Evidence Integration in Deriving Toxicity-Based Benchmarks for Trichloroethylene

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Abstract

An important public health function within the Army is balancing the critical mission of national defense with the risks associated with exposure to various substances by Soldiers, workers, and their families. Developing toxicity-based benchmarks for risk assessment requires the integration of evidence from human, laboratory animal, and mechanistic studies, each with varying study designs that are collected independently from each other. Here, we use the development of an occupational exposure level (OEL) for trichloroethylene as an example of a process for assessing the weight of evidence of various toxicity endpoints. Following collection of relevant studies via a systematic literature search, we developed a quantitative process for evaluating the controlled animal studies with respect to study quality, strength of effects, relevance, data consistency, and risk of bias. Studies were then graphically compared within each non-cancer health effect domain (occupational exposure level for each health effect category). Physiologically-based pharmacokinetic (PBPK) modeling was used to quantify the total human equivalent concentration (THC) and uncertainty factors were employed using a Bayesian approach to estimate the OEL for each health effect category. Previous OELs were revised using mechanistic data and these studies served as the primary basis for determining causal endpoints. Potential cancer risks were also evaluated and this dose-response was estimated at various risk levels for the purpose of comparison to the non-cancer OEL.

Methods

- TCE is a volatile industrial and commercial solvent that has been widely used throughout the Department of Defense (DOD), for example, as a metal degreaser or cleaner for the maintenance of engines and weapon systems.
- Workers may be exposed to TCE via either direct contact during work tasks or via indirect exposure due to vapor intrusion. The primary route of exposure for workers is inhalation.
- Thousands of in vivo, in vitro, and epidemiological studies demonstrate widespread effects due to TCE exposure.
- Exposure standards endorsed by various governmental regulatory agencies span a 250,000-fold difference.
- OSHA Permissible Exposure Limit: 100 ppm
  - NIOSH Recommended Exposure Limit: 25 ppm
  - ACGIH Threshold Limit Value: 50 ppm
  - EPA Regional Screening Level- Composite Worker Air (non-cancer: 0.0016 ppm; 1x10-6 cancer risk: 0.0006 ppm)
  - EPA Reference Concentration: 0.0006 ppm

- EPA has occasionally directed evacuation of DoD workplaces based on environmental standards, leading to confusion among commanders. A single occupational exposure level (OEL) is needed that applies to all workers, including those impacted by vapor intrusion.

Objective

To develop an occupational exposure level (OEL) for TCE inhalation based on an assessment of all the current toxicology evidence, utilizing methods that maximize scientific robustness and transparency, while balancing timelines (Figure 1).

Results

Figure 1. Overview of the process for deriving an occupational exposure level for TCE, including integration of toxic endpoints across multiple study designs.

Figure 2. Flow chart of evidence identified and included in the toxicity assessment, based on a systematic literature search and other targeted searches. Studies published prior to 2010 were obtained from expert reviews. Mechanistic data was included in targeted searches that informed coherence and plausibility.

Figure 3. Overview of quantitative assessment tool designed to evaluate controlled animal studies on a 100 point scale. Qualitative assessments of critical effects from each study were stratified into non-cancer toxicity categories.

Figure 4. Top Panel: Points of departure (Y-axis) and total score (inside/adjacent to circle) for all 63 critical endpoints, stratified by health effect category. Bottom Panel: Summary of total scores.

Figure 5. Comparison of all experimental studies included in POD assessment. All exposure concentrations tested in each study (adjusted to 40 h/wk) are determined to be those most informative for deriving the overall POD, and these studies were analyzed via PBPK modeling. Pink boxes identify supporting human data.

Figure 6. Comparison of all experimental studies included in POD assessment. All exposure concentrations tested in each study (adjusted to 40 h/wk) are determined to be those most informative for deriving the overall POD, and these studies were analyzed via PBPK modeling. Pink boxes identify supporting human data.

Table 1. Examples of incorporation of mechanistic evidence into the toxicological assessment.

Table 2. Points of departure, human equivalent concentrations and occupational exposure levels for each health effect category.

Conclusions

- In vivo, in vitro, and epidemiological studies were integrated and used to support derivation of an occupational exposure limit.
- Dose-response data were strong for in vivo controlled laboratory studies, and these studies served as the primary basis for determining causal relationships between TCE and toxicity (inhalation and oral).
- Determination of non-cancer OELs was developed from inhaled and oral PODs (concentrations and divided PODs) using PBPK modeling; derivation of DEU incorporated application of uncertainty factors using a Bayesian approach. Human and mechanistic data provided supporting evidence that informed coherence, relevance, and plausibility of the in vivo laboratory findings.
- Points of departure were derived from human data supported by laboratory animal and mechanistic data.
- An OEL of 0.3 ppm was selected based on the most sensitive non-cancer effect (sensitization). This is supported by a 1.5x cancer risk in the kidney assuming a 45 year occupational exposure to TCE.

Reference

Sussan, TE; Scharf, G; Covington, TR; Scharf, JM; Johnson, MD. (2019). Trichloroethylene: Occupational Exposure Level for the Department of Defense. Aberdeen Proving Ground, MD.