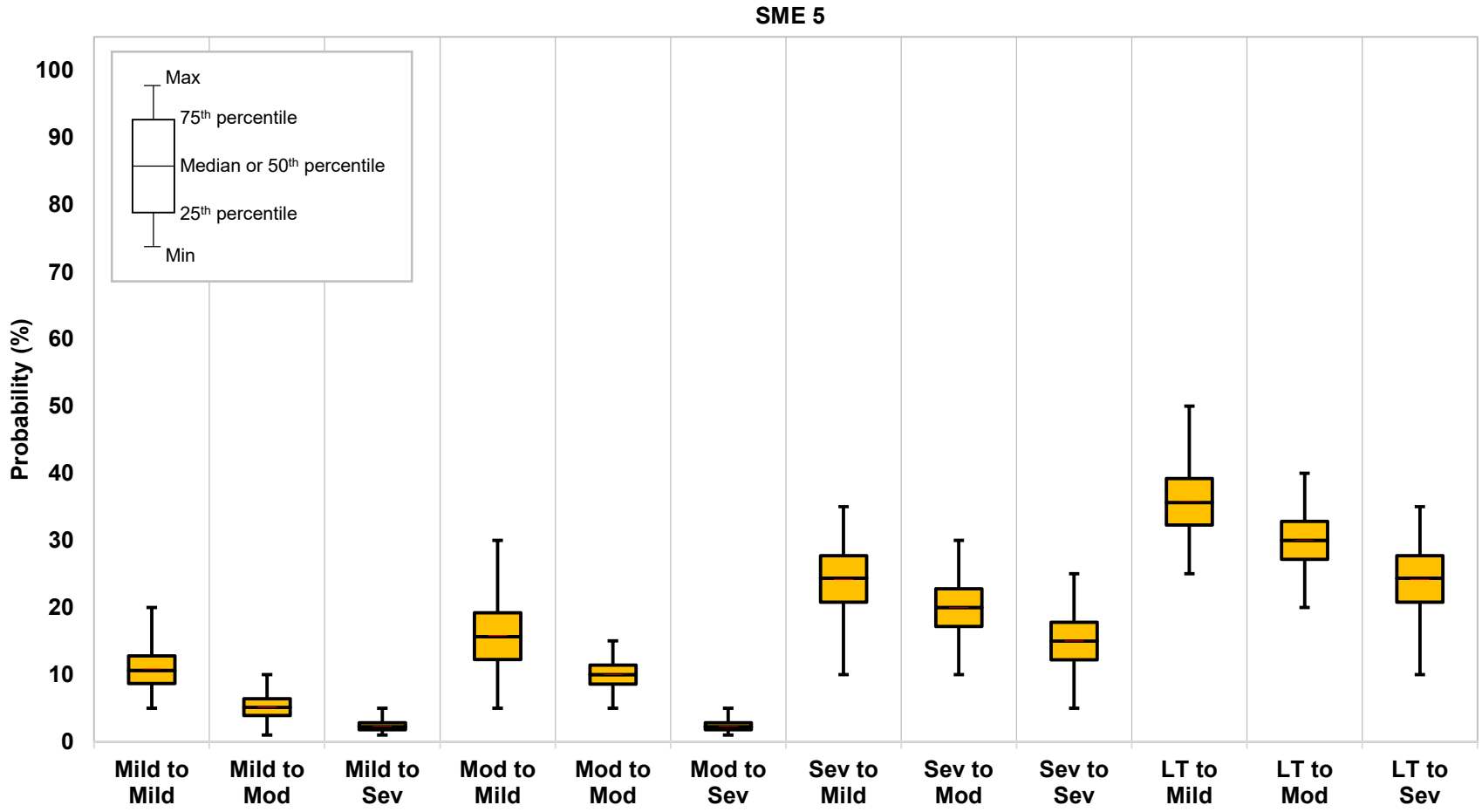

Figure D-5. SME5 Input to the Feasibility Study

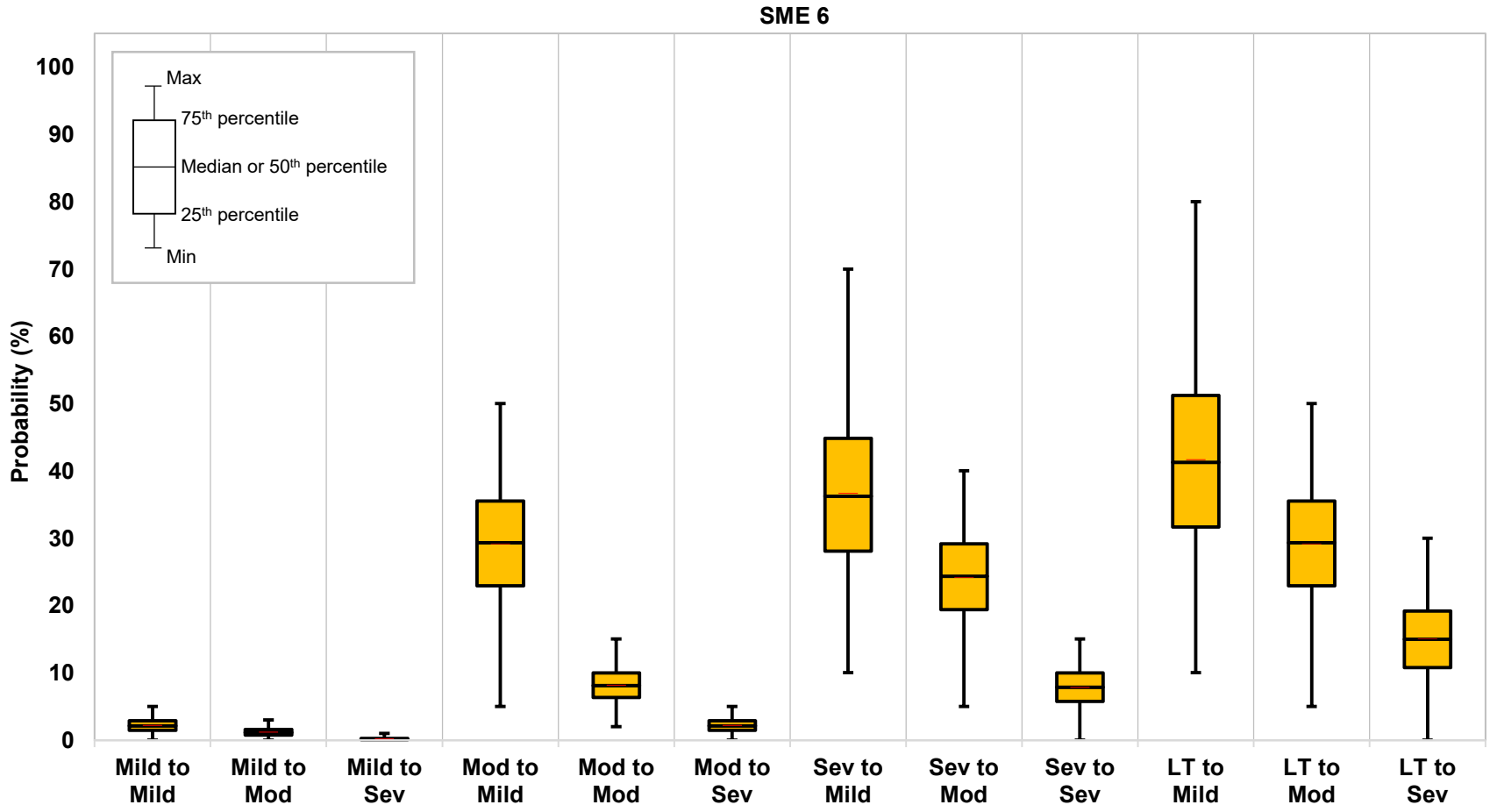

Figure D-6. SME6 Input to the Feasibility Study

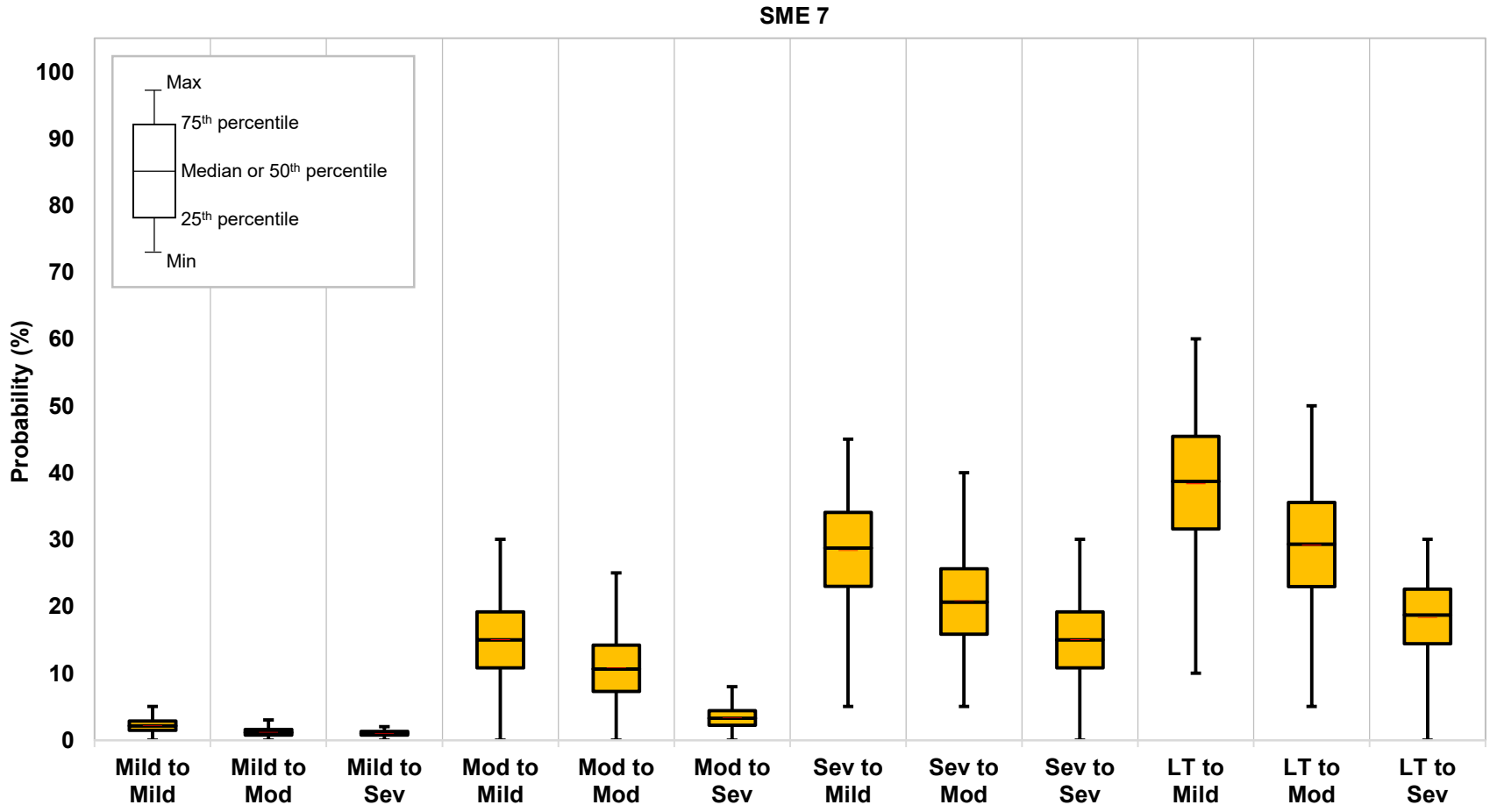

Figure D-7. SME7 Input to the Feasibility Study

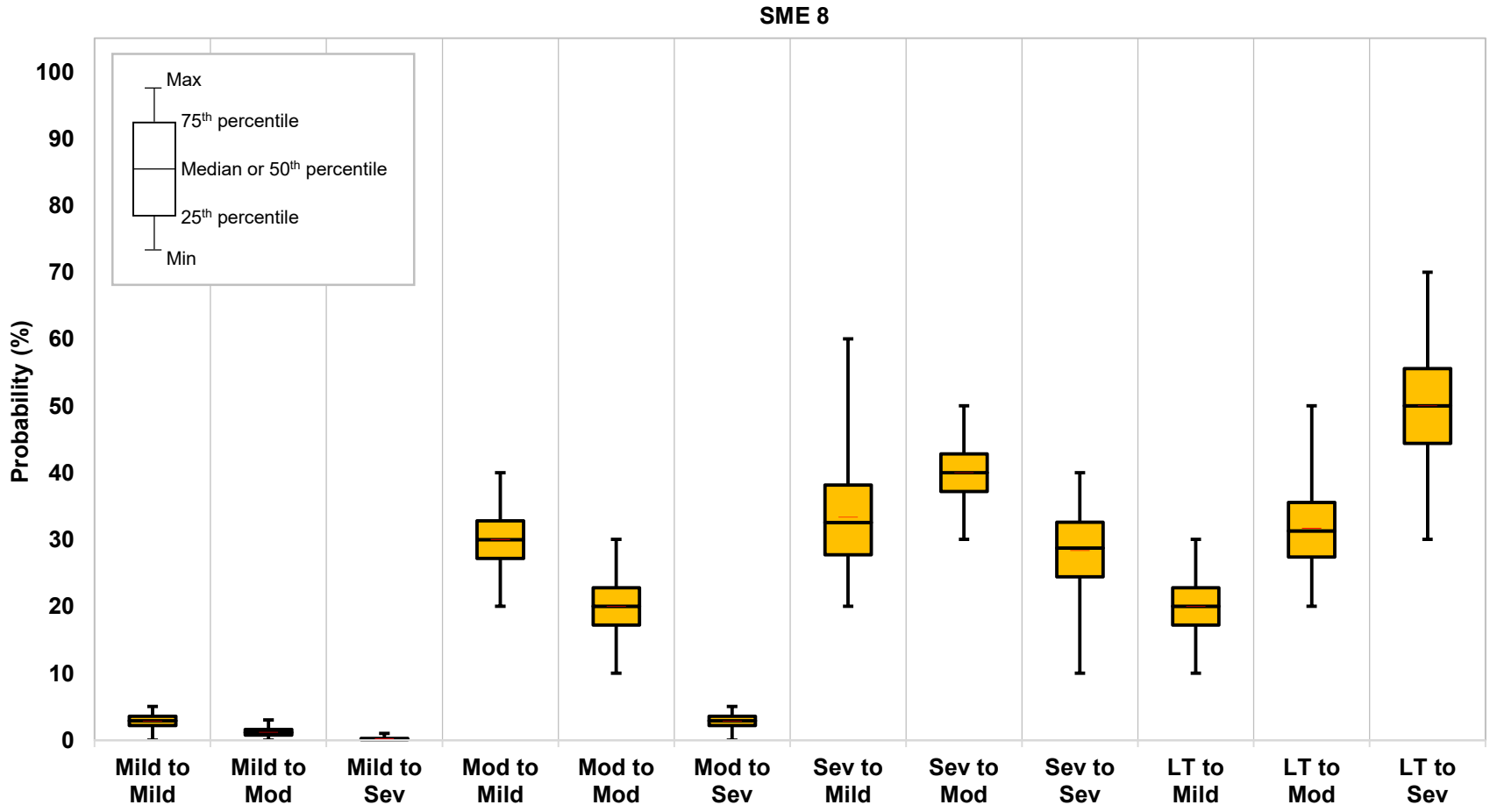

Figure D-8. SME8 Input to the Feasibility Study

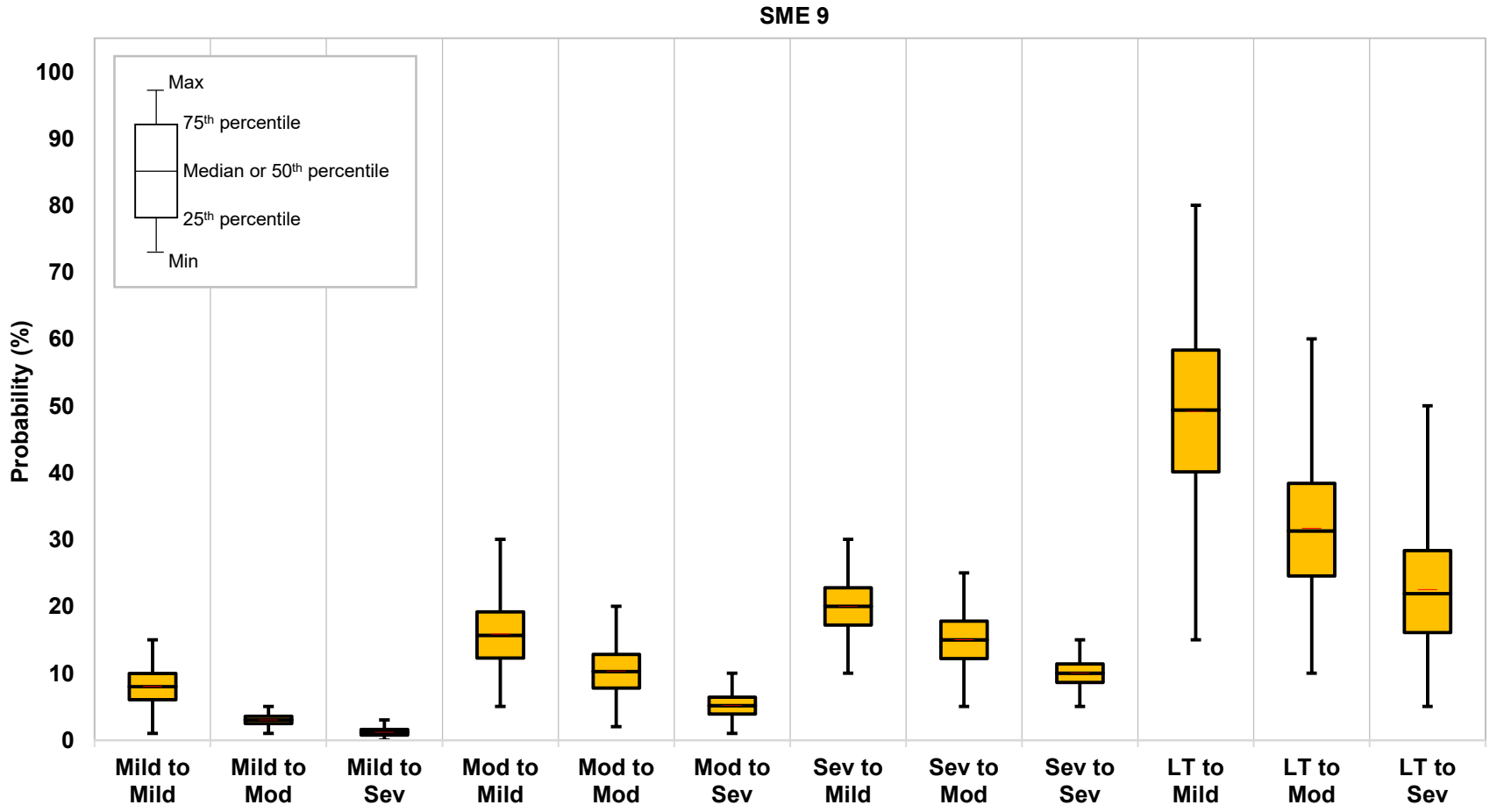

Figure D-9. SME9 Input to the Feasibility Study

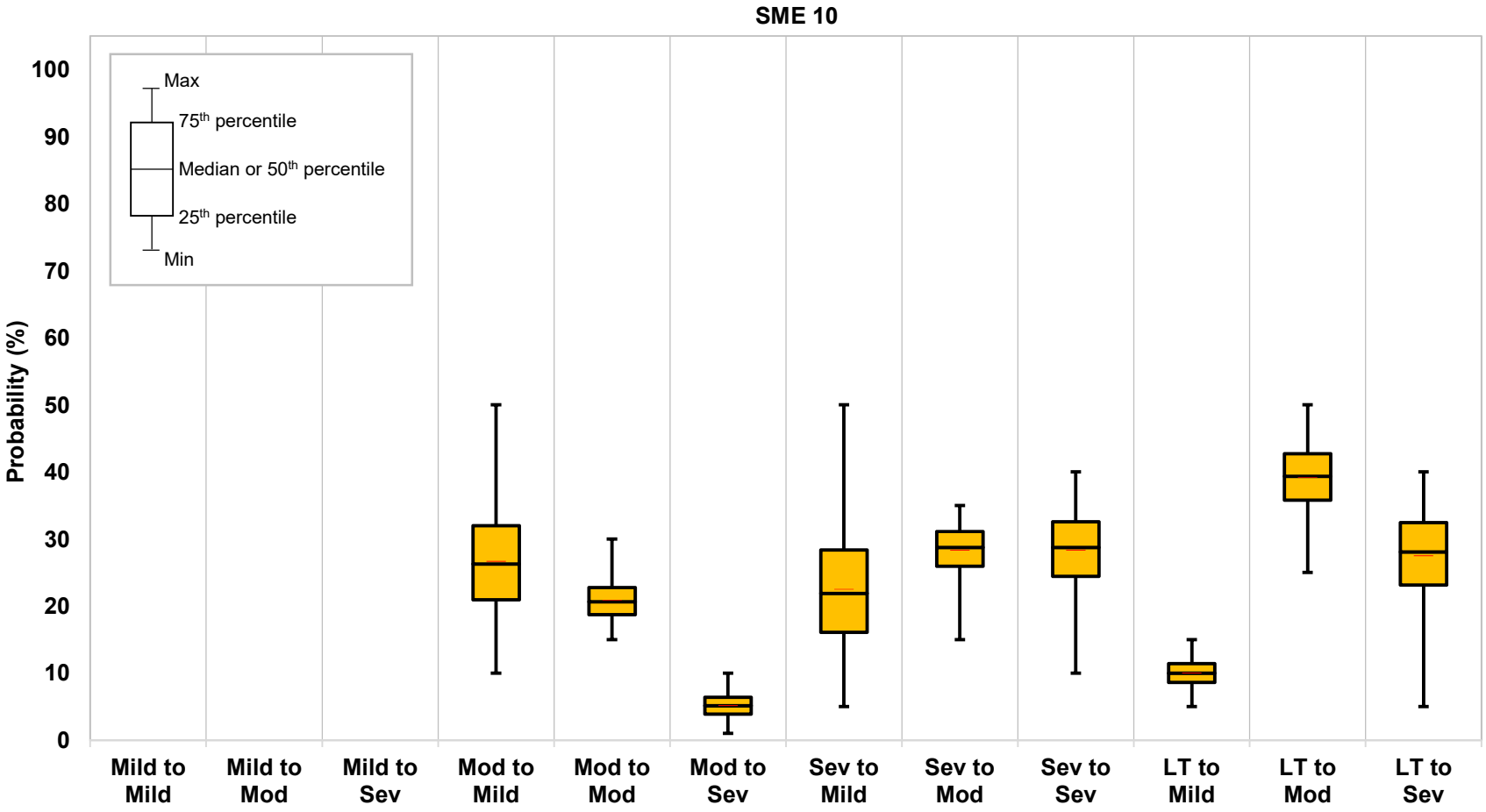

Figure D-10. SME10 Input to the Feasibility Study

APPENDIX E

NOTES ON SME REVIEW MEETING DISCUSSIONS

This section provides a high-level summary of SME discussions during the review meeting. The summaries are presented in groups of three (where a given group contains the same acute exposure estimates [e.g., mild acute to mild long-term, mild acute to moderate long-term, and mild acute to severe long-term]).

Mild Acute Effects:

- Although there was essentially no literature data on which to base estimates, SME consensus was that these likelihood estimates should be low.
- An SME commented that there are animal studies in which life-threatening exposures showed little to no long-term effects. Thus, it is difficult to justify a mild acute exposure having any significant likelihood of long-term effects.
- In the discussion of mild acute to mild long-term, an SME commented that because the mild acute effect resolves (according to the definition of mild effects), an average likelihood greater than 10% is difficult to justify.
- SMEs viewed the estimates as having logical, appropriate decreases as the long-term effects become more severe.
- Overall, there was limited discussion on these estimates given that there was largely good agreement among the SMEs and a lack of literature data.

Moderate Acute Effects:

- SMEs felt that unlike previous estimates for mild acute effects, estimates for moderate acute effects could be informed to a limited degree by leveraging/interpreting literature data; SMEs described using literature data to estimate rough, quantitative acute to long-term probabilities.
- Multiple SMEs mentioned the methyl isocyanate release in Bhopal as an event that had useful data; SMEs specifically identified the Vijayan (1998) and Cullinan (1997) references from the reference packet. For example, of 31 Bhopal victims described as moderately exposed in the Vijayan reference, 12 (39%) showed abnormal pulmonary function.
- Several SMEs used the Vijayan data point to structure their estimates for moderate acute effects. They noted, however, that a breakdown of the severity of the long-term pulmonary abnormalities was not provided and thus had to be estimated. In addition, there were minimal details on the exposure. In general, SMEs described difficulties binning literature data into the different health effect categories (for both acute and long-term effects). Cullinan (1997), for example, provided separate overall population data for subjects having cough, phlegm, dyspnea and wheeze, and spirometry results. These comments apply to this and subsequent estimates that utilized this literature.
- Some SMEs utilized animal studies in addition to or rather than the human studies.
- While SMEs described leveraging/interpreting the literature data, the degree to which SMEs balanced literature data with personal experience/expertise varied.
- The SMEs agreed that all responses were within normal or acceptable limits of judgment and interpretation of the limited literature data.

Severe Acute Effects:

- Similar to the previous estimates for moderate acute effects, estimates for severe acute effects could be informed by leveraging/interpreting literature data; SMEs described using literature data to estimate rough, quantitative acute to long-term probabilities.
- The methyl isocyanate release in Bhopal was again specifically mentioned by multiple SMEs as an event that had useful data, with Vijayan (1998) and Cullinan (1997) once again being

discussed. For example, of 49 Bhopal victims described as severely exposed in the Vijayan reference, 31 (63%) showed abnormal pulmonary function.

- As with the moderate acute effect estimates, several SMEs used the Vijayan data to structure their estimates for severe acute effects. Some SMEs specifically discussed the total number of long-term effects (mild + moderate + severe) for severe acute exposures, with ~80–85% being noted by an SME as his assumed average (i.e., the sum of his means would be around 80–85%). Another SME thought this was reasonable given that the 63% value from Vijayan likely included moderate and severe long-term effects but not mild.
- As with the moderate acute effect estimates, other SMEs utilized animal studies in addition to or rather than the human studies. An SME noted that that there were many instances with severe acute effects but no long-term effects (which would support lower likelihood estimates). Other SMEs concurred.
- Additional SME discussions noted the challenges associated with interpreting biopsy findings in animal studies and how they correlate to functional losses. The SMEs recognized that this challenge is one reason why this feasibility study was undertaken and that there is room for differences in interpretation of these types of studies.
- While SMEs described leveraging/interpreting the literature data, the degree to which SMEs balanced literature data with personal experience/expertise varied.
- Most SMEs believed that given a severe acute health effect, the most likely (if any) long-term effect would be mild, followed by moderate, and then severe (i.e., a monotonically decreasing triplicate). Other SMEs did not follow this trend. For example, SME8 suggested that moderate long-term effects would predominate (an inverted-U triplicate).
- The SMEs agreed that all responses were within normal or acceptable limits of judgment and interpretation of the limited literature data.

Life-Threatening Acute Effects:

- The majority of the discussion of life-threatening acute effects centered on the trends of this triplicate of estimates, rather than on specific literature data. For example, an SME explained how he started by devising an estimate for the moderate long-term effects (with most survivors falling into this group) and then filled in the mild and life-threatening estimates around the moderate estimate. As mentioned in the previous section, this SME's triplicate of estimates represents an "inverted-U" shape. This SME specifically mentioned studies by Ferguson and Alarie (1991) and Harkonen et al. (1983); the SME noted that in the Harkonen study, 100% of subjects had moderate long-term illness.
- Another SME explained how his estimates are unique in that they are monotonically increasing, meaning that a severe long-term outcome was more likely than a moderate or mild long-term outcome, and a moderate long-term outcome was more likely than a mild long-term outcome. His rationale was that if the individuals had experienced life-threatening acute effects (and thus perhaps should have died), their long-term effects would be severe, and that some subset would have lesser effects (mild or moderate) pending their ability to get adequate treatment. This SME briefly mentioned that the Cullinan (1997) study results at distances close to the release suggested a trend other than monotonically decreasing.
- SMEs that estimated a monotonically decreasing triplicate suggested that it was a more intuitive approximation.
- SMEs may have approached these relationships differently, but all relationships were considered to be valid estimates. The SMEs reiterated that there is limited quantitative evidence in the literature and with this limited evidence, it is simply an SME judgment as to how to interpret and apply that limited evidence in this elicitation exercise.
- An SME described his efforts to use the literature data to form strictly literature-based results, but the approach "fell apart" because of the heterogeneity among the limited data. For example, one

source indicated an 80% probability of effect while another study indicated 6%. This SME's analysis points to the need for this study.

- One SME commented that the current results indicate that a life-threatening acute effect will almost certainly lead to some type of long-term effect as an interesting and potentially meaningful result.

APPENDIX F

ADDITIONAL LONG-TERM HEALTH EFFECT CURVES DERIVED FROM EXISTING ACUTE EFFECT DOSE-PROBIT ESTIMATES

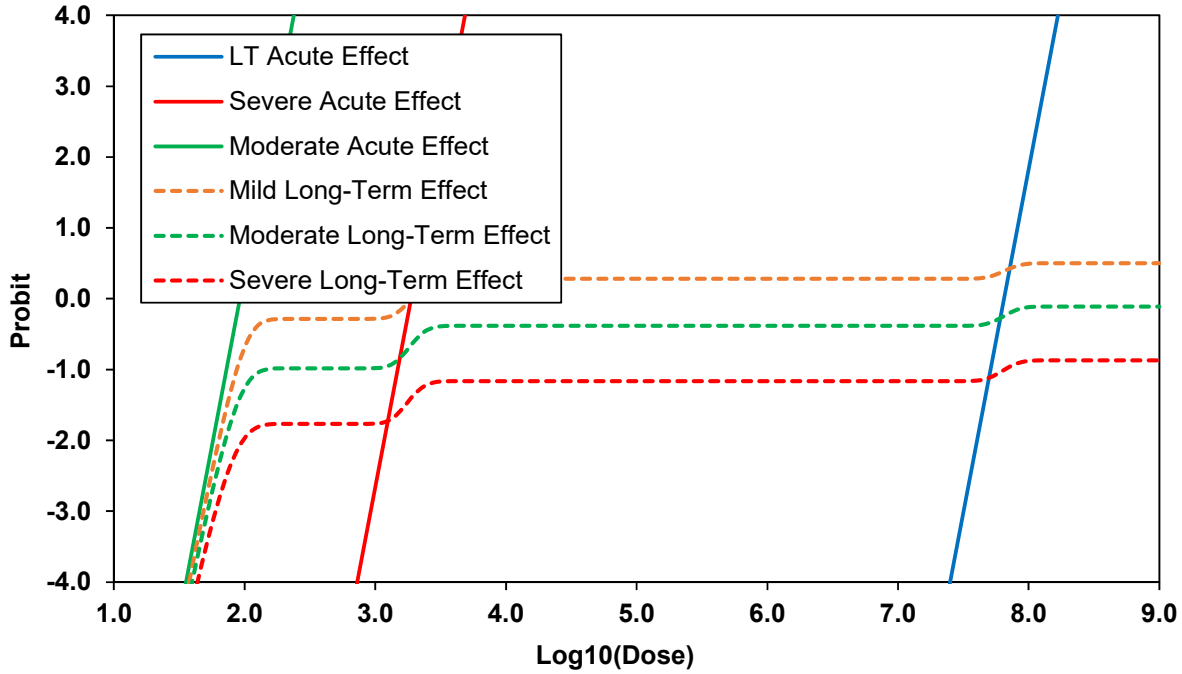

Figure F-1. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Bromine

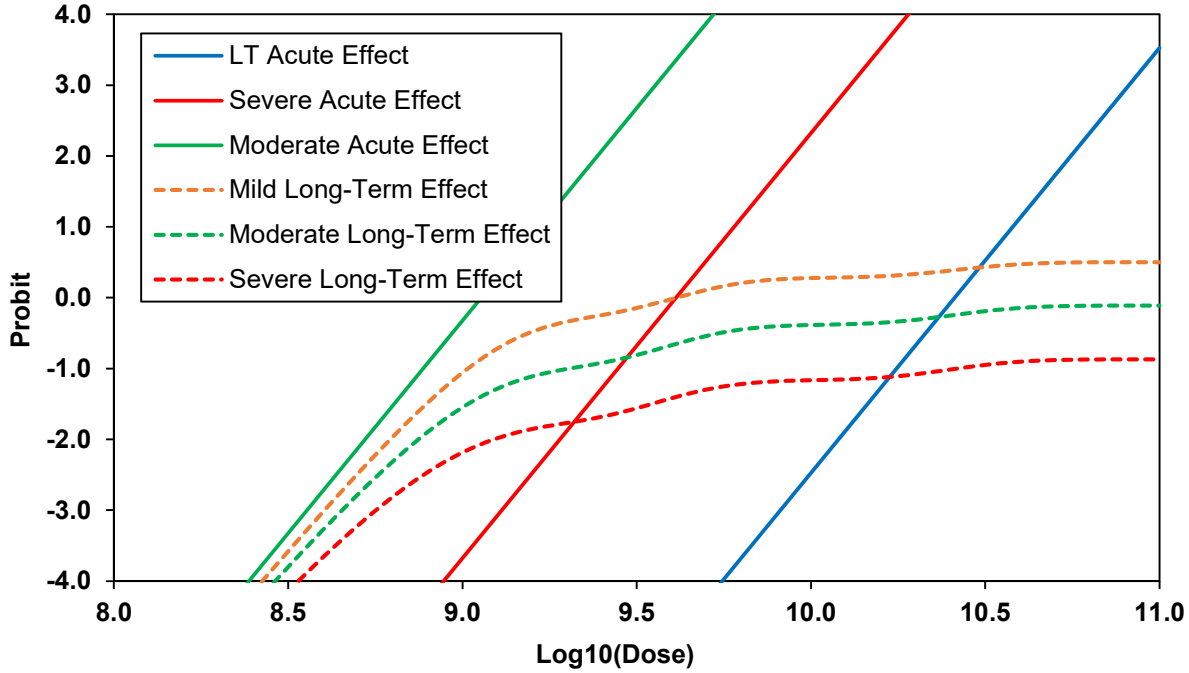

Figure F-2. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Chlorine

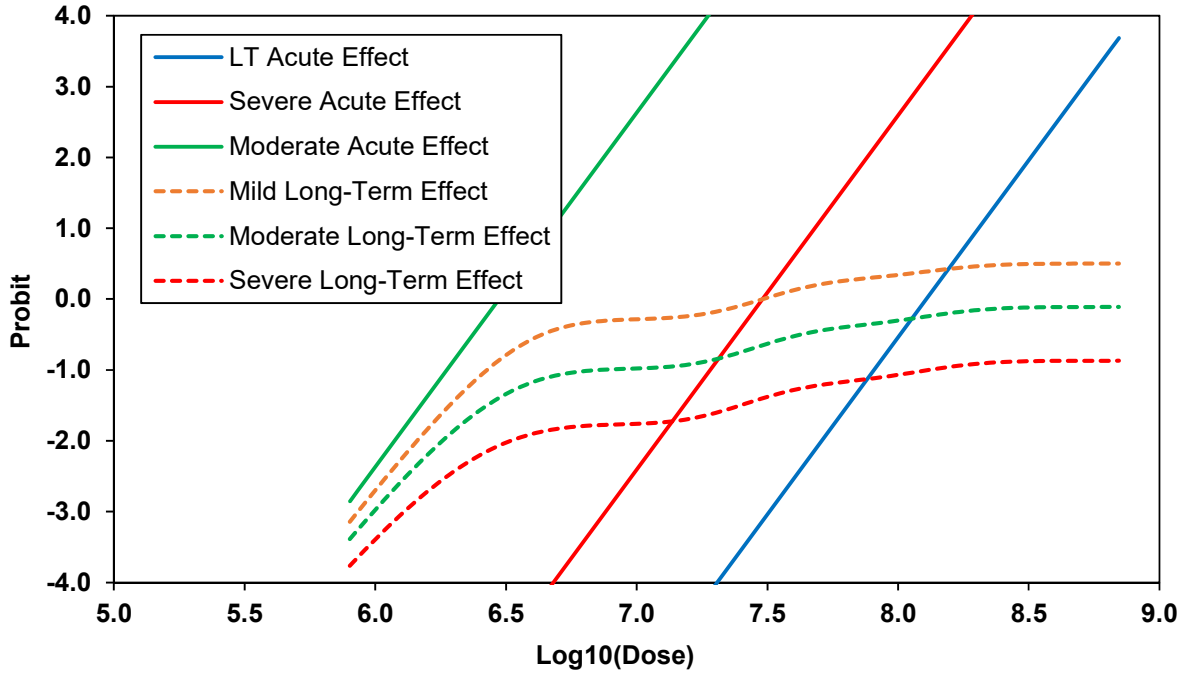

Figure F-3. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Chlorine Dioxide

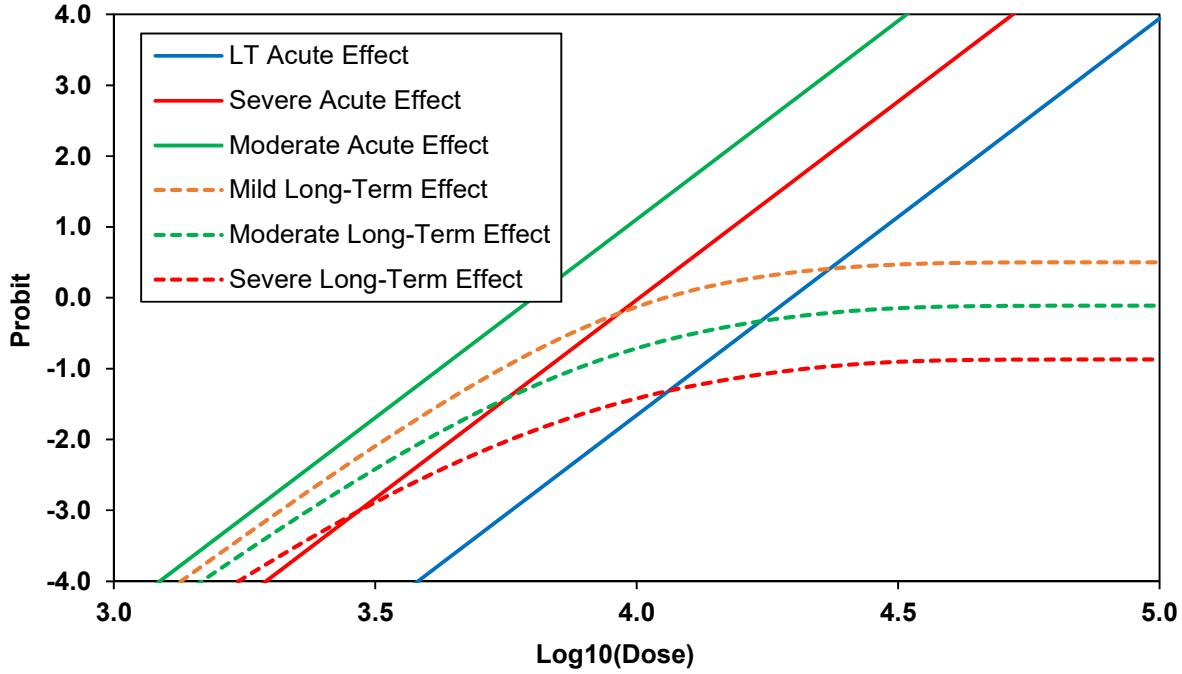

Figure F-4. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Chloropicrin

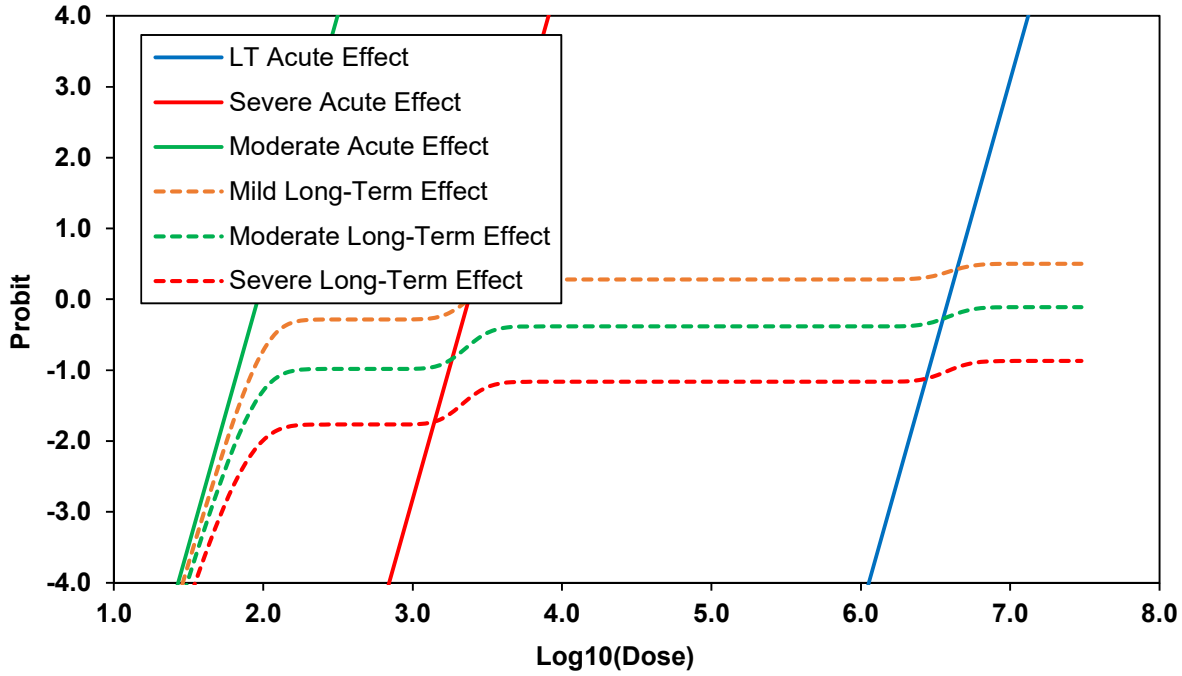

Figure F-5. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Dimethyl Sulfate

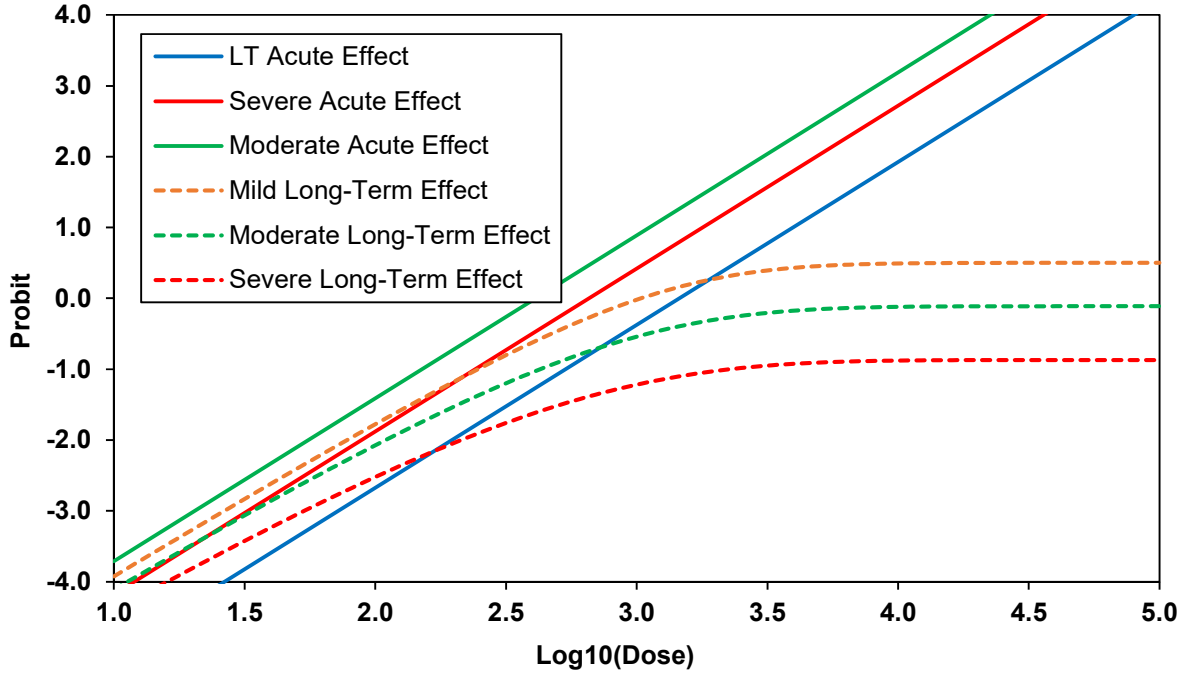

Figure F-6. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Ethyl Isocyanate

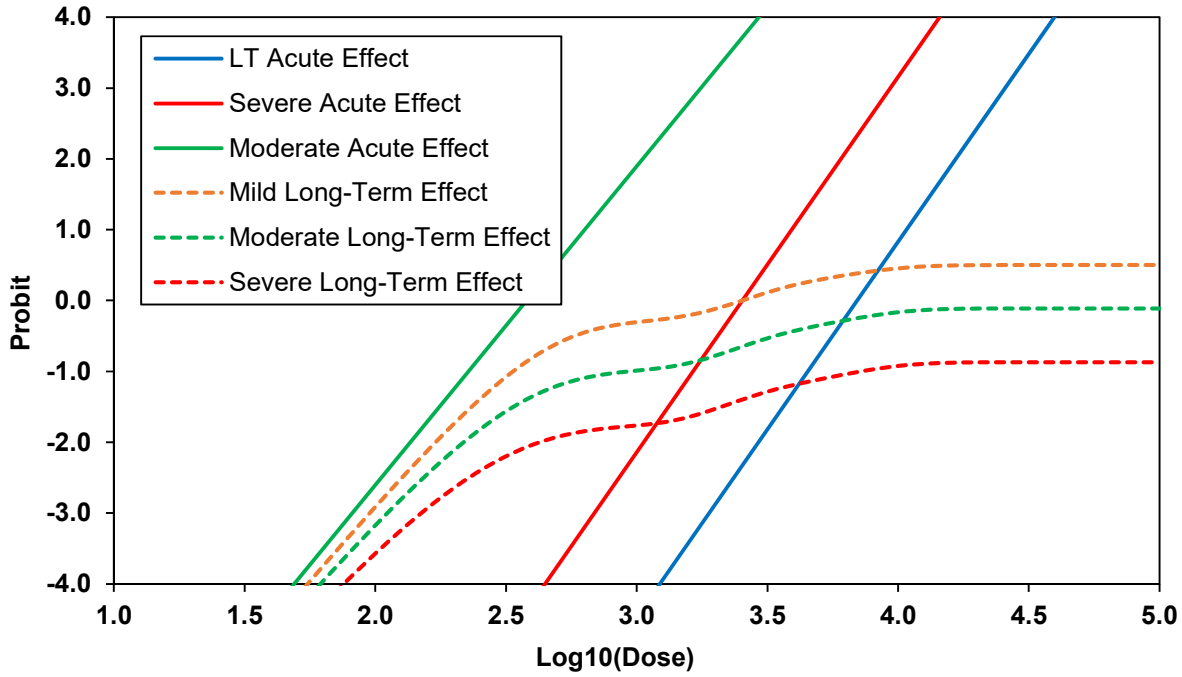

Figure F-7. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Hexachlorocyclopentadiene

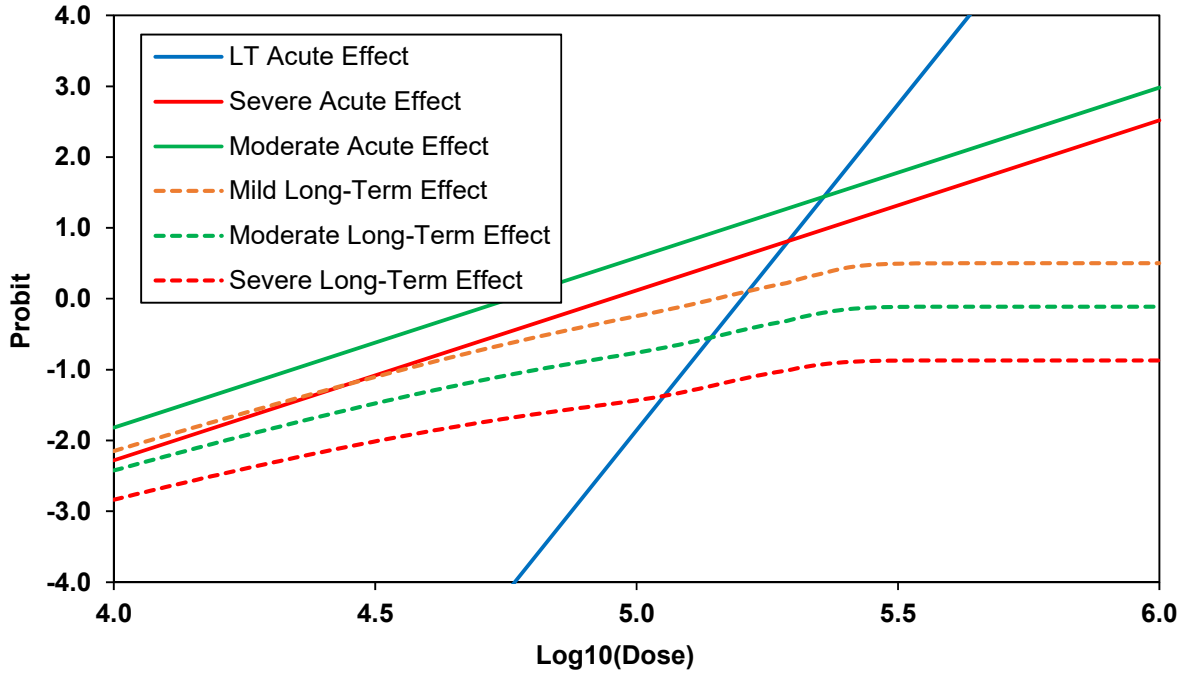

Figure F-8. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Hydrogen Selenide

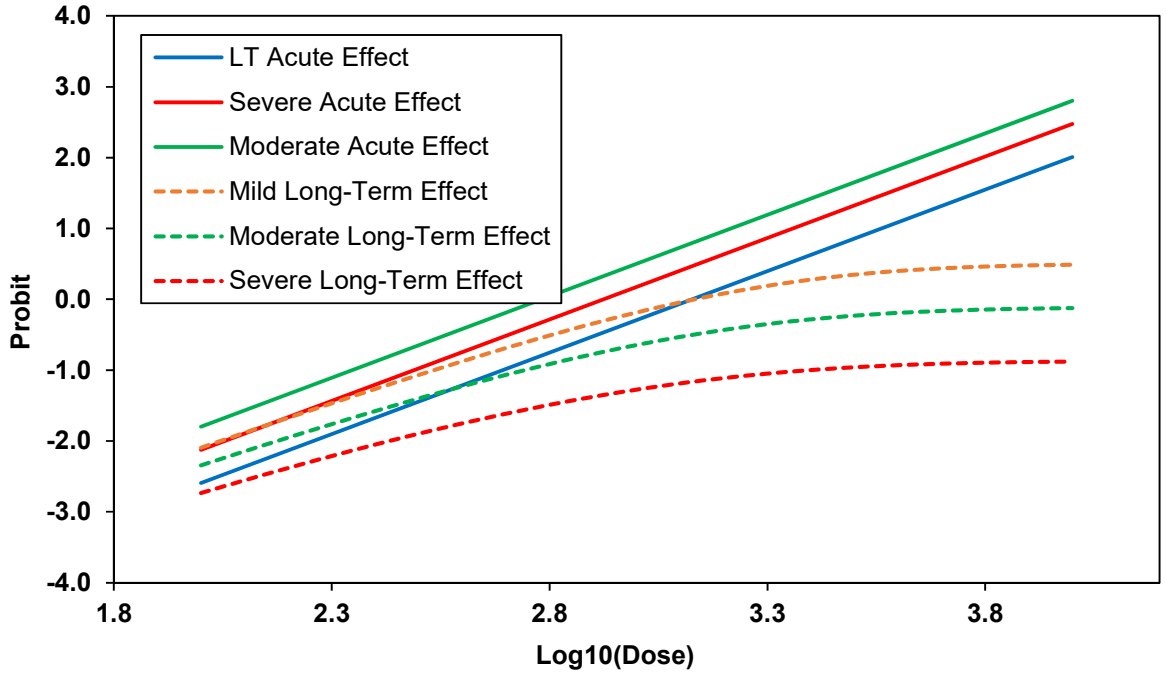

Figure F-9. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Methyl Isocyanate

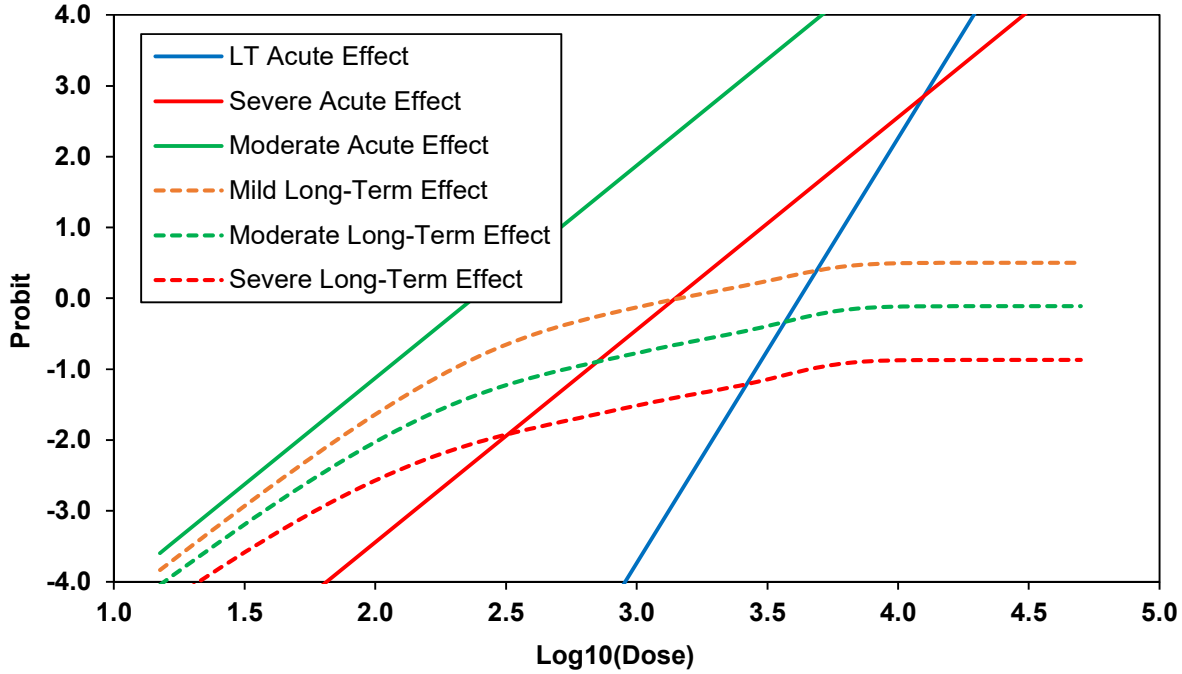

Figure F-10. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Perchloromethyl Mercaptan

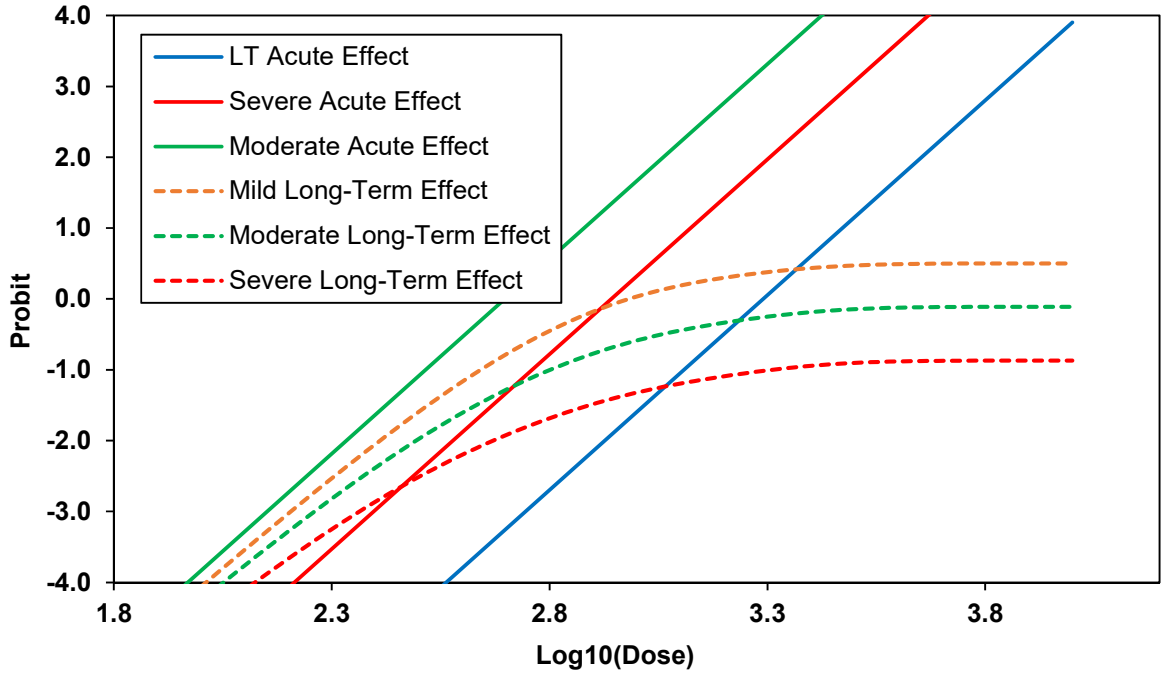

Figure F-11. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Perfluoroisobutene

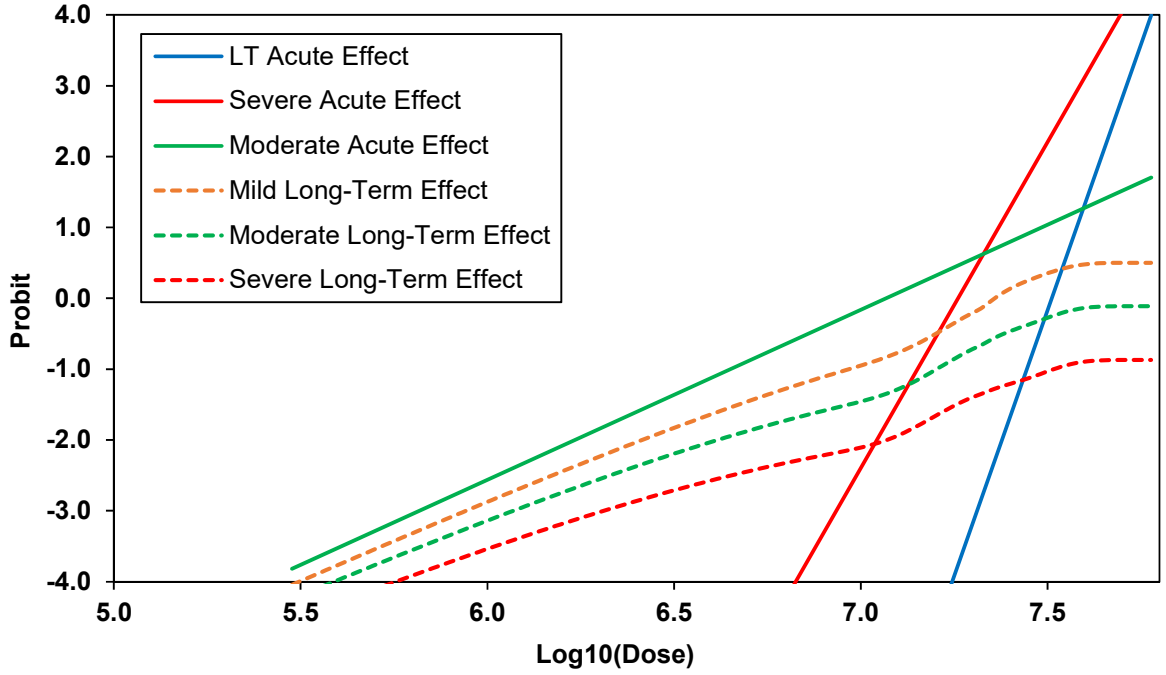

Figure F-12. Summed Mild, Moderate, and Severe Long-Term Health Effect Curves Derived from Existing Acute Effect Dose-Probit Estimates for Thiophenol

APPENDIX G

Further Explanation of Capturing Uncertainty in Individual SME Inputs through a BetaPERT Distribution and Formulating a Single Resultant Estimate Distribution

An initial approach based on a systematic review of existing literature data was explored, including an analytical approach focusing on chronic effects from acute chlorine exposures. Such an approach is challenging; however, as chronic effects are not studied as readily or as thoroughly as acute effects. There are very limited human data available for modeling long-term effects following short-term chemical exposures, and animal studies do not always address this exposure-effect paradigm. An alternative approach was developed to address the issue of limited data by collecting toxidrome-based input from subject matter experts (SMEs). The values elicited in this study have inherent uncertainty; this uncertainty was captured by eliciting each SME estimate as a distribution. The equally weighted SME estimates can then be combined into a single, representative distribution, the desired endpoint for the study.

It is common practice in modeling efforts to describe a physical phenomenon through a distribution capturing the uncertainty associated with the value. Distributions are defined using a set number of parameters, each of which relates to a statistic of the phenomenon. Some distribution types are inherently difficult to quantify due to their non-intuitive parameterization. One method to facilitate elicitation of values which are intuitive is through the use of a PERT distribution. A PERT distribution is estimated by requesting three easily quantified values. The following questions are representative of those asked of the SMEs for each acute to chronic pairing:

- What is the most likely probability of long-term effect following this acute effect?
- What is the minimum expected probability of long-term effect following this acute effect?
- What is the maximum expected probability of long-term effect following this acute effect?

In contrast, quantification of uncertainty through the use of a normal distribution is unintuitive and difficult. A normal is parameterized through a mean value and a standard deviation. The mean value may be an intuitive value that an individual unfamiliar with modelling or statistics would be comfortable estimating (i.e. one can ask “What is the average response?”). The standard deviation value, however, is non-intuitive in nature and difficult to quantify.

Following collection of the three responses, the probability of long-term effect following an acute injury is described as a distribution. The distribution is assumed to be a beta distribution, and the parameters are formed into a beta distribution using the following method:

Let:
$a = minimum\ value$
$b = maximum\ value$
$m = mode\ value$
$\mu = mean\ value$
$\alpha = beta\ distribution\ first\ shaping\ parameter$
$\beta = beta\ distribution\ second\ shaping\ parameter$

Then given a, b and m:

$$\mu = \frac{a + b + 4 \cdot m}{6}$$

$$\alpha = \frac{(\mu - m) \cdot (2 \cdot m - b - a)}{(m - \mu) \cdot (b - a)}$$

$$\beta = \frac{\alpha \cdot (b - \mu)}{\mu - a}$$

The probability density function of the response is then described as:

$$P(x) = \frac{x^{\alpha-1} \cdot (1-x)^{\beta-1}}{\frac{\Gamma(\alpha) \cdot \Gamma(\beta)}{\Gamma(\alpha+\beta)}}$$

Where $\Gamma(x)$ is the gamma function evaluated at x.

A notional example illustrating the conversion of SME inputs to distributions is shown below. Table G-1 displays the inputs for three SMEs used in this notional example. Figure G-1 shows the resulting likelihood curves.

Table G-1. Notional SME Input Values

	MINIMUM (%)	MOST LIKELY (%)	MAXIMUM (%)
SME 1	0	5	50
SME 2	0	25	50
SME 3	0	45	50

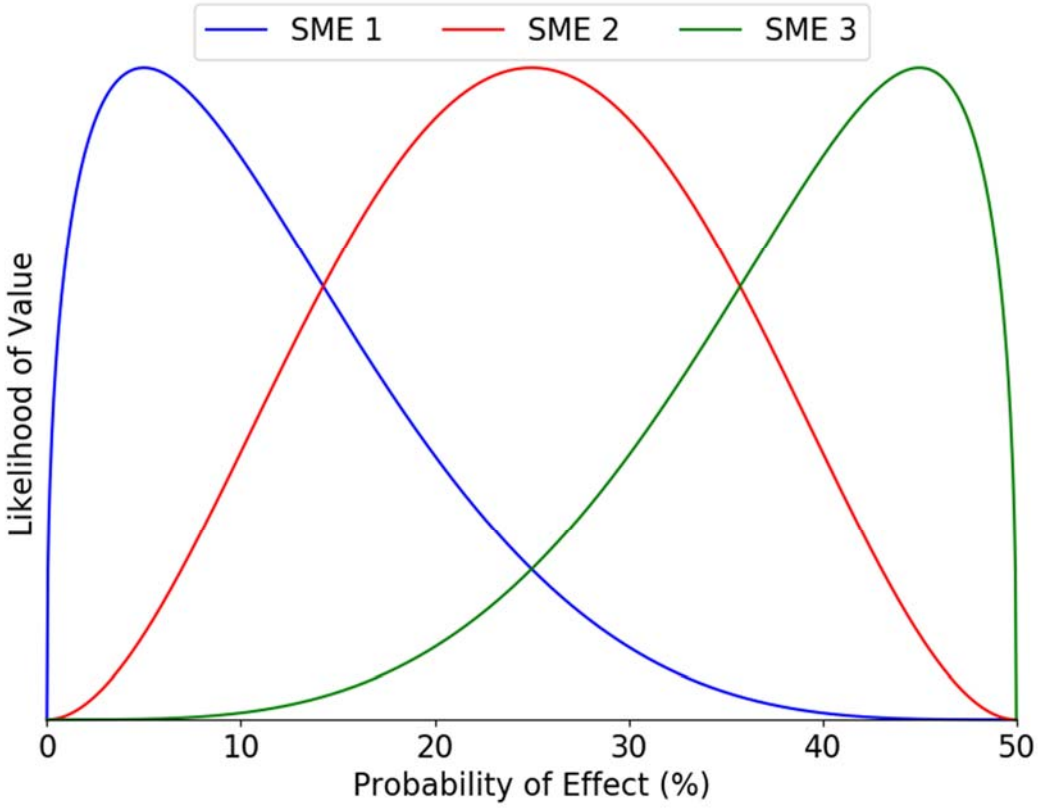

Figure G-1. Distributions Resulting from Notional SME Inputs

Specific percentile values can be calculated by numerically solving the equation shown above for a given $P(x)$. Microsoft Excel™ has a function, which allows users to calculate the inverse of a beta. The function "Beta.Inv" takes three inputs, the percentile at which to evaluate the inverse, the alpha parameter identified in the equations above, and the beta parameter identified in the equations above. Percentile values calculated from each SME resultant distribution, including the minimum, 25th percentile, median, 75th percentile and maximum, are shown in Table G-2. For illustration and comparison, Figure G-2 shows the resultant percentile values can be represented using box plots.

Table G-2. Notional SME Input Values

	MINIMUM (%)	25TH (%)	50TH (%)	75TH (%)	MAXIMUM (%)
SME 1	0	5.3	10	17	50
SME 2	0	18	25	32	50
SME 3	0	33	40	45	50

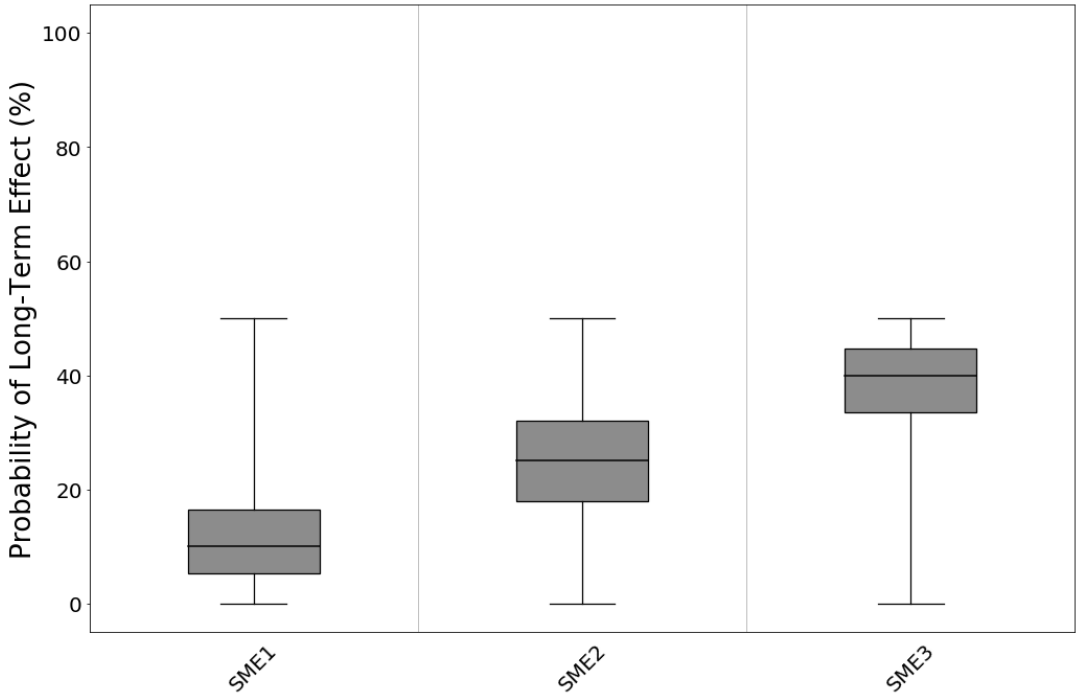

Figure G-2. Box Plots Resulting from Notional SME Inputs

GLOSSARY

Acronyms/Abbreviations

ACMT
American College of Medical Toxicology

APHC
U.S. Army Public Health Center

AR
Army Regulation

AVG
Average

CBRN
Chemical, Biological, Radiological, and Nuclear

CSAC
Chemical Security Analysis Center

CT
Computed Tomography

CTRA
Chemical Terrorism Risk Assessment

DHS
Department of Homeland Security

DOD
Department of Defense

DOEHRM
United States Army Deployment Occupational and Environmental Health Risk Management

ECt_{50}
Effective Dose (expressed as concentration x time) in 50% of those exposed

ED
Effective Dose

FEV1
Forced Expiratory Volume in one second

HC
Hexachloroethane

HSPD
Homeland Security Presidential Directive

IPCS
International Programme on Chemical Safety

JP
Joint Publication

MEG(s)
Military Exposure Guideline(s)

MIC
Methyl Isocyanate

PFT
Pulmonary Function Test

SME
Subject Matter Expert

TG
Technical Guide

TIC(s)
Toxic Industrial Chemical(s)

USACHPPM
United Stated Army Center for Health Promotion and Preventive Medicine