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Development of Exposure Guidelines for Chronic Health Effects Following Acute Exposures to Toxic Industrial Chemicals – A Toxidrome-Based Approach

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15. SUBJECT TERMS
Toxic industrial chemical, TIC, chlorine, exposure, toxidrome

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1. SUMMARY

1.1 Purpose

This information paper describes a toxidrome-based approach to developing exposure guidelines for assessing the risk of chronic health effects following acute exposures to toxic industrial chemicals (TICs). The approach relies on subject matter expert (SME) input to bridge the key data gaps. A working example with notional data is provided to illustrate how the approach could be applied.

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 military exposure guidelines (MEGs) into risk estimates can provide commanders with a mechanism to consider both short- and long-term chemical risks. Current MEGs address acute exposures leading to acute effects and sub-chronic exposures leading to chronic effects. However, the current MEGs have not directly addressed acute exposures leading to chronic effects. This problem is of particular concern for acute exposure to non-lethal concentrations of 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.

The white paper titled Development of Exposure Guidelines for Chronic Health Effects Following Acute Exposures to Toxic Industrial Chemicals focused on developing an approach to estimate acute exposures that lead to chronic effects (Winkel 2014). 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. The white paper focused on the guideline development process when applied to chlorine and a preliminary model was developed using the limited available data (Winkel 2014). Given that only limited data was available for what was considered to be a “data rich” chemical (chlorine), there may be difficulties in applying the approach described in the previous white paper to a large number of chemicals. An alternative approach is described in this information paper to address the issue of limited data by collecting toxidrome-based input from SMEs to bridge the data gap.

1.3 Recommendations

The toxidrome-based approach described in this information paper is considered more likely to result in establishing usable guidelines compared to the previous approach. It is recommended that this approach to estimating acute exposures that lead to chronic effects be socialized prior to being deployed. The ability of SMEs to bridge the data gap is critical to the success of this approach. Therefore, socialization of the approach should be aimed at 1) determining if SMEs are capable of providing the desired information and 2) obtaining buy-in of the approach from a wider technical community of medical and/or toxicology experts.

2. REFERENCES AND TERMS

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

3. BACKGROUND

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. Military Exposure Guidelines (MEGs) are concentrations of chemicals in air, water, and soil that can assist in evaluating the military significance of field exposures to chemical hazards during deployments (US Army Public Health Command, 2013). 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 leading to acute effects and sub-chronic exposures leading to chronic effects. However, the current MEGs have not directly addressed acute exposures leading to chronic effects. This problem is of particular concern for acute exposures to non-lethal concentrations of TICs. This gap 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 methyl isocyanate 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.

The white paper “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. As discussed in that report, 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. The logistics of such a study are inherently more difficult and, as a result, there is less chronic effect data available. Relevant literature data on this topic is minimal and generally characterized by several challenges, including:

- Quantitative exposure details (concentration, duration) are rarely available (and when available, may not be reliable).
- 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.
- There are difficulties/inconsistencies in identifying long-term effects.
- There is no formal definition of a “chronic” or “long-term” effect, including whether effects require the presence of physical symptoms or irregular pulmonary function test (PFT) results. Different types of results 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. The use of epidemiological data requires an approach to manage data sets that are small, incomplete, or lacking in details. The previous white paper discussed such an approach when applied to chlorine, a chemical considered to be “data rich.”

Given that only limited data was available for what was considered to be a “data rich” chemical, there may be difficulties in applying the previously developed approach (Winkel 2014) to a large number of chemicals. An alternative approach is described in this information paper 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.

4. OVERVIEW OF ALTERNATIVE TOXIDROME-BASED APPROACH

This section provides an overview of an alternative approach to establishing guidelines for long-term health effects following acute exposure to TICs. The following sections outline the steps to complete an analysis for a given toxidrome and exposure route combination, using the pulmonary toxidrome and the inhalation exposure route as a working example with notional data.

4.1 Identify Acute and Chronic, Non-Lethal Medical End Points and Associated Dose-Response Data

Step 1 in the process is to identify acute and chronic non-lethal medical end points for a short-term exposure to a chemical within the selected toxidrome by the selected exposure route. All chemicals within a toxidrome are assumed to have the same toxic mechanism (this will be confirmed through searches of appropriate databases) and, therefore, will result in the same medical end points upon exposure (although the exposure required to result in those end points will vary among chemicals in the toxidrome). Furthermore, it is assumed that similar acute injuries caused by different chemicals within the same toxidrome have the same probability of causing the long-term health effects typical to that toxidrome. Therefore, it is essential that dose-response data exists for chemicals within the toxidrome. Data will also be collected for chronic effects. The estimation of the long-term effect guidelines will be based on acute dose-response relationships and informed by mechanistic data and data on chronic effects. In some cases, such relationships may already exist. If they do not exist, and there is a desire to estimate long-term effect guidelines, the relationships need to be determined.

When identifying medical end points, it may be necessary to group them into effect categories (such as mild and severe) to increase the likelihood that dose-response data are available. While “cough” is an end point for the pulmonary toxidrome, for example, it will be difficult to identify dose-response data specific to only cough. Such data will likely group coughing with other respiratory symptoms. These groupings may align with existing exposure guidelines, such as Acute Exposure Guideline Levels (AEGLs) and Emergency Response Planning Guidelines (ERPGs). It should be noted, however, that guidelines such as AEGLs and ERPGs are protective guidelines meant for civilians rather than tactical guidelines for military use. Such values are often derived with conservative uncertainty and safety-sided factors. The end points outlined by those guidelines are of value, but the actual exposure guidelines are likely too conservative for this application (though the underlying data are valuable to the derivation of a dose-response relationship). In contrast, mild and severe health effect curves such as those used by Army Public Health Center (Provisional) (APHC (Prov)) to develop MEGs may serve as a better source of acute exposure, acute effect dose-response data. Other potential sources of dose-response data that have been reviewed by these authors in previous work include a report by Sommerville et al. (2012) in which provisional severe health effect probit parameters were generated. In addition, efforts by the Chemical Security Analysis Center have produced probit parameters for mild/moderate and severe health effects as part of the Chemical Terrorism Risk Assessment.

The exit criteria for Step 1 are identifying one or more acute, non-lethal medical end points following acute chemical exposure and identifying a dose-response relationship (e.g., a probit curve) for the end point(s). Note that the dose-response relationship can take more than one form. A dose response curve is the most desirable form, as it is more robust than simple threshold value, although either may be acceptable. If no dose-response data are identified, the process should not continue.

Working example: An inhalation exposure to a pulmonary chemical was selected as the chemical-exposure route combination of interest. The probit parameters in Table 1 satisfy Step 1 of the process

(assuming specific severe/incapacitating effects are identified) for multiple chemicals in the pulmonary toxidrome, including chlorine. For this example, pulmonary edema was selected as the severe effect associated with the data. Note, however, that Sommerville et al. do not identify pulmonary edema as a severe or incapacitating effect. It is suggested here for illustrative purposes only.

Table 1. Provisional Probit Parameters for Severe/Incapacitating Effects from Exposure to Chemicals Causing Pulmonary Effects (from Sommerville et al. 2012)

Chemical	ECt50 Value (Dosage) (mg-min/m^3) at 2 min[(a)]	Toxic Load Exponent	Concentration-Based Probit Slope (Base 10)
Ammonia	7,800	2.0	17
Chlorine	1,300	2.75	8
Phosgene	250	1.0	11

Notes: Only the "fit" values are shown here. Also reported by Sommerville et al. (2012) are upper and lower limits based on confidence intervals.

4.2 Identify and Engage Appropriate Medical SMEs to Identify Long-Term Medical End Points

As described previously, the biggest obstacle to establishing acute exposure, long-term health effect guidelines is the absence of reliable long-term effect data in the literature. It is proposed that input from SMEs be used to fill this data gap. In Step 2 of the process, SMEs must be identified and engaged to provide this input. A qualified SME must be knowledgeable of the long-term effects associated with the given toxidrome (e.g., a medical toxicologist, a pulmonologist for the current example) and must also be capable of making quantitative judgments on the likelihood of long-term effects as a result of an acute exposure.

SMEs will identify specific long-term health effects (referred to here as long-term medical end points) that can result from exposure to chemicals within the given toxidrome that result in the acute, nonlethal medical end points ascertained in Step 1. It is envisioned that this happens in a group setting, as working with SMEs individually will make it difficult to reach a consensus among the group. It is critical that the SMEs are comfortable with the linkage between the acute and long-term medical end points, as they will need to quantify the probability associated with those linkages in Step 3. As with the list of acute end points, it is recommended that the long-term end points be grouped and categorized into levels of severity (e.g., mild and severe long-term effects).

The exit criteria for Step 2 are engaging SMEs and collecting SME-generated specific long-term medical end points (with SMEs realizing that these end points will be quantitatively linked to the short-term medical end points developed in Step 1). One strategy for facilitating this process is identifying a core group of SMEs (or single SME) in advance to actively participate in interactions with other SMEs, assist in presenting the problem in an SME-friendly way (e.g., help define what is meant by long-term effect), and champion the effort among the other SMEs. There is no minimum or maximum number of SMEs recommended for the effort (the more SMEs, the better), and the approach will work for any number of SMEs. Note that this step is expected to be the most difficult step in this process, as identifying appropriate SMEs and socializing the necessary quantitative estimates is likely to be challenging.

Working example: A collection of SMEs reached a consensus on a long-term medical end point that may result from an acute severe/incapacitating injury following exposure to a chemical in the pulmonary toxidrome. The end point is termed "severe long-term health effects" and is a grouping of end points that incorporate the following conditions: obstructive respiratory disease and restrictive respiratory disease. A

single end point was selected in this example for simplicity. As mentioned, it is possible that SMEs outline several potential long-term health effects or categories.

4.3 Elicit Long-Term Effect Probabilities from SMEs

In Step 3, SMEs will quantitatively define the likelihood of an individual exhibiting the long-term effects described in Step 2 given the acute effects identified in Step 1. Responses will be recorded to capture the uncertainty associated with SME estimates. The use of a betaPERT distribution, for example, requires SMEs to specify only a minimum value, maximum value, and most likely/ best guess value (i.e., a mode value). It is envisioned that the SMEs provide input via Microsoft® Excel spreadsheets that includes visualization of the specified distribution.

A single SME could quickly and easily provide input to multiple toxidromes at once (provided the SME was both qualified to make those assignments and comfortable doing so). Adopting such a tool will lend itself toward distribution of the spreadsheet to a wide audience, whereby participants could provide input on as few or as many toxidromes as was appropriate. Such an approach will maximize efficiency in the data collection process.

The proposed elicitation effort is rooted in the methodology of the Delphi Method (Ziglio 1996). Specifically, the SMEs will be directed to define long-term effect probabilities independent of other SMEs participating in the effort. Upon receipt and combination of all SME input (to be explained in the next step), the SMEs will be convened (in a method appropriate for the number of participants) to view the combined result. The SMEs will then be asked to reach a consensus agreement on the combined result or identify/resolve any SME input that was deemed invalid.

The exit criterion for Step 3 is collecting quantitative long-term effect probabilities based on acute effects from multiple SMEs. Assuming an Excel tool is used to collect input, the exit criterion is the receipt of completed Excel sheets.

Working example: An SME provided the following values describing the likelihood of an individual exhibiting severe long-term health effects following a severe acute injury after exposure to a pulmonary toxidrome chemical: 0.05 (minimum), 0.20 (maximum), and 0.10 (mode or most likely). Note that these data are notional. Figure 1 illustrates the input of these values into an Excel-based elicitation tool and the resulting visual representation of the distribution. The distribution is shown as a box and whisker plot. The box encompasses the 25^{th} to 75^{th} percentiles of the distribution, with the whiskers extending to the minimum and maximum values defined by the SME. The median is noted by the black line within the box, and the mean is noted with a red dash within the box. In this simple example, the SME provides input to the pulmonary toxidrome as well as additional hypothetical toxidromes that were selected for illustrative purposes only. All data are notional. Visualization of all toxidromes allows the SME to compare as necessary.

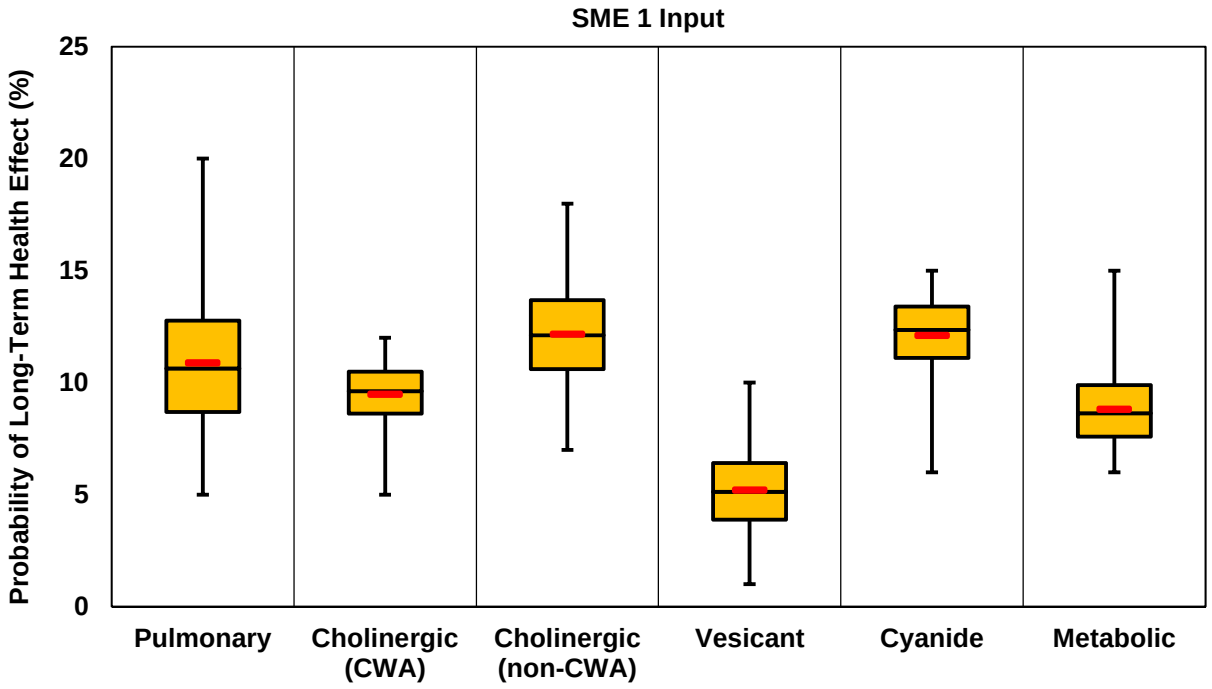

Figure 1. Visualization of Multiple Parameterized Distributions for Different Toxidromes (All Data are Notional)

4.4 Combine SME Input, Apply to Specific Chemicals, and Convene SMEs for Approval

After all individual SME input is collected in Step 3 for a given toxidrome, the input will be combined into a single, representative distribution in Step 4. The distribution will then be applied to the chemical-specific dose-response data collected in Step 1 to produce the long-term effect health curve. Since 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 in the working example.

Participating SMEs will be convened and presented with the summary input and resulting long-term health effects curves. SMEs will review the individual SME inputs that comprise the representative distribution, and SMEs will be permitted to update their individual contribution if desired. The SMEs will also review the long-term health effect curves to ensure that the representative values produced acceptable results across specific chemicals. Chemicals for which the elicited values seemed inappropriate will likely have to be re-assigned to a new toxidrome or sub-toxidrome.

The exit criterion for Step 4 is approving the quantitative long-term effect probabilities based on acute effects by the group of SMEs (including review of the resulting long-term health effect curves). Updates or changes to individual inputs will not be permitted after approval, as any changes impact the representative distributions that had been approved by the group.

Working example: A series of SMEs provided the component distributions shown in Figure 2 for the pulmonary-inhalation toxidrome-exposure route combination. This input is combined into a single, representative distribution in Step 4 (also shown in Figure 2). The color scheme in the figure links one color to one SME for easy identification of one's inputs (e.g., contributions of SME 3 appear as light green for input to any toxidrome). The distribution is applied to the chemical-specific dose-response data

collected to produce the long-term effect health curve (Figure 3). In Figure 3, the median, 5th, and 95th percentiles of the representative distribution were each applied to the acute effect curve.

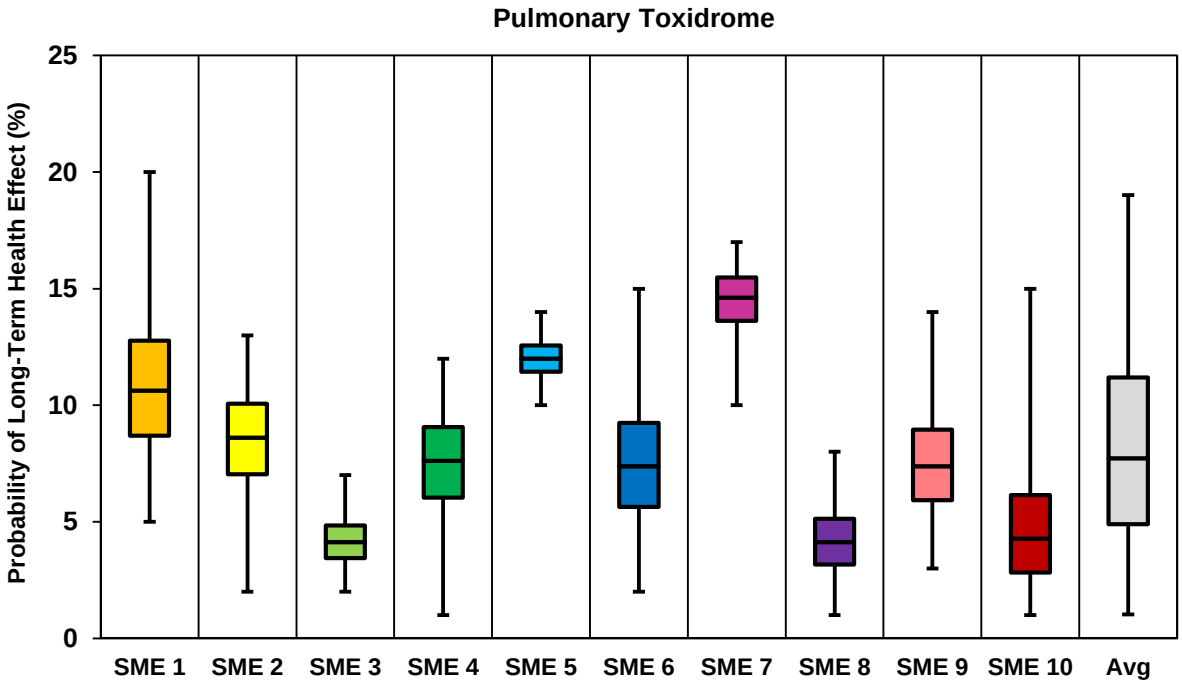

Figure 2. SME-Specific Distributions and Representative Distribution (All Data are Notional)

(Figure best viewed in color)

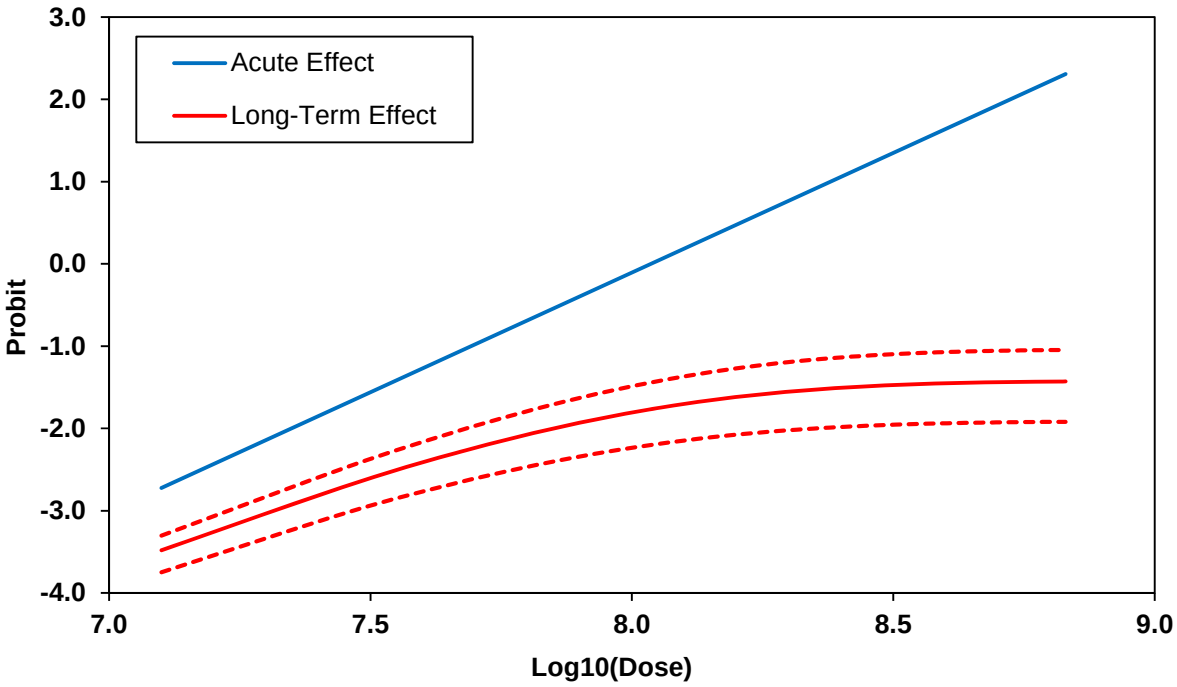

Figure 3. Long-Term Health Effect Curve for Chlorine after Application of SME-Derived Distributions to Existing Dose-Response Data (All Data are Notional)

(Figure best viewed in color)

Note that in Figure 3, the shape of the long-term health effect curve is different from that of the acute health effect curve. The straight line acute effect curve was developed from a probit analysis of dose-response data (an S-shaped curve). The long-term health effect curve represents a constant reduction in probability (8% in the working example) 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 is 8% (as shown in Figure 4, which presents the same notional data as Figure 3 but the y-axis has been converted from a probit scale to a probability scale). The corresponding probit transform plateaus at a value equal to the probit transform of 8% (or -1.4 on a probit scale, as seen previously in Figure 3). There is no simple linear representation of the long-term health effect curve (i.e., there are no probit parameters). However, knowledge of the representative distribution allows for straightforward calculation of the probability of a long-term effect from the acute injury probit parameters. More specifically, the probability of acute injury is first determined according the acute injury probit parameters. The acute injury probability is then reduced by the elicited probability of a long-term effect resulting from that acute injury.

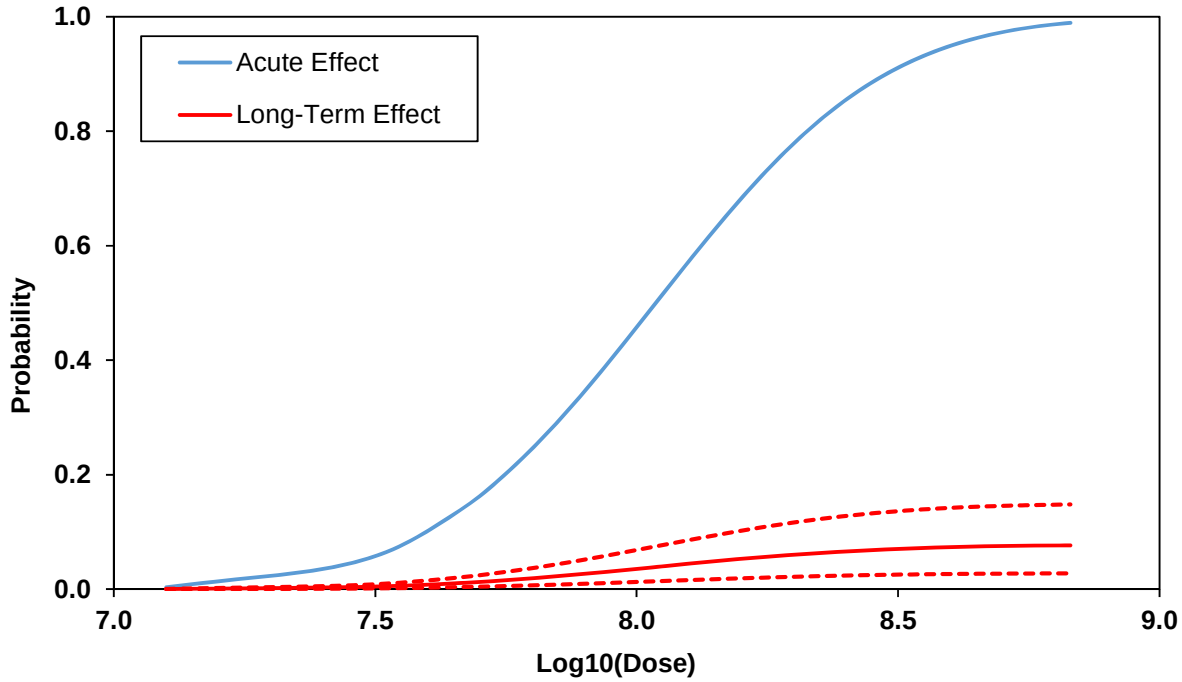

Figure 4. Long-Term Dose-Response Curve for Chlorine after Application of SME-Derived Distributions to Existing Dose-Response Data (All Data are Notional)

(Figure best viewed in color)

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. The underlying assumption that drives this statement (and the overall approach) is that similar acute injuries 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 5 for example, long-term health effect curves can be generated for the three chemicals in the pulmonary toxidrome whose acute injury probit parameters were listed in Table 1. The three plots on the right side of Figure 5 are similar to the plot in Figure 4 and show the acute (blue) and notional long-term (red) health effect curves for chlorine, ammonia, and phosgene. The acute curves are drawn using the provisional probit parameters from Sommerville et al. (2012) provided in Table 1. The long-term curves are drawn utilizing the SME-elicited probabilities (median, 5^{th}, and 95^{th}) of a long-term health effect for the pulmonary toxidrome. These probabilities are multiplied by the probability of acute injury at a given dose to give the probability of a long-term health effect (as seen previously in Figure 4).

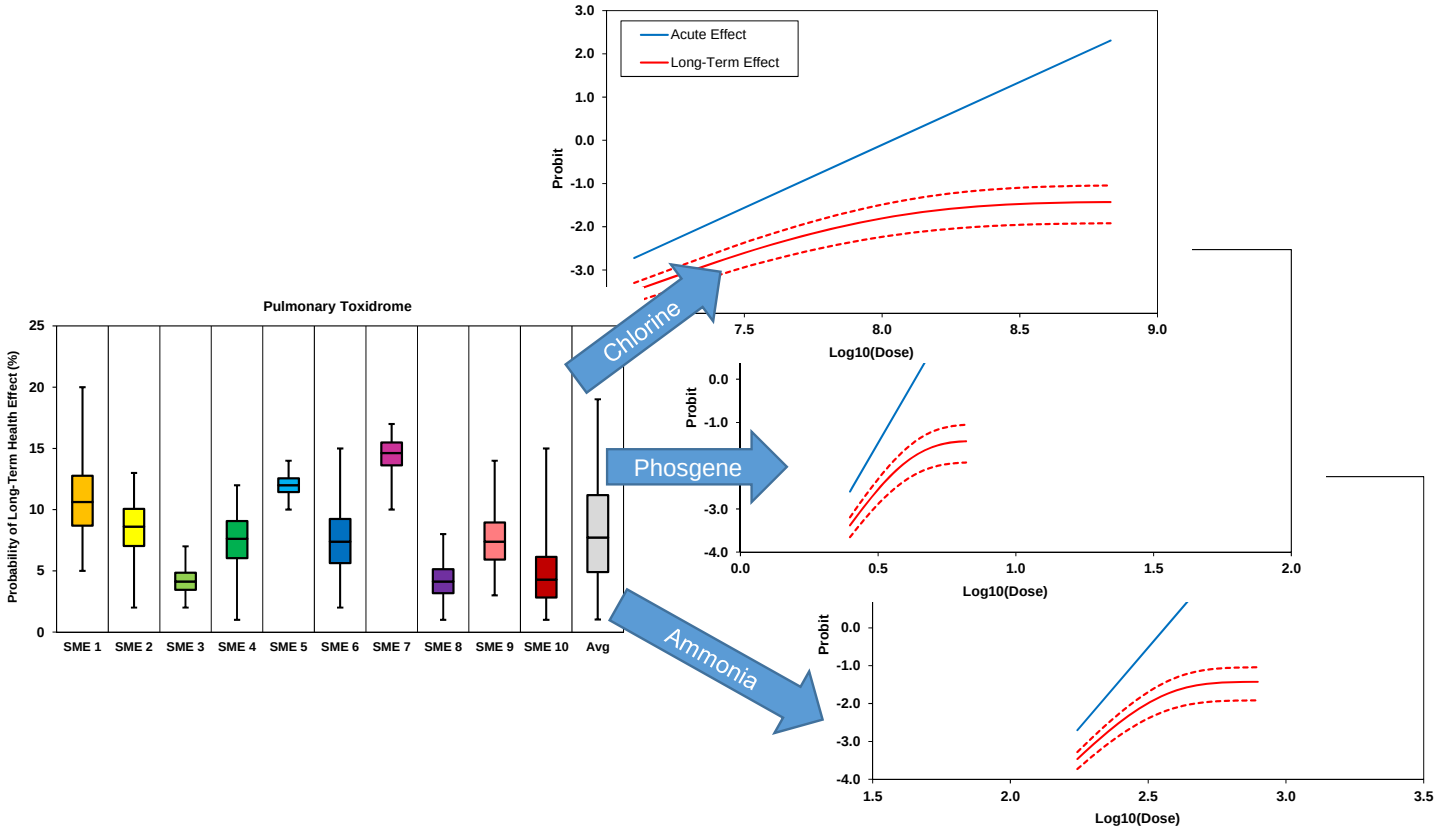

Figure 5. Long-Term Health Effect Curve for Multiple Chemicals in the Pulmonary Toxidrome after Application of SME-Derived Distributions to Existing Dose-Response Data (All Data are Notional)

(Figure best viewed in color)

4.5 Report/Socialize Results

The long-term exposure guidelines determined in Step 4 will then be assembled and documented in a report for further socialization. The report will be accompanied with an explanation of the value development process (i.e., an explanation of Steps 1 through 4), including visualizing the component distributions provided by the SMEs.

5. CONCLUSIONS AND RECOMMENDATIONS

The primary objective of this information paper is to present a toxidrome-based approach to establishing guidelines for long-term lethal health effects following acute exposure to TICs that overcomes literature data limitations identified in previous efforts. A notional example is provided to illustrate the steps of this process. Given the difficulties in establishing these guidelines based on literature data (Winkel 2014), the approach explained here is considered more likely to result in establishing usable guidelines. It is recommended that this approach be socialized prior to being deployed. The ability of SMEs to bridge the data gap is critical to the success of this approach. Therefore, socialization of the approach should be aimed at determining if SMEs are capable of providing the desired information and obtaining buy-in of the approach from the wider technical community of medical and/or toxicology experts.

Appendix A

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Glossary

Acronyms/Abbreviations

AEGL
Acute Exposure Guideline Level

APHC (Prov)
Army Public Health Center (Provisional)

AR
Army Regulation

CBRN
Chemical, Biological, Radiological, and Nuclear

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

ERPG
Emergency Response Planning Guideline

JP
Joint Publication

MEG(s)
Military Exposure Guideline(s)

MIC
Methyl Isocyanate

PFT
Pulmonary function test

SME
Subject Matter Expert

TG
Technical Guides

TIC(s)
Toxic Industrial Chemical(s)