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Hanford Tank Farm Occupational Exposure and Risk Assessment Plan

Health Process Project

November 2018

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under Contract DE-AC05-76RL01830

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Pacific Northwest National Laboratory
Richland, Washington 99352

Summary

The overall objective of the Hanford Tank Farm Occupational Exposure and Risk Assessment Plan (hereafter referred to as the “Assessment Plan”) is to provide the Tank Operations Contractor (TOC), Washington River Protection Solutions, and the U.S. Department of Energy with a plan for developing a transparent, peer-reviewed process for assessing potential health risks associated with worker exposures to chemical emissions from the Hanford tank farms. When fully implemented, the recommendations from the Assessment Plan will facilitate future risk-management decisions that are grounded in state-of-the-science measurement, simulation, and assessment practices. This Assessment Plan is based on recommendations provided by the independent Tank Vapor Assessment Team that focused on dose-response and risk characterization. The assessment approach will interface with other ongoing activities focused on site characterization, exposure assessment, risk management, and communication. The plan will establish a transparent framework for prioritizing tank farm chemical waste constituents of concern, establishing a process for proposing new Occupational Exposure Limits for chronic exposures, and recommending Transient Effect Concentrations for short-duration acute exposures to workers at the Hanford tank farms.

A critical recommendation of this Assessment Plan is for the TOC to establish a Hanford Tank Farm Occupational Exposure and Risk Assessment Advisory Team that will include a technical Working Group and management Internal Review Panel, hereafter referred to as the “Assessment Team.” The members of these two organizations are envisioned to consist of a diverse group of members from the TOC (or other Hanford contractors), Pacific Northwest National Laboratory, the Department of Energy, and local/regional academic and medical institutions that have the necessary scientific backgrounds to interpret and use existing and new information associated with the Hanford tank farm emissions (e.g., chemistry, toxicology, risk assessment, industrial hygiene, occupational medicine, health physics, exposure and dosimetry modeling, etc.). The Assessment Team will be responsible for prioritizing emission constituents by categories of concern, recommending Occupational Exposure Limits and Transient Effect Concentrations for emission constituents with known toxicity profiles, or where those limits or concentrations are unknown, defining a strategy for addressing critical knowledge gaps. The Assessment Team will serve as a central resource for the TOC that will be responsible for the integration of all information about tank farm emissions, exposure guidelines, and critical data or research needs that enable risk-management decisions and stakeholder communications.

To ensure transparency and assurance that the assessment processes incorporate the latest information and best practices, we further recommend that an External Expert Panel be established to review all processes and recommendations for Occupational Exposure Limits and research recommendations prior to their implementation. Members of the External Expert Panel should include well-established, nationally or internationally recognized scientists, risk assessors, and stakeholders who can serve multi-year appointments to maintain continuity and “corporate memory.”

The Assessment Team will require administrative support to facilitate scheduling, meetings, record-keeping, budgeting, and reporting requirements. Information technology technical support also will be needed to develop and maintain Hanford databases of constituent analyses, exposure measurements, industrial hygiene surveys, and key scientific literature and exposure guidelines through either commercially available software or software developed in-house. This database should have a user-friendly, secure interface that is accessible to registered contributors and users of the data and information.

Once the overall Assessment Plan has been reviewed, evaluated, and refined, a detailed implementation plan should be developed to establish the Assessment Team, the External Expert Panel, and the Hanford tank farm database and associated budgets, timelines, and milestones. The proposed overarching strategy with specific functional components is illustrated in Figure S.1. The strategy should exploit both measurement science and modeling approaches to inform the risk assessment process. The resulting risk assessments will be transparent and effectively communicated among all key stakeholders.

This revision of the Assessment Plan incorporates changes to the original draft plan prepared in 2016. This current document presents updated strategies based on initial implementation of the originally recommended actions.

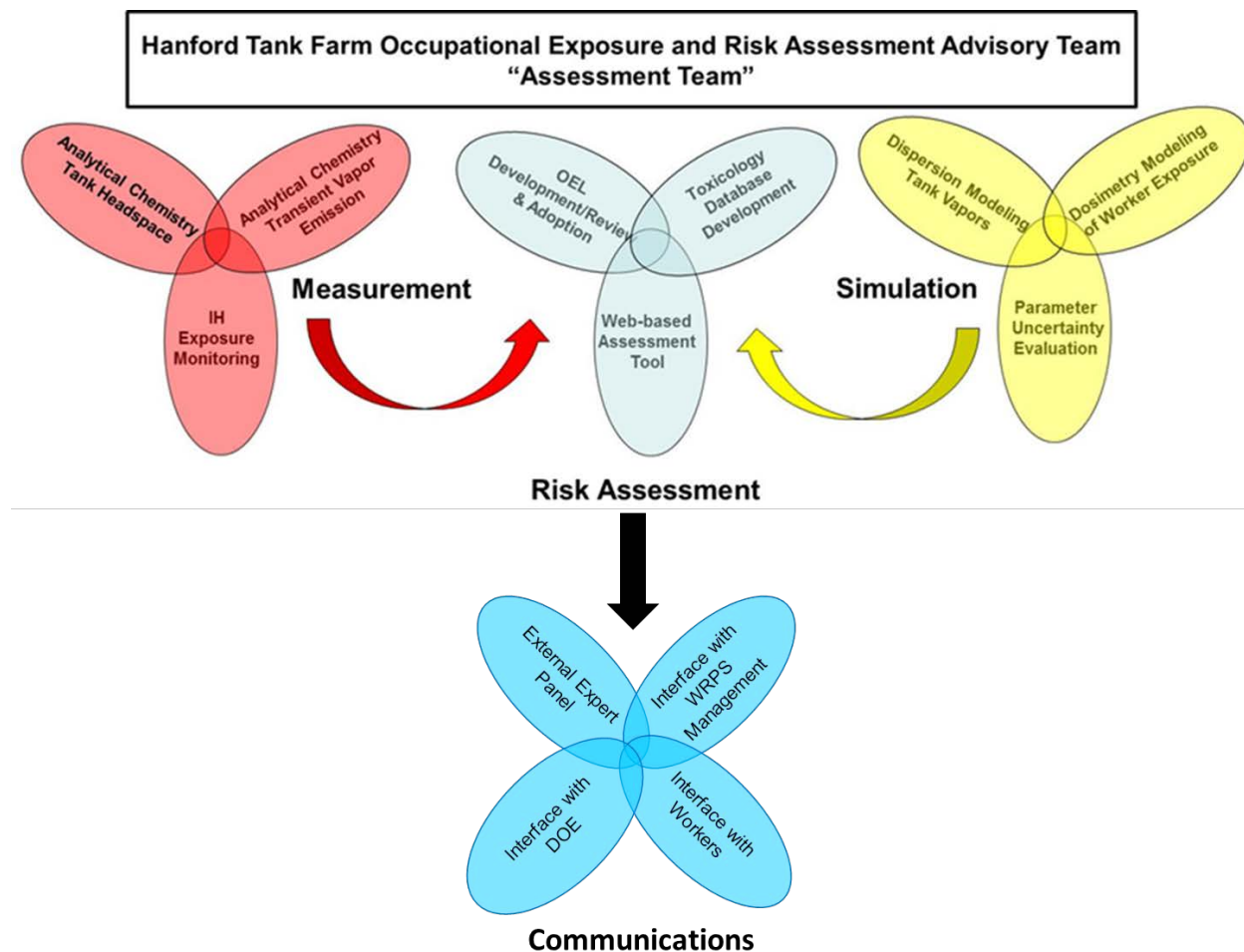


Figure S.1. Functional Components of the Assessment Team

Acronyms and Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Levels
AIHA	American Industrial Hygienist Association
CMM	Chemical Mixture Methodology
COPC	chemical of potential concern
DOE	U.S. Department of Energy
DR	dose-response
EEP	External Expert Panel
EPA	U.S. Environmental Protection Agency
ERPG	Emergency Response Planning Guidelines
HCN	Health Code Number
hr	hour(s)
HPP	Health Process Plan
HSDB	Hazardous Substances Data Bank
_{HTF} OEL	Hanford Tank Farm Occupational Exposure Limit
_{HTF} TEC	Hanford Tank Farm Transient Effect Concentration
IARC	International Agency for Research on Cancer
IH	industrial hygiene
kg	kilogram(s)
LC ₅₀	Lethal Concentration for 50% of test population
LD ₅₀	Lethal Dose for 50% of test population
LOEL	lowest observed effect level
MF	modifying factor
mg	milligram(s)
min	minute(s)
MOA	mode of action
NAS	National Academy of Science
NLM	National Library of Medicine
NOEL	no-observed-effect levels
OEL	Occupational Exposure Limit
OEL-C	Occupational Exposure Limit-Ceiling
OR	overarching recommendation
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria

ppm	parts per million
ppmV	parts per million volume
PNNL	Pacific Northwest National Laboratory
RCH	risk characterization
RTECS	Registry of Toxic Effects of Chemical Substances
TCD	Tank Characterization Database
TEC	Transient Effect Concentration
TEEL	Temporary Emergency Exposure Limit
TLV	Threshold Limit Value (ACGIH-specific)
TOC	Tank Operations Contractor
TOXNET [®]	Toxicology Data Network
TVAT	Tank Vapor Assessment Team
TWINS	Tank Waste Information Network System
UF	Uncertainty Factor

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1.0 Introduction

At the request of Washington River Protection Solutions, Savannah River National Laboratory assembled a panel of nationally recognized experts to assess worker exposure and potential health issues associated with vapors from Hanford waste storage tanks. Experts in the fields of occupational and environmental health, environmental engineering and science, toxicology, health physics and industrial hygiene (IH) conducted the scientific and technical assessment. In October 2014, this expert panel—known as the Tank Vapor Assessment Team (TVAT)—issued its final report entitled *Hanford Tank Vapor Assessment Report* (SRNL 2014). The TVAT report included 10 overarching recommendations (OR) that reflected the scope of issues identified across all technical assessment areas and more than 40 specific recommended improvements (for details see the TVAT). This Assessment Plan focuses on specific recommendations associated with dose-response (DR) in the TVAT report and risk characterization (RCH) for both current and future tank vapor chemicals of potential concern (COPCs). The specific recommendations, as they were designated in the TVAT report, include the following:

DR-1. Conduct an additional review and re-prioritization of COPCs under tank-disturbing conditions to provide adequate emission characterization, OEL [Occupational Exposure Limit] development, and worker exposure surveillance.

DR-2. Conduct a rigorous review of the COPC list to ensure it is current, and develop a process to document the mechanisms used to ensure COPC updates and the basis for changes in the COPC list over time.

DR-3. Conduct additional evaluations of COPC toxicological studies to provide insight into the sensory and pathophysiological irritation response, including the role of mixture interactions and the potential need for additional toxicological evaluation.

DR-4. Perform a comprehensive evaluation of acute odor thresholds and toxicity effect levels for all COPCs to facilitate the establishment of action levels based on the relationship between odor and toxicity thresholds.

DR-5. Continue to evaluate COPC OELs within the context of observed symptomatology, verses 10% of the irritation thresholds and develop a “new” acute OEL list.

DR-7. Evaluate tank vapor mixture toxicological interactions at concentrations associated with transient plume exposures to modify OELs to accommodate mixture effects.

DR-9. Develop a research strategy roadmap in partnership with DOE [U.S. Department of Energy], national laboratories, and university faculty subject matter experts to address critical questions regarding tank vapor emissions and exposures.

RCH-1. Identify an Occupational Exposure Limit–Ceiling (OEL–C) for each constituent in Hanford tank head space(s).

RCH-2. Classify and conduct toxicological testing on a reasonable number of distinct types of Hanford tank headspace vapors (e.g., potential classes of tank vapor types such as ammonia rich, ammonia poor, nitrosamine rich, etc.).

RCH-3. Use the OEL–C from analysis or subsequent toxicological testing to characterize the hazard index and risk from the tank vapor mixtures, and control to 10% of the value.

RCH-4b (Acute). Transient vapor/gas exposures concentrations (i.e., high dose rate) are substantially greater than what is currently measured as a time-weighted average; alternative strategies for evaluating transient plume like vapor exposures is recommended and adherence to excursion limit principles must be implemented (3 times OEL) in the absence of appropriate OEL–C values.

Although the Assessment Plan focuses on implementation of specific recommendations associated with DR and RCH, the overarching goal is to interface with key ongoing activities noted in the TVAT report that deal with site characterization, exposure assessment, risk management, and stakeholder communications (see Figure S.1). The ORs, as designated in the TVAT report, include the following:

OR3. Establish a program to sample proactively the headspace of tanks to validate and enhance chemical characterization.

OR4. Accelerate development and implementation of a revised IH exposure assessment strategy that is protective of worker health and establishes stakeholder confidence in the results for acute as well as chronic exposures.

OR5. Modify the medical case evaluation process and reporting procedures to recognize the appropriate uses and limitations of the available monitoring data and other potential exposure information when evaluations are made regarding tank chemical vapor exposures.

OR6. To reduce the impacts of bolus exposures, utilize real-time personal detection and protective equipment technologies specifically designed to protect individual employees.

OR7. Accelerate implementation of tailored engineering technologies to detect and control vapor emissions and exposures experienced in the Hanford tank farms (“tank farm of the future”).

OR9. Effectively communicate vapor exposure issues and actions proactively with all stakeholders.

To successfully implement the specific DR and RCH recommendations and achieve integration with other key activities recommended in the TVAT report, this Assessment Plan recommends that a Hanford Tank Farm Occupational Exposure and Risk Assessment Advisory Team (Assessment Team) be established along with an External Expert Panel (EEP) that will serve as a central resource to the Tank Operations Contractor (TOC) and DOE (see Sections 4 and 5 and Appendix A for details).

2.0 Key Elements of the Assessment

The assessment involved processes for prioritizing constituents of concern and for proposing exposure limits.

2.1 Process for Prioritizing Constituents of Concern

Because of the large number (>1800) of chemicals present or predicted to be present in the Hanford tank headspaces (Burgeson et al. 2004), a process must be established to prioritize assessments of COPCs that could be present in the breathing zones workers encounter at Hanford tank farms. In 2004, Pacific Northwest National Laboratory (PNNL) established such a process by grouping chemicals present or potentially present in tank headspaces into categories of toxicological concern for occupational inhalation exposure based on previously established occupational and chronic allowable exposure levels (Burgeson et al. 2004). Upon reviewing that approach, authors of the TVAT report noted a number of limitations that warranted modification of the process. First, health impacts from radiolytically generated free radicals need to be considered within the COPC prioritization strategy. Some of these radicals may be highly transient in nature making them difficult to measure, but they might produce significant respiratory system irritation following acute inhalation exposure. Second, exposure to aerosols has not been previously considered but needs to be a component of the current evaluation and prioritization strategy. Finally, to help facilitate differentiation between odor and respiratory irritation effects, the dosimetric relationship between odor and irritant thresholds needs to be determined and included in the evaluation process. For the majority of chemicals originally identified in tank headspaces that had no acceptable occupational exposure data or OELs, PNNL developed a process for identifying the chemicals that would be further assessed for potential health risk to tank farm workers (Poet et al. 2006). The process involved establishing headspace chemical concentration screening values using available IH and toxicological data. The screening values were defined as the chemical concentrations being an order of magnitude below concentrations that may cause adverse health effects in workers (40 hr/week occupational exposure). The screening values then were compared to the maximum reported headspace concentrations; any concentrations that exceeded the screening value were further evaluated. Poet et al. (2006) assigned screening values to 606 chemicals, of which 72 were determined to be in the tank headspaces at or above these values.

Each of these methods used in the past to prioritize COPCs from tank farm headspace measurements should be exploited as starting points for future assessments. However, additional information that addresses the potential transient nature of occupational exposures needs to be developed and supplemented with additional approaches such as:

- Computational modeling of headspace emissions under static and tank-disturbing conditions
- Fate and transport of emissions within the tank farm local environment
- Screening procedures established to evaluate hazardous properties of headspace mixtures (e.g., based on common modes of action such as irritation, cytotoxicity, inflammation, mutagenicity, etc.) as new data become available
- Assessments of chronic and acute adverse health effects due to exposure of chemical mixtures emitted from the headspace or encountered in the facility using the DOE Chemical Mixture Methodology.

Furthermore, a process must be developed to ensure COPCs are regularly updated and the reasons for any changes are documented as new information becomes available. Additional details are provided in Appendix A.

2.2 Process for Proposing Exposure Limits

Prior approaches for developing OELs for the Hanford tank farms (termed _{HTF}OELs) focused on worker exposures that may cause adverse health effects over a normal workday or workweek (Poet and Timchalk 2006). The strategy for screening COPCs and assigning _{HTF}OELs is described in detail in the Appendix A (Sections A.2 and A.3). In the past, _{HTF}OELs were called acceptable OELs,¹ a terminology that recently was changed to _{HTF}OELs. In addition, as recommended in the TVAT report (SRNL 2015), new procedures must be established for setting short-term Transient Effect Concentration (TEC) guidelines for episodic exposures (see Appendix A for details).

The need for establishing short-term TEC guidelines is based on the following TVAT assertion:

The TVAT developed a hypothesis that vapors coming out of tanks in high concentration (bolus) plumes sporadically intersected with the breathing zones of workers, resulting in brief but intense exposures to some workers. The TVAT then sought additional data and information to support or refute the hypothesis. The hypothesis was substantiated by computer modeling, which indicated that under certain weather conditions, concentrations approaching 80% of the head space concentration could exist 10 feet downwind from the release point and potentially in workers' breathing zones. To affirm further the likelihood of a causal linkage between tank vapor exposure and the adverse health effects reported by tank farm workers, the TVAT applied the principles of Hill's Criteria of Causation. Established by English epidemiologist Sir Austin Bradford Hill in 1965, Hill's Criteria of Causation comprise a group of minimal conditions necessary to provide adequate evidence of a causal relationship between an incident and a consequence. Based on the body of data and information the team has examined, analysis of the Hill's criteria strongly suggests a causal link between chemical vapor releases and subsequent health effects, particularly upper respiratory irritation, experienced by tank farm workers.

To accomplish this goal, initially exploiting the approach established by the National Academy of Science (NAS) Subcommittee on Acute Exposure Guideline Levels (AEGLE) (NAS 2001) is recommended. It is worth noting that AEGLEs were developed for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority chemicals for the general population. Therefore, AEGLE values are not directly transferable as TECs for occupational exposure. However, the scientific principles and knowledge established in the AEGLE development process are useful for evaluating TECs and making recommendations. Specifically, AEGLEs are threshold exposure limits ranging from 10 min to 8 hr (10 min, 30 min; 1, 4, and 8 hr) of exposure with three levels of toxic-effect severity defined by NAS as follows (NAS 2001):

- AEGLE-1 is the airborne concentration (ppm or mg/m³) of a substance above which it is expected the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible on cessation of exposure.

¹ Acceptable Occupational Exposure Limit is the historical term for OELs developed for Hanford tank farm chemicals that have not been based on existing regulatory guidelines. These exposure limits now are referred to as _{HTF}OELs.

- AEGL-2 is the airborne concentration (ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
- AEGL-3 is the airborne concentration (ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

The NAS process is currently the most comprehensive, peer-reviewed approach for recommending short-term exposure limits for acutely toxic chemicals. Therefore, the NAS process is a credible template for establishing _{HTF}OELs while acknowledging that additional refinements might be required to address transient mixed chemical exposures in the tank farms. For example, DOE developed Protective Action Criteria (PAC) based on AEGLs and Emergency Response Planning Guidelines (ERPG) (Rusch 1993; Rusch et al. 2000, 2002), and Temporary Emergency Exposure Limits (TEEL), in that priority, as the emergency exposure limits (DOE 2005, 2010, 2012) for DOE and its complexes. Similarly, successive PACs (i.e., PAC-1, -2, and -3) are benchmark values associated with increasingly severe acute health effects due to short-term (60 min) exposures (DOE 2008) (see Appendix A, Section A.3, for details).

It is important to emphasize that any initial recommendations for OELs or TECs, must be independently peer reviewed. After revising the exposure guidelines based on the external peer review the recommendations and supporting documentation will be submitted to the TOC and DOE for final review and approval. It also should be emphasized that for many, if not most of the chemicals that have historically been measured in the headspaces of waste storage tanks at the Hanford tank farms, insufficient toxicological data are available for establishing short-term exposure guidelines under the NAS process. Consistent with the TVAT report recommendations, alternative strategies will need to be considered. These strategies may include, but not be limited to, establishing short-term excursion limits for chemicals with some limited data (Jayjock et al. 2000), recommending preliminary total organic/inorganic chemical exposure levels based on known highly toxic constituents, recommending additional testing for prioritized COPCs or representative headspace mixtures, or developing computational exposure and dosimetry models based on physical/chemical properties, Quantitative Structure-Activity Relationships, etc., to establish preliminary exposure limits. In addition, atmospheric dispersion models can be integrated with evaluated exposure values for near real-time forecasting and guiding industrial hygienists for worker protection and exposure prevention using the database as a platform.

3.0 Hanford Tank Farm Occupational Exposure and Risk Assessment Advisory Team

Establishing the Assessment Team is an essential component of the response to recommendations of the TVAT report (SRNL 2014). The Assessment Team should have two primary components: 1) a Working Group responsible for developing the technical information, analysis, and recommendations and 2) an Internal Review Panel responsible for reviewing Working Group recommendations and assessing implementation decisions. The team will serve as a central resource for the TOC and DOE and will be responsible for integrating all information about tank farm emissions (including analytical data, simulations, and IH surveys), establishing exposure guidelines for constituents with known toxicities, prioritizing constituents for toxicity screening (individual components or mixtures), and recommending screening approaches that enable more effective risk-management decisions and stakeholder communication.

Roles and Responsibilities of the Assessment Team

- Establish a Team Charter for organization, membership, record-keeping, decision processes, and communications.
- Prioritize constituents and mixtures for toxicity screening.
- Establish standard operating procedures and recommended exposure guidelines for constituents of concern.
- Develop and maintain an information database on tank farm analyses, exposure monitoring, and peer-reviewed literature.
- Organize and administer the EEP.
- Serve as a central resource for Hanford/DOE risk management decisions and stakeholder communication.

The Assessment Team should include members who have expertise in multiple scientific disciplines, such as toxicology, occupational health, IH, analytical chemistry, risk assessment, and exposure/dosimetry modeling. Core membership should be drawn from multiple organizations including the TOC, PNNL, other Hanford contractors, DOE Office of River Protection, and local/regional medical and academic institutions as long as they have the appropriate expertise, availability, and ability to meet regularly onsite. To be successful, this must be a fully funded, not volunteer, activity with administrative and information technology technical support.

Ideally, Assessment Team members should serve a minimum of one 3-year term to establish and maintain operational continuity and core expertise on Hanford tank farm occupational exposures. A Chairman (preferably a TOC manager) and a Vice-Chairman, with administrative support, will lead the team. Once established, the team will develop a charter for operation, membership (core and ad hoc), and decision processes that will be evaluated and approved by TOC and DOE. The Assessment Team charter also should include organizational principles for establishing an EEP (see below) along with clear roles and responsibilities for reviews and decision processes associated with the establishment of OELs and recommendations for new research. The Assessment Team and EEP will require administrative support to facilitate scheduling, meetings, record-keeping, budgeting, and reporting requirements.

4.0 External Expert Panel

An EEP will be established to provide the Assessment Team (including the Working Group and the Internal Review Panel), TOC, and DOE with critical, external peer reviews of standard operating procedures and recommended OELs, and to serve in an advisory role for proposed research and assessment strategies. Like the Assessment Team, the EEP should include nationally recognized experts in risk assessment, exposure science, chemistry, toxicology, occupational health, and IH, who can serve multi-year terms to maintain operational continuity and core expertise on tank farm occupational exposures. The final organization, roles, and responsibilities of the EEP will be delineated as part of the Assessment Team charter. Assistance from the Assessment Team should be provided to the EEP to facilitate meetings, record-keeping, travel, and overall coordination of activities and recommendations.

5.0 Hanford Tank Farm Occupational Exposure and Risk Assessment Databases

To assist the Assessment Team and EEP in their deliberations, we further recommend that updatable electronic databases be established that allows for the documentation and integration of:

- Available environmental and toxicology literature (published and unpublished reports)
- Available exposure guidelines
- Existing and new data on tank vapor measurements (e.g., head space and site-specific emissions)
- Existing and new IH exposure surveys (e.g., personnel monitoring, dosimetry, and biomonitoring)
- Site-specific and worker-specific exposure simulations (e.g., vapor and aerosol transport).

These databases are not substitutes or duplicates of existing IH databases (i.e. Site-Wide Industrial Hygiene Database or Tank Waste Information Network System), but will incorporate information from those databases as well as other sources of data that are of key importance to the Assessment Team and Washington River Protection Solutions management. Such database should have a user-friendly, secure interface that is accessible to registered contributors and users of the data and information. It should also be based on a platform that is most amenable to being updated over time as hardware and operating systems evolve. Sources for data and information that support the development of recommended exposure guidelines are provided in the Appendix A.

6.0 Health Process Plan Implementation Status

The initial implementation of the Health Process Plan (HPP) plan began in late FY 2016, and work in this area will continue through FY 2019. The effort has focused on four primary areas outlined in the plan: 1) defining and implementing processes for prioritizing constituents of concern and proposing exposure limits, 2) implementing an internal Assessment Team and EEP, 3) soliciting EEP feedback and recommendations, and 4) establishing an HPP database to support the plan implementation. This section summarizes the status of HPP implementation through FY 2018 and outlines the research scope for FY 2019.

6.1 Process for Prioritizing Constituents of Concern

Guidelines for identifying COPCs were originally developed over 10 years ago and have been documented in a number of PNNL and Tank Operations Contractor reports, including the IH Chemical Vapor Technical Basis (Meacham et al. 2006). The screening criteria used to determine whether a tank vapor chemical should be added to the COPC list is based on its detection at $\geq 10\%$ of the OEL value or screening criteria used in prior analysis (if no OEL had been identified).

The process to update and prioritize COPCs was implemented in 2016 (Hoppe et al. 2016) to ensure that tank vapor source data collected over the past 10 years since the IH Chemical Vapor Technical Basis was issued has been systematically evaluated. A subsequent, incremental update was completed in 2017 (Mahoney and Hoppe 2017) to address new headspace and exhaust data collected between 2015 and 2017 that were not available for the 2016 update. As a result of these updates and recommendations, two additional COPCs—dimethyl mercury and 2-propenal—were added to the COPC list.

6.2 Process for Proposing Chronic and Acute Exposure Limits

A general approach outlined in the IH Chemical Vapor Technical Basis (Meacham et al. 2006) established a process for defining and updating chronic OELs for all COPCs. The OELs of COPCs for chronic exposures have been updated annually based on the most recent toxicological literature (Weber et al. 2018, Smith et al. 2018). Acute exposure levels for COPCs with regulatory guidelines were also surveyed and evaluated (Yu et al. 2018). COPCs with significant interest such as furans and nitrosamines were evaluated separately resulting in two reports that have not yet been published.^{2,3}

The process to update chronic exposure guidelines for all COPCs was initiated in 2016 with a broad literature review of current regulatory guidelines and toxicological research results to evaluate for potential updates to current Hanford Tank Farm OELs. In 2017–2018, a series of reports documented the review of the current exposure guideline data and recommended changes to exposure guidelines for specific COPCs. Specifically:

² Smith, JN, JG Teeguarden, and TJ Weber. 2017. *Proposed Risk-Based Approach for Nitrosamine Chemicals of Potential Concern*. PNNL-26787 Rev. A, Pacific Northwest National Laboratory, Richland, Washington. Not published.

³ Smith, JN, JG Teeguarden, and TJ Weber. 2017. *Proposed Occupational Exposure Limits for Furans*. PNNL-26775 Rev. A, Pacific Northwest National Laboratory, Richland, Washington. Not published.

- Thirty-four COPCs with available chronic regulatory guidelines, as defined by government or private agencies engaged in OEL development, were reviewed and recommended updates were documented (Weber et al. 2018). Updates to regulatory guidelines were recommended for four existing COPCs and two new COPCs.
- Nine additional COPCs with available chronic regulatory guidelines⁴ were reviewed and documented in a separate report (Smith et al. 2018). A separate review was necessary to clarify potential conflicting information identified in the literature review. The conflicting information was attributed to a change in weight-of-evidence used in the updated risk assessments. Based on this finding, no changes to the current regulatory guidelines were recommended for these COPCs.
- Eighteen COPCs underwent risk assessment as carcinogens and, therefore, do not have regulatory chronic OELs. Rather, COPCs with carcinogenic potential are regulated as low as reasonably achievable using a risk-based approach to establish risk-specific doses for occupational exposures. Four nitrosamine compounds, and 14 furan or substituted furan compounds were evaluated, and recommendations were documented in two draft reports.^{2,3} These reports and corresponding recommendations are undergoing external peer reviews and technical and economic implementability assessments before implementation decisions are made and the final reports are published.

Acute exposure levels for tank vapor constituents also were evaluated and recommendations were proposed (Yu et al. 2018). Several key resources were used to identify existing acute exposure guidelines, including Short-Term Exposure Limit, AEGL, and ERPG values. Priority in identifying acute exposure sources was given to values reported by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA) due to contractual obligations of Hanford cleanup contractors to adhere to specific ACGIH exposure limits and OSHA as a legal authority. This follows the same principle used in the chronic OEL development for COPCs (Weber et al. 2018).

- Twelve COPCs with available acute regulatory guidelines, as defined by authoritative government or private entities engaged in OEL development, were reviewed and proposed exposure guidelines documented (Yu et al. 2018).
- Acute exposure guidelines for the remaining 49 COPCs have not yet been fully established, largely because only a small fraction of COPCs have acute exposure guidelines established by authoritative sources. In these cases, an approach for identifying short-term exposure concentrations (i.e., TECs) was proposed and a preliminary evaluation completed in FY 2017 for 16 of the remaining COPCs with a higher potential for available toxicological data.⁵ This analysis and corresponding recommendations are undergoing external peer review, and technical and economic implementability assessment before implementation decisions are made and the final report is issued.

In addition to identification of chronic and acute exposure guidelines for specific COPCs, work activities were undertaken in FY 2017 to assess the potential impacts of chemical mixtures, including adaptation of existing DOE risk assessment tools to the Hanford Tank Farm vapors application.

⁴ For some nitrile-class COPCs, the chronic _{HTF}OEL is based on the use of a surrogate chemical with a regulatory guideline because no regulatory information on the specified nitrile COPC could be identified.

⁵ Yao, J, X-Y Yu, TM Brouns, JG Teeguarden, and TJ Weber. 2017. *Assessing the Potential for Chronic or Acute Health Effects from Exposure to COPC Mixtures*. PNNL-27089 Rev. A, Pacific Northwest National Laboratory, Richland, Washington. Not published.

- Adaptation of the CMM for evaluating the potential cumulative hazard of exposure to mixtures of COPCs was undertaken in FY 2017, and preliminary assessment documented⁵. The approach relies on COPC-specific health code numbers (HCN) that are used to summarize the target organs that have been adversely affected by the specific chemical. Only 28 of the 61 COPCs have HCNs assigned based on prior DOE analysis. Therefore, direct application of the CMM requires additional HCN development, which is being pursued in FY 2019. CMM analysis and corresponding recommendations are undergoing external peer review and technical and economic implementability assessment before implementation decisions are made and the final report is published.
- New approaches for direct measurement of respiratory effects resulting from exposure to chemical mixtures are potentially feasible using in vitro assay systems, which could potentially provide data on both mixture effects as well as new toxicological data for TEC development in cases where data is lacking. However, this method is at the research level and has not been demonstrated or proven for this application. The suggested approach is undergoing external peer review and technical and economic implementability assessment before making implementation decisions and publishing the final report.

6.3 Occupational Exposure and Risk Assessment Advisory Team and External Expert Panel

Recommendations on the development of both a TOC advisory team and an EEP documented in this report were considered and used in the development of a process and procedure within the TOC. The resulting “Charter 71” process (TFC 2017, 2018) included an Internal Review Panel, to review HPP reports and recommendations, and make implementation decisions within TOC. An EEP also was formed, and it held its first meeting in FY 2018 to serve as an additional review body for those reports and recommendations that warranted external input.

6.4 Hanford Tank Farm Occupational Exposure and Risk Assessment Database

An HPP project database was developed and deployed in FY 2016 through FY 2018. The database provides a readily accessible repository for source materials (e.g., toxicological literature, reports, etc.) and also a report generation tool for tracking the basis for exposure guidelines and updating guidelines in the future as new toxicological data becomes available.

7.0 Technical Details/Appendix

Appendix A contains additional technical details about the recommended organizational structure and technical approaches that should be considered. These recommendations should be considered a starting point for the Assessment Team. It is fully anticipated that as strategies and procedures are implemented, modifications will be implemented to improve the overall process.

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Appendix A

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Technical Details Concerning Recommended Organizational Structure and Approaches

Appendix A

Technical Details Concerning Recommended Organizational Structure and Approaches

This appendix presents additional details regarding the recommended organizational structure of the standing Hanford Tank Farm Occupational Exposure and Risk Assessment Advisory Team (Assessment Team) and External Expert Panel (EEP) that are to be established. Technical details are presented related to updating screening values/maximum headspace concentrations, a strategy for establishing acute/transient and chronic exposure limits, computational methods for predicting exposure and delivered dose, methods for prioritizing mixtures of concern, and methods for evaluating and prioritizing odor threshold and sensory/irritation response.

A.1 Tank Contractor Assessment Team and External Expert Panel

A.1.1 Tank Contractor Assessment Team

A potential structure for the Assessment Team organization is illustrated in Figure A.1.

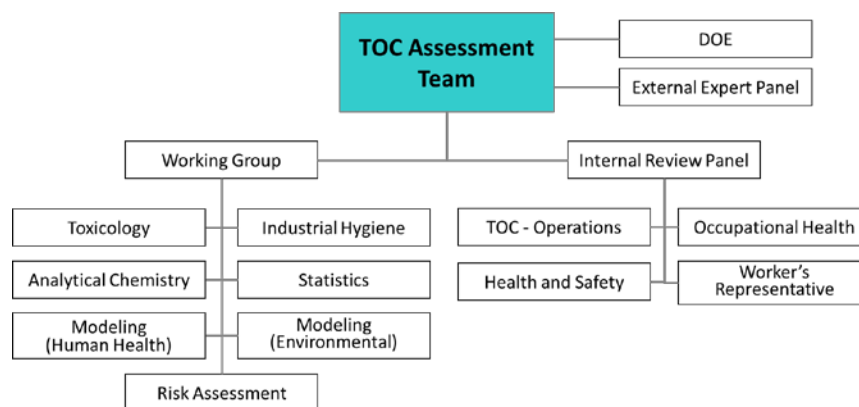


Figure A.1. Proposed Tank Operations Contractor (TOC) Assessment Team Organization

As previously noted in the main body of this report, the Assessment Team will include two components: 1) a technical Working Group that will serve as a central resource for the TOC and 2) an Internal Review Panel. The team will be responsible for integrating all information about tank farm emissions, exposure guidelines, and critical data or research needs that enable risk-management decisions and stakeholder communications. The Assessment Team should be a TOC function under the leadership of a senior manager who has overall responsibility for worker health. This individual will be the conduit for communications among the Working Group, Internal Review Panel and other TOC managers, the U.S. Department of Energy (DOE), and the EEP. In addition, it is desirable to have regular DOE participation or briefings from the team to provide oversight and guidance and to facilitate transparent communication among the team, the TOC, and DOE. The Assessment Team is anticipated to include expertise, when available, from the TOC as well as outside consultants/contractors (as needed) to be selected by TOC management. It is recommended that the key technical capabilities/stakeholders, as outlined in Figure A.1., include at a minimum the following technical expertise:

- **Analytical Chemistry.** A senior analytical chemist with expertise in quantitative analytical chemistry methods and free radical chemistry will support the identification of priority chemical tank farm vapor/aerosol constituents. Ideal candidates will have previous experience in analyzing tank farm vapors and/or experience in complex mixture chemistry. Along with expertise associated with the detection and identification of key contaminants, expertise associated with the identification of transient reactive chemical species would be useful to support environmental exposure modeling.
- **Modeling (Environmental).** Because of the inherent challenges associated with detecting and quantifying transient releases of tank vapors, it is imperative that alternative approaches for estimating tank vapor releases be in place. To accomplish this, the Assessment Team should include a scientist who has expertise in computational dispersion modeling of complex vapor mixtures. In addition, expertise in modeling complex atmospheric chemical reactions and dispersion kinetics is needed. It is anticipated that these modeling activities will be used to establish maximum atmospheric concentrations of tank vapors based on headspace concentrations and relevant environmental conditions that will affect vapor concentrations and dispersion rates within the tank farms. Results will be used to establish theoretical vapor concentrations for risk assessment in the absence of analytical quantification. It is anticipated that the implementation may differ from this plan, as the plan is to highlight key technical elements and guide how the scientific principle can be carried out.
- **Modeling (Human Health).** Quantitative dosimetry modeling should be used to predict delivered dose to target organ(s) based on quantitative analytical chemistry assessment and/or computational dispersion modeling of vapors. Scientific expertise will be needed to support dosimetry model development for specific tank constituents and complex chemical mixtures. The approach should exploit both physiologically based pharmacokinetic and computational fluid dynamic modeling methods to quantify dose/exposure. Results should be used to support assessments of occupational health risk and establish target exposure guidelines.
- **Occupational Health.** The team should include an occupational physician who has specific experience dealing with worker exposure to tank vapors. The occupational health specialist should be capable of providing clinical perspective on the signs and symptoms associated with tank vapor exposures, and important linkages among exposures, clinical observations, and toxicological endpoints of concern. In addition, this team member should provide perspective on available epidemiology studies, particularly as related to both long- and short-term tank vapor health effects.
- **Risk Assessment.** Because a critical outcome for the Assessment Team is the recommendation of acute and chronic Occupational Exposure Limits (OEL), it is important to include risk assessment expertise on the team. Statistically based risk assessment approaches (cancer and non-cancer) will be important for the establishment of acceptable thresholds of exposure. Technical approaches need to be based on current best practices that are acceptable to both state and federal authorities (Occupational Safety and Health Organization [OSHA], National Institute for Occupational Safety and Health, U.S. Environmental Protection Agency [EPA], DOE, Washington State Department of Health, etc.).
- **Toxicology.** Health effects data based on both human and animal (laboratory-based) chemical exposure studies are the key foundational components for establishing human health risk. The toxicological risk analysis should include hazard identification, dose-response (DR) assessment, and linkage to exposure assessment, based on analytical chemistry determination and computational modeling of exposure.

- **Industrial Hygiene (IH).** The Assessment Team should include a senior TOC IH member who has extensive experience associated with the tank farm IH program. This is especially important because an IH specialist can provide key insights into issues that are specific to the tank farms and can help guide the Assessment Team, particularly with regard to understanding what solutions are, or are not, feasible based on the IH member's experience.
- **Tank Operations.** The inclusion of tank farm operations expertise can provide the Assessment Team with key perspective on operational procedures and, from a practical perspective, insight into the feasibility of implementing proposed personal protective equipment or safety procedures onsite. The operations as well as IH team members also can provide important insight into potential sources of exposure within each tank farm.
- **Worker's Representative.** Including a team member who represents tank farm workers facilitates transparency and provides a voice for worker concerns.

A.1.2 External Expert Panel

Including an EEP with the mandate to advise the TOC Assessment Team's activities should be a key component of the overarching strategy and of particular importance for demonstrating process transparency and external validation. A potential organizational structure for the EEP is illustrated in Figure A.2. The EEP would be expected to provide input on a number of key processes, including setting exposure guidelines (acute and chronic), developing strategies for evaluating mixture responses, determining the relationships between odor thresholds and adverse effects, determining the role of computational modeling, and identifying research gaps.

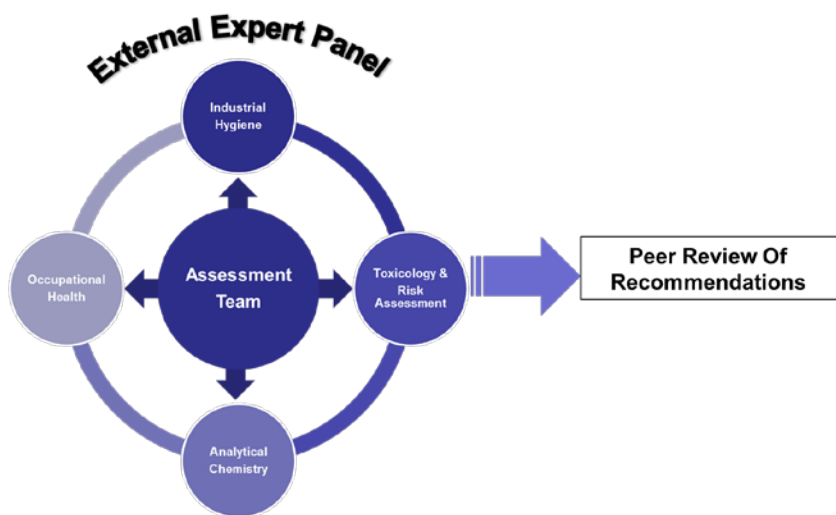


Figure A.1. External Expert Panel Organization

The specific individuals who would be recruited for the EEP should be chosen by TOC management with input from DOE. However as indicated in Figure A.2, it is recommended that senior scientists with technical expertise in the areas of IH, occupational health, toxicology/risk assessment, and analytical chemistry be considered for inclusion. EEP participants should be well recognized and respected in their fields of expertise and have some experience in dealing with complex mixture health effects. TOC management with input from the Assessment Team should specifically define the scope of responsibility for the EEP and the process that would be used for Assessment Team/EEP interactions.

A.2 Updating Screening Values/Maximum Headspace Concentration

A.2.1 Purpose

A previous evaluation reported by Poet et al. (2006) identified chemicals in the tank waste headspace for which OELs had not been established. Those chemicals should be further assessed for their potential health risks to tank farm workers. This was accomplished by establishing headspace concentration screening values for each chemical using available IH and toxicological data. The primary goal for establishing screening values was to facilitate identification of chemicals that could be elevated to COPCs, therefore requiring the establishment of both acute and chronic occupational exposure levels based on their maximum headspace concentrations. Screening values were highly conservative and intended to be more than an order of magnitude below concentrations that may cause adverse health effects in workers, assuming a 40-hr/week occupational exposure. Screening values were compared to the maximum reported headspace concentrations and any chemical with a reported maximum concentration that exceeded the screening value was further evaluated. In light of the potential for new IH and toxicology data and new data on maximum headspace concentrations for tank waste constituents, updated screening values are warranted. In addition, the assessment of screening values should now include adverse health effects associated with transient short-term exposures, mixture interactions, and odor/sensory irritation thresholds versus toxicity effects, if possible.

Further analysis of chemicals with screening values below maximum headspace concentrations will include re-evaluation of their presence in the tank headspaces to verify chemicals were correctly identified. New and more sensitive analytical tools that are capable of identifying unknown species in the headspace to protect worker's safety need to be employed. Chemicals verified to be components of the headspace then will undergo a more detailed toxicological reevaluation to refine OEL guidelines and establish Transient Effect Concentrations (TEC) for worker protection as needed. The general procedure for developing Acute Exposure Guideline Levels (AEGL) will be considered when developing TECs. Sampling and analytical methods will be developed as necessary and deployed to determine which, if any, of these chemicals are present in workers' breathing zones and at what concentrations. Based on these additional evaluations, exposure guidelines will be established as needed by the Assessment Team and peer reviewed by the EEP. Chemicals deemed to present no health risks (with maximum headspace concentrations below their screening values) will be listed as low-risk chemicals and only re-evaluated as new toxicological data become available.

Headspace characterization data that was collected after July 2005 (date of previous evaluation) and entered into the Tank Characterization Database via the Tank Waste Information Network System (TWINS) will be considered. In addition, new data collected during waste-disturbing conditions (tank mixing) will be a high priority for evaluation as well as associated stack, ventilation, and vent system data.

The resulting data will be identified by the sampling device used and the laboratory performing the analyses for each day of sampling from a given source (tank, vent system, etc.). This process will result in individual sample results, thereby preserving the distinction between results from different devices (e.g., sorbent traps and SUMMA[®] canisters) and the various analytical laboratories involved. The sampling strategy should consider the following:

- Any changes toward sampling considerations and analytical methodology must be deliberated through a coordinated effort that includes the analytical team.
- Addressing sampling issues can be a complex issue that must include consideration for the end use of the data.

- Is the data to represent the breathing zone?
- What adjustments should be made to account for the environmental and meteorological conditions (temperatures of the source and surroundings, boundary layer conditions such as wind speed and direction)?
- Are the contaminants lighter or heavier than air?
- How are replicate samples obtained (desorption tubes require chemistry considerations and multiple sampling trains, SUMMA canisters provide enough sample for many analytical attempts)?
- Are the compounds thermally labile (thermal desorption sampling can destroy compounds or produce artifacts)?

These new data will be compared against previously reported concentrations that were used to establish screening values (Poet et al. 2006); further assessments will focus on previously unidentified chemicals and the chemicals where headspace concentrations are now greater than the analysis reported by Poet et al. (2006). When possible, faster in situ data acquisition should be employed to capture sporadic transient species, accidental release of trace species, or unexpected leaks in the facility (Huckaby et al. 2004). Online measurements are necessary for reactive and unstable free radicals and volatile organic compounds that are suspected to form and transform in the head space. Such measurements are complementary to the routine monitoring and they provide additional insight on the nature of potential short-term acute exposures (SRNL 2014).

A.2.2 Establishing Headspace Concentration Screening Values

Screening values will be developed for each chemical as previously described (Poet et al. 2006). In brief, data used to develop the screening values will be ranked according to relevance to occupational exposure. For example, screening values based on inhalation exposure would take precedence over oral exposure because inhalation is highly relevant to tank farm exposures. If no appropriate exposure guidelines for the chemical of interest are identified, an OEL based on a structurally related chemicals (i.e., a surrogate) will be used. When no OEL for the chemical or a chemical surrogate is available, the assessment will be based on identification of toxic effects that are most relevant to occupational exposure. Toxicological parameters will be assessed on the basis of metabolic analogies, persistence, chemical and physical properties, chemical structures, and biological activity.

A.3 Strategy for Establishing Acute/Transient and Chronic Exposure Limits

A.3.1 Purpose

A large number of volatile compounds have been identified in the headspaces of single- and double-shell tanks used to store mixed chemicals and radioactive waste at Hanford. Concern about the potential exposure of workers to vapors during tank farm operations has prompted efforts to evaluate the potential health risk associated with exposure to these chemicals. OELs have not been established for many of these chemicals.

The proposed process is based on the strategy previously used for establishing and/or revising OELs for tank waste (Poet and Timchalk 2006) and represents a framework of technical guidance that is a common approach used by toxicologists and/or risk assessors. The overarching goal is to outline a process that can be used by the Assessment Team to assign OEL and TEC values needed to address both chronic/repeated

exposures and short-term transient exposures, respectively. The target agents are chemicals or families of chemicals that may not have established OELs or acute exposure guidelines or require revisions based on new health effects information found in the available literature. An OEL is defined as an upper limit on the acceptable concentration of airborne hazardous substances for which the majority of workers could be repeatedly exposed over a working lifetime without experiencing adverse health effects (8-hr, time-weighted average); whereas, TECs represent acute exposure guidelines for transient and reversible human health effects from sporadic, or rare, exposure to airborne chemicals in an occupational environment. Existing exposure guidelines that do bear the acute and short-term nature yet result in reversible effects include Short-Term Exposure Limits, Threshold Limit Value-C (TLV-C), AEGL-1 and PAC-1. However, AEGL-1 is evaluated for the general population. Although PAC-1 is developed for DOE uses, its scientific basis is strongly attached to AEGL and Emergency Response Planning Guidelines (ERPG) values. Therefore, neither AEGL-1 nor PAC-1 can be directly translated into an occupational exposure TEC for a particular chemical. AEGLs are threshold exposure limits ranging from 10 min to 8 hr (10 min, 30 min, 60 min, and 4 and 8 hr) of exposure with three levels of toxic-effect severity (AEGL-1, -2, and -3) as defined by the National Academy of Science (NAS 2001). Of particular relevance for transient exposures are the AEGL-1 action levels for short-term (10 min) exposures. DOE developed PACs based on AEGLs and ERPGs (Rusch 1993; Rusch et al. 2000, 2002), and Temporary Emergency Exposure Limits (TEEL), in that priority, as the emergency exposure limits (DOE 2005, 2010, 2012). Similarly, successive PACs (i.e., PAC-1, -2, and -3) are benchmark values associated with increasingly severe acute health effects due to short-term (60 min) exposures (DOE 2008).

A.3.2 Established Exposure Guidelines

OELs established by OSHA are legal obligations for defined industries. The National Institute for Occupational Safety and Health is an arm of the Centers for Disease Control and Prevention and makes recommendations to OSHA regarding OEL values. The American Conference of Governmental Industrial Hygienists (ACGIH) is a private organization that recommends OEL values to industry for voluntary application. Other human exposure standards have been published (e.g., by the ERPG Committee of the American Industrial Hygiene Association [AIHA], the AIHA Workplace Environmental Exposure Levels, the AEGL Committee of the EPA, and the NAS). However, their applicability as OEL/TEC values must be evaluated in each case. The DOE mandates the need to comply with OSHA and ACGIH standards in its contract with the TOC; in cases where two standards exist, the more stringent of the two standards will be applied.

Because of the nature of potential sporadic short-term exposure of the complex and unique organic vapor mixtures at the Hanford Site and associated concerns about health effects, TECs are proposed for assessment of acute toxic effects when acute exposure values are not available. The DOE PAC values are a resource during TEC development (Craig et al. 1999, 2000). This data set encompasses more than 3100 chemicals present at various sites (DOE 2008, 2016a), covering more chemicals than the AEGLs and ERPGs combined. When a regulatory acute value does not exist for a chemical, a TEC value can be developed, depending on availability of adequate toxicological data.

The principal differences between AEGLs, ERPGs, and TEELs are how they are developed. There also are subtle differences in how they are defined. AEGLs pertain to the "... general population, including susceptible individuals," but ERPGs and TEELs pertain to "... nearly all individuals." AEGLs are defined as the level "above which" certain health effects are expected, while ERPGs and TEELs are defined as the level "below which" certain health effects are not expected. ERPGs refer to an exposure duration of 1 hr (with shorter periods for some chemicals); AEGLs are developed for five time periods; and TEELs are defined for a 15-min period (Craig et al. 1999). When TEELs were first developed, the exposure severity was based on a peak 15-min time-weighted average concentration (DOE 2008). In recent revisions, PAC

values are recommended to be developed by direct comparison with the 60 min AEGLs (DOE 2008). Considering the nature of acute exposure and sporadic occurrences of vapor release, the 15-min TEC development may be preferable for the tank farm application.

A.3.3 Overview of Approach

NAS (1983, 1994, 2001) and the Government Accounting Office (GAO 2001) have provided overall guidance for chemical risk assessment as further developed and applied by U.S. regulatory agencies. The process for establishing exposure guidelines for tank waste chemical exposure is modeled after the generalized scientific approaches used by OSHA and ACGIH to establish OELs for worker exposure; the scientific approach used by other regulatory agencies such as NAS and EPA to establish AEGLs for airborne pollutants also are considered. A standard operation procedure will be developed for TEC evaluation to properly reflect the unique need of occupational health applications of acute exposure guidelines in the vapor project.

The flow diagram shown in Figure A.3 illustrates the key steps in the assessment process. The approach first requires identifying specific chemical agents or classes of chemical agents that are detected in a tank headspace at or above previously established screening values. Chemical agents that exceed the screening values will undergo a more extensive evaluation with the goal of establishing suitable TEC values for tank farms operations.

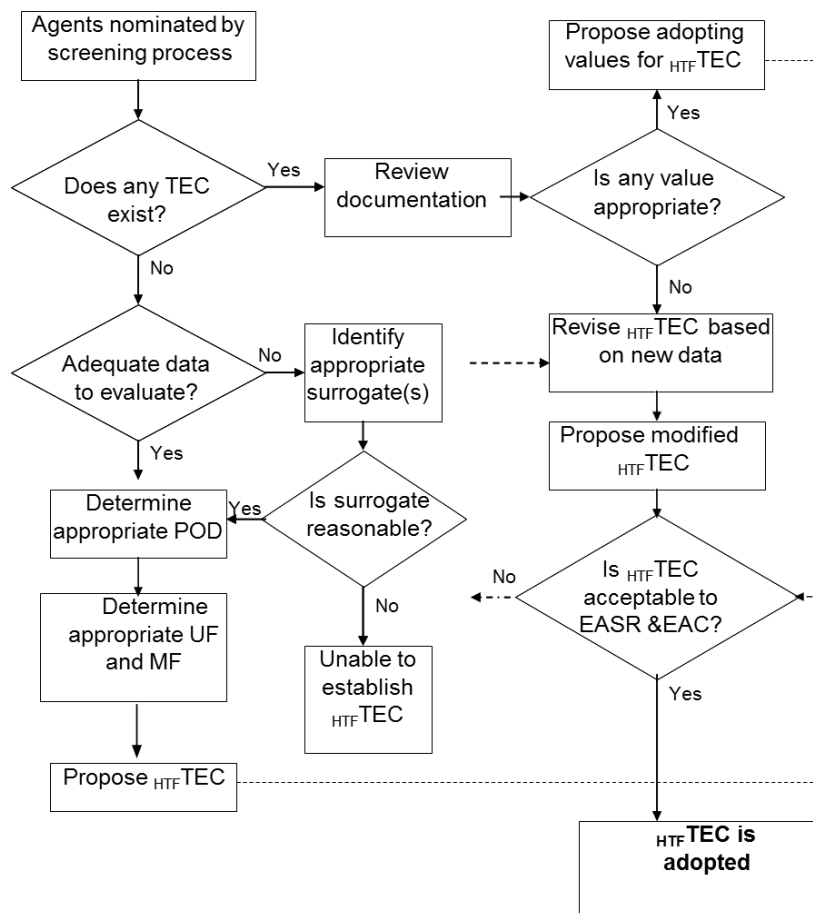


Figure A.2. Strategy Outline for Establishing HTF TEC Values

Exposure Guideline Evaluation

First, a detailed review of relevant exposure guidelines will be undertaken. In the absence of appropriate exposure guidelines, available epidemiology and toxicology information about a given chemical or chemical class will be reviewed to identify potential hazards, select critical effects, and estimate a DR to determine suitable exposure levels (Haber and Maier 2002). Consistent with the technical approaches ACGIH uses for establishing a TLV, the exposure guidelines will be based on the best scientific information available and will include a critical evaluation of all supporting information (ACGIH 2005). The goal of the process will be to delineate the most important adverse effects for specific chemicals within the waste tanks. In evaluating the health effects, human data such as epidemiology studies would be of prime importance, but for many of the chemicals of concern, there will be little, if any, available data from human exposures. The second tier evaluation will focus on the most relevant and sensitive animal toxicity data for the chemical and/or chemical class. In this case, the basis for the exposure guidelines will be the DR relationship of the toxic effects of greatest concern, and the point of departure for calculating the OELs/TECs will be the associated no-observed-effect-levels/lowest-observed-effect-levels (NOEL/LOEL). The rationale for the selection of a given toxic effect for establishing the exposure guidelines will be documented.

When setting an exposure guideline, an appropriate risk assessment approach will be used; it will be selected based on the critical toxicological effect, the observed DR, and the quality of the data used for the assessment (ACGIH 2005). This approach may include the use of quantitative DR models such as the benchmark dose, and/or the application of added safety factors to a NOEL/LOEL to address uncertainty.

Before establishing and implementing a formal exposure guideline for worker protection in the tank farms, the proposed exposure level for a given chemical and/or chemical class will be documented, reviewed by the Internal Review Panel, and as appropriate submitted to the EEP for peer review. Ideally, the peer reviewers will include a range of health and science professionals, who could include representatives from occupational health, toxicology, risk assessment, IH, analytical chemistry, and worker groups. The objective of the review will be to critically assess the rationale for establishing the OELs/TECs, provide the broad base of stakeholders an understanding of the rationale for the exposure limits, and provide stakeholders an opportunity to submit appropriate input to the assessment.

A.3.4 Database and Literature Evaluation

Database Searches

It is imperative that relevant human exposure, epidemiology, and toxicological information be considered when establishing exposure guidelines. A methodical analysis of the available literature as it relates to hazard identification and quantitative DR toxicity evaluation is central to the risk assessment process. Internet databases such as The Toxicology Data Network (TOXNET®), TOMES®, PubMed®, the International Agency for Research on Cancer (IARC), and/or STN® should be primary sources for initiating searches. The searches should include both the name and Chemical Abstracts Service registry number of the compound of interest (see Table A-2). These databases contain information applicable to toxicological assessment of chemicals, and the information they provide may overlap. For example, both TOXNET and TOMES contain Registry of Toxic Effects of Chemical Substances (RTECS®) and Hazardous Substances Data Bank (HSDB®) files. In the event RTECS and/or HSDB files do not exist for a compound or are considered insufficient, the TOXNET literature and/or PubMed databases should be searched and the original literature evaluated for any relevant information. If relevant information is not located in this manner, PubMed may be searched directly and/or the chemical abstracts database searched through STN. If information is found in one or more of the above sources but is incomplete, conflicting,

or considered insufficient, other sources such as the National Institute of Environmental Health Sciences National Toxicology Program, IARC, EPA, and Agency for Toxic Substances and Disease Registry Monographs may also be searched. Frequently, more in-depth information about a chemical of interest or its surrogate can be located in this way and may be useful in assigning an exposure limit.

A.3.5 Literature Evaluation of Published Exposure Guidelines

Initial efforts should focus on a comprehensive evaluation of the available literature that will identify any published exposure guidelines for the chemical of interest or for a reasonable surrogate. The summary documentation used to support the establishment of the exposure limits should be reviewed to ascertain its relevance, and any exposure limit that is adopted based on these published OELs/TECs should include appropriate documentation justifying the scientific rationale for its use.

Surrogate

If there are no appropriate exposure guidelines for the chemical of interest, it may be reasonable to identify and assign an exposure limit based on a structurally related chemical (surrogate). In addition to being structurally related, ideal surrogates could have a similar toxicological profile (i.e., similar target organs and response), although they may display greater or lesser potency than the chemical of concern. The basis for the choice of the surrogate should be explained and the explanation should include a brief discussion of the rationale for the assigned exposure limit for the surrogate.

A.3.6 Toxicology Evaluation

Toxicity Review Criteria

In evaluating the toxicity profile for a chemical or chemical class, the assessment should be prioritized based on identification of toxic effects that are particularly relevant for occupational exposure. This would include the following steps:

- Identify chemical agents that have a high acute toxicity potential, such as Category 1 chemicals, as defined by the Organization for Economic Co-operation and Development (OECD 2004). Chemicals in Category 1 that are considered to have high acute toxicity potential and have lethal dose for 50% of test population (LD₅₀) and Lethal Concentration for 50% of test population (LC₅₀) values of ≤5 mg/kg oral and ≤100 ppmV inhalation, respectively. These would be of particular concern if the LD₅₀/LC₅₀ values do not have large safety margins (<100) between observed toxicity and potential exposure levels.
- Give priority to the evaluation of studies that use the most relevant occupational exposure routes (Inhalation >> Oral > Dermal > Others [intravenous/intraperitoneal]).
- Give priority to well-characterized DR toxicity studies, particularly those that include a more comprehensive evaluation of the toxicity, which includes quantitative in vivo (Acute → Sub-Chronic → Chronic) experiments.

The toxicity testing paradigm suggests that with increasing length of chemical exposures (i.e., acute → chronic), effective dose levels generally decrease such that the lowest NOEL/LOEL will be determined from long-term studies. In addition, long-term chronic studies can identify chemicals that have the potential to produce a broad range of chronic health effects. An important strength of this testing paradigm is that it provides a fairly comprehensive in vivo toxicological evaluation that can be used to link DR results across a very broad range of exposure routes (oral versus inhalation), doses (low doses

versus high doses), durations (sub-chronic chronic), and species (rat versus dog). The use of this type of testing data will provide greater confidence (less uncertainty) in the exposure limit that is established.

Minimal Data Sets

As discussed by Haber and Maier (2002), a number of regulatory authorities, including the Health Council of the Netherlands (Health Council 2000) and EPA (1994), have established minimum data requirements based on the rationale that any value derived from data that is less than the minimum prescribed would have too much uncertainty. An alternative approach is to identify the types of data that are particularly useful and use a weight-of-evidence approach in the evaluation that looks at the sum total of all available information (SCOEL 1999; Haber and Maier 2002). In this case, a weight-of-evidence review for the development of exposure guidelines would focus on evaluating the types of studies that have greater relevance to occupational exposure and can be used to establish a DR relationship.

For the purpose of this assessment process, a minimum data set would not be established and a weight-of-evidence approach would be used. Because of the anticipated lack of robust toxicity data, a minimum data set would most likely be difficult to achieve for the broad number of chemical agents being evaluated, particularly when there is a need to apply surrogate chemical data in the assessment. The documentation and the peer reviewers are anticipated to provide the means to assess the degree of confidence that should be placed on the exposure limit. It is important to recognize that with the unique chemistry associated with chemical/radioactive tank waste, appropriate toxicity data on the chemicals of interest or their reasonable surrogates may be absent, making the establishment of a defensible exposure limit problematic. In these cases, it may not be possible to establish OELs/TECs with any confidence, pending the availability of additional toxicity data from the literature.

Use of Surrogate Toxicity Data

When forced to use a surrogate chemical or chemical class for developing an exposure guideline, it is important that the surrogate have as robust a toxicology database as possible. The use of a surrogate chemical with a well-characterized toxicity database means that it will have a clear DR relationship and a clearly defined NOEL to use as a point of departure for establishing OELs/TECs. Substantially more uncertainty should be assigned when using surrogates that lack a robust toxicity database. A written assessment of the overall strengths and weaknesses of the surrogate chemical should be included in the documentation.

Procedure for Calculating OELs/Acute Exposure Guidelines

Point of Departure

The overarching goal in evaluating the toxicity databases is to determine a point of departure for developing an exposure guideline. Haber and Maier (2002) defined the point of departure as the concentration to which uncertainty factors (UF) are applied to derive an OEL. The point of departure is most likely the NOEL/LOEL that was determined from the most appropriate toxicity study. In practice, this is usually the lowest determined NOEL that was derived experimentally. It also is possible to use a benchmark dose approach, as described below, to determine a point of departure, particularly when the experimental studies did not identify a NOEL (Fillipsson et al. 2003; Haber and Maier 2002; Crump 1984; Dourson et al. 1985).

Approach for Developing Exposure Limits for Non-Cancer Effects

As suggested by Bailey (2002) and others, there are numerous sources of uncertainty in the establishment of an acceptable exposure level. The approach used for identifying an acceptable exposure level for the general population or for occupational-related exposures is to adjust the NOEL or LOEL downward. The magnitude of the downward adjustment reflects the degree of uncertainty concerning the acceptable exposure limits. To address these uncertainties, empirical factors may be used to account for inadequate experimental data, interspecies variability, human variability, or extrapolation for short-term to long-term studies (EPA 2002; Dorne and Renwick 2005). In addition to UFs, additional modifying factors (MF) also have been occasionally used by some regulatory agencies such as EPA to reflect uncertainties not addressed by other factors. Equation (A.1) will be used to calculate the OEL/TECs.

$$OEL \text{ or } TEC = (NOEL \text{ or } LOEL) \div (UF \times MF) \quad (A.1)$$

The application of empirical UFs to determine the exposure guideline is based on the methods the EPA uses for deriving a Reference Concentration (EPA 2002). The default UF generally covers a single order of magnitude (i.e., 10^1), or a value of 3 is used in place of one-half powers (i.e., $10^{0.5}$). Additional factors also could be considered for inadequate data and for extrapolation from less than a lifetime to lifetime exposures. As the EPA suggests, supporting documentation should include the justification used for the individual factors selected. In addition, as recommended by the EPA (2002), it is advisable to limit the total UF applied to any particular chemical to no more than 3000 and avoid deriving an exposure guideline that involves the full tenfold UF in four or more areas of extrapolation. The following uncertainty and MFs could be applied:

- *Extrapolation from animal data to humans (interspecies UF)*. This factor is intended to account for the uncertainty in extrapolating animal data to the case of average healthy human. It assumes that humans are more susceptible to the toxicity than the animal species evaluated.
- *Variability in the human population (intraspecies UF)*. This factor is intended to account for the variation in sensitivity among humans.
- *LOEL to NOAEL UF*. This factor is intended to address the uncertainty associated with extrapolation from LOELs to NOELs.
- *Sub-chronic to chronic duration UF*. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOELs to chronic NOELs.
- *Inadequate database UF*. This factor is intended to account for the inability of any single animal study to adequately address all possible adverse outcomes in humans.
- *MF*. This factor is intended to account for any other scientific uncertainties in the study or databases that are not explicitly treated by other UFs. The magnitude of the MF principally depends on professional judgment.

Establishing a NOEL Using Benchmark Dose

As noted by Dorne and Renwick (2005), the use of a benchmark dose as proposed by Crump (1984) defines a lower statistical confidence for the dose that corresponds to a predefined low level of increase in adverse effects over background. The benchmark dose approach provides a more quantitative alternative to the first step in the DR assessment of the NOEL/LOEL process (EPA 2000). This is particularly useful when a NOEL has not been adequately defined from the experimental data.

The EPA guidance document (EPA 2000) provides a detailed discussion of a number of important considerations, including the types of studies that are appropriate for benchmark dose, selection of the benchmark response values, choice of models for computing benchmark dose, and details concerning the computation of confidence limits for the benchmark dose. Based on the EPA criteria, a 10% response is at or near the limit of sensitivity in most cancer and non-cancer bioassays, and will be used as an appropriate Effective Dose₁₀ for the benchmark dose. As indicated in the EPA guidance (EPA 2000), the primary goal of the mathematical modeling is to fit a model to DR data, particularly at the low end of the observable DR range. The Akaike's Information Criterion is recommended for selection of an appropriate model for computing the benchmark dose limit. The values are computed for each of the models used in the benchmark dose calculation and compared to select the most appropriate model from the analysis. Once a benchmark dose value is selected, a lower confidence is placed on the benchmark dose to obtain a dose (benchmark dose limit) that assures with high confidence (95%) that the benchmark response is not exceeded. The benchmark dose limit can then be used in the numerator of Equation (A.1) to calculate the _{HTF}OEL, as described above.

Carcinogens

For chemicals that are known or suspected carcinogens, the ability to derive an OEL depends on the intrinsic toxicological properties of the compound in question. In developing its guidelines, EPA notes the importance of elucidating a mode of action (MOA) for a particular cancer response in animals or humans (EPA 2005). In this regard, as suggested by the Health Council of the Netherlands (Health Council 2012), four general categories of carcinogen MOAs can be distinguished:

1. Non-genotoxic carcinogens that can promote various phases of the cancer process without directly or indirectly damaging DNA.
2. Genotoxic carcinogens with a non-stochastic mechanism of action. These compounds do not directly interact with DNA but can ultimately result in indirect DNA damage.
3. Genotoxic carcinogens with a stochastic mechanism of action. These compounds can directly interact with DNA, thus resulting in DNA damage.
4. Genotoxic carcinogens with an unknown MOA.

In considering MOAs for chemical carcinogens in a risk assessment context, initial efforts should focus on determining if MOAs are associated with a linear or non-linear (threshold) DR. A linear response assumes that even one molecule has the ability to damage DNA and initiate cancer, whereas a non-linear threshold response assumes there is a dose, below which compensatory mechanisms are in play that effectively do not lead to a carcinogenic response. Based on these definitions, the linear DR is by far more conservative. In this regard, some MOAs are anticipated to be mutagenic and have historically been considered genotoxic with no threshold and have subsequently been assessed with a linear approach. Other MOAs may be modeled with either linear or non-linear approaches after a rigorous analysis of available data (i.e., weight-of-evidence) under the guidance provided in the framework for MOA analysis (EPA 2005). Those carcinogens with a non-genotoxic or non-stochastic genotoxic mechanism are generally assumed to exhibit a specific threshold concentration (dose) that needs to be exceeded to result in a cancer response. Establishing OELs for these chemicals may be addressed using similar approaches as described for non-carcinogens where a point of departure is defined and additional safety factors can be applied to establish an exposure limit based on known criteria and uncertainty. According to EPA (2005), a point of departure marks the beginning of extrapolation to lower doses. The point of departure is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses. However, for genotoxic carcinogens with a stochastic mechanism of action or unknown mechanism of action, current scientific insights do not allow for establishing a safe exposure levels where there is no risk. In this regard, any level of exposure is assumed

to entail a certain risk of developing cancer. Hence, for these chemicals, a cancer risk value is an exposure level (i.e., air concentration) corresponding with a predefined extra risk of developing cancer (Health Council 2012).

Linear Approach

The EPA guidelines on carcinogen risk assessment (EPA 2005) notes that linear extrapolations should be considered when the MOA for a carcinogen is expected to have a linear component below the point of departure, which can be anticipated for chemicals that are DNA-reactive and have direct mutagenic activity. In addition, linear extrapolation is likewise the procedure of choice when the weight-of-evidence evaluation for all available data is insufficient to establish a plausible MOA. EPA recommends the use of non-linear approaches when there is adequate data supporting an MOA that is non-linear at low doses and the agent does not demonstrate mutagenic activity (i.e., linear response) at low doses (Health Council, 2012). For linear extrapolation, the assessment does not use UFs but rather a straight line is drawn from the point of departure for the observed data to the origin (zero). The slope of this line, called the cancer slope factor, is used to calculate excess cancer risk. For occupational cancer risk, a working period of 40 years (8 hr/day, 40 hr/week) is assumed, and risk estimates are determined based on available human epidemiology data and/or animal carcinogenicity studies.

In evaluating cancer risk for COPCs that do not have risk assessments from U.S. or internationally recognized entities, it is recommended that careful consideration be given to establishing risk levels based on approaches that are used by governmental and non-governmental entities that historically evaluate cancer risk. Table A.1 is an example from the Health Council of the Netherlands (Health Council 2012) that illustrates a potential range of risk levels for limiting occupational and environmental exposure to carcinogens.

Table A.1. Risk Levels used for Limiting Exposure to Carcinogens in the Workplace and in the Environment. Adapted from the Health Council of the Netherlands (2012).

		Risk Period	Exposure Period ¹	Risk Level
Occupational Health and Safety	Prohibitive Risk	Life	Working Life One Year	4×10^{-3} 1×10^{-4}
	Target Risk	Life	Working Life One Year	4×10^{-5} 1×10^{-6}
Environment	Maximum Tolerated Risk	Life	Lifetime One year	1×10^{-4} 1×10^{-6}
	Negligible Risk	Life	Lifetime One year	1×10^{-6} 1×10^{-8}

¹ For the calculation of the risk related to the exposure during a full (working) lifetime, a period of 40 years for workplace exposure and a period of 100 years for environmental exposure is taken into account.

A.4 Computational Approaches for Predicting Exposure and Delivered Dose

As noted in the TVAT report (SRNL 2014) and described in detail in Appendix I of that report, computational modeling was previously used to study fugitive tank vapor emissions (Droppo 2004). The Droppo report simulated measured tank ventilation rates under worst-case meteorological conditions and concluded, “Peak concentrations over a few second time-period can involve exposure to relatively undiluted air from the tank. Such exposures are limited to being quite localized because of the very small volumes of air.” The TVAT report also acknowledged that given the limited volume of any release and the potentially narrow plume path, the probability of any worker encountering the plume would be low and sporadic. Hence, the ability to actually “capture” a plume event for analytical quantification may remain particularly challenging.

Although the TVAT report recommends a number of technical strategies for measuring plume release and dynamics, and for developing sampling and analytical methods to measure “... all chemicals of health concern,” it also is recognized that the consistent measurement of potentially random events is problematic; hence, alternative computational approaches for simulating plume behavior, reactive chemistry, and human dosimetry are warranted.

A.4.1 Exposure Modeling

A proposed computational modeling strategy could focus on predicting exposure based on both plume behavior under relevant meteorological conditions as well as the dynamics of reactive chemistry. The TVAT report (SRNL 2014) clearly notes the importance of considering radiolytically generated free radicals (Bryan and Pederson 1995; Stock 2004) that would not be readily detected by most standard analytical methods because of their transient nature. Although previous strategies have primarily exploited computational fluid dynamic modeling to simulate plume behavior, a more robust computational strategy, similar to what is used to simulate the complex integrated nature of atmospheric chemistry, may be warranted. Extensive computational capabilities do exist, including modeling for atmospheric dispersion, chemical atmospheric mixing, trace gas and aerosol chemistry transport, and multi-scale modeling frameworks that can be exploited to support exposure assessment. These strategies have been developed to advance the prediction of highly complex chemical and meteorological atmospheric interactions at scales ranging from localized/regional events to global climate change. In addition, the capability to couple the toxicity evaluation of chemical mixture releases with atmospheric dispersion models can be appealing for consequence assessment in near real time that provide protective measure for worker safety. Feasibility has been demonstrated for such applications (Yao 2014). It is anticipated that these computational models could be exploited to simulate and predict transient vapor plume chemistry and behavior under a broad range of environmental conditions and therefore can be used to estimate worker exposures (see <http://www.pnnl.gov/atmospheric/modeling/>).

A.4.2 Biologically Based Modeling (Personal Exposure)

Although exposure modeling clearly provides important insight into tank vapor plume chemical concentrations available for inhalation, these models cannot directly predict the dose of chemical vapors/aerosols delivered to the respiratory tract (i.e., the delivered dose). The ability to simulate and predict the delivered dose of inhaled toxicants under a broad range of environmental conditions and human behaviors represents a major advancement in our ability to understand health risk, particularly under the highly transient worker exposure scenarios suggested by the TVAT report (SRNL 2014). Recent advances in the development and application of computational fluid dynamic/physiologically

based pharmacokinetic (computational fluid dynamic/physiologically based pharmacokinetic) modeling of dosimetry in the human respiratory tract could be exploited (Corley et al. 2012, 2015; Schroeter et al. 2008). These models are well suited to calculating respiratory tissue exposure to inhaled materials, particularly under realistic, transient breathing patterns (Corley et al. 2015). The ability to model breath-by-breath (i.e., transient) exposure is highly relevant for simulating sporadic tank vapor plume exposures that may last for a few seconds or minutes. A computational fluid dynamic/physiologically based pharmacokinetic model was recently used to simulate exposure to mixtures of relevant aldehydes (acrolein, formaldehyde, and acetaldehyde), and with additional chemical-specific model parameters such models can be advanced to address a broader range of chemical species of relevance to the tank farms.

Although biologically based modeling is useful for quantifying delivered dose, it is unrealistic to exploit this modeling strategy for the broad range of COPCs associated with tank vapors. Rather, careful consideration should be given to using biological modeling, in particular where the modeling of delivered dose can provide significant insight into health risk from tank vapor exposures.

A.4.3 Iterative Experimental Support for Modeling

Recent advances in the culture of human cells and their growth as organotypic cultures provide new and powerful opportunities to support safe tank farm operations. Damage to different subcellular compartments can provide biological readouts for chemical MOAs that can be used to advance our understanding of tank vapor toxic potential. As an example, a number of transcription factors that are activated by oxygen free radicals could be used to assess the importance of radiolytically generated free radicals as sources of toxicity in tank vapors. Human lung culture systems also can provide a rapid screening tool to assess chemical mixture interactions and test critical model assumptions. Where feasible, these tools could be employed to improve the interpretation of modeling and simulation results.

A.5 Prioritizing Mixtures of Concern

As noted in the TVAT report (SRNL 2014), the OSHA Mixture Rule was used to evaluate the impact of mixtures of chemicals that have similar health effects. The generalized approach was to group detectable chemicals at each sampling location (i.e., tank) according to their toxic effects and adding the mean concentrations divided by the OEL in accordance with the OSHA formula (see Equation A.2). If the equivalent exposure calculation (Em) is greater than unity (>1), mixture interactions are plausible. The TOC IH program action level for mixtures was set at $Em \geq 0.5$.

$$Em = (C1 \div L1) + (C2 \div L2) \cdots (Cn \div Ln) \quad (A.2)$$

Acute toxicity (any route of exposure), skin corrosion or irritation, serious eye damage or eye irritation, respiratory or skin sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, specific target-organ toxicity (single or repeated exposure), aspiration hazard, and asphyxiant all pose potential hazardous health effects (29 CFR Part 1910). Acute and chronic are generally used to differentiate between health effects according to severity or exposure duration. Acute effects usually happen rapidly in response to short-term exposures. Chronic effects occur because of long-term exposure. A most frequently used definition of acute effects from the American National Standards Institute refers to irritation, corrosivity, sensitization, and lethal dose. Other target organs, such as respiratory and nervous systems, may also suffer from short-term exposures.

When grouping toxic health effects, the Chemical Mixture Methodology (CMM) developed by the DOE Subcommittee on Consequence Assessment and Protective Actions should be considered (Craig et al. 1995). The CMM assesses mixtures of chemicals that can be separated into their component elements or compounds by pure physical processes. The mixtures are defined at the receptor location; the individual chemicals may have been stored as a mixture prior to the event that initiated their atmospheric release or may have been stored separately and only mixed after their release to the atmosphere. The CMM does not account for chemical reactions in the atmosphere between source and receptor. The CMM uses the “additive” model (Craig et al. 1999); therefore, it gives a conservative estimate of potential hazardous health effects.

The CMM quantifies the effects of exposure to the individual chemicals in a mixture based on Target Organ System Effect and Specific Target Organ Effect (Yu et al. 2016). Both short-term (i.e., acute) and long-term (i.e., chronic) toxic health effects are included.

The threshold delineating acute and chronic effects in the CMM is 7 days considering the nature of unplanned or accidental occurrence of chemical emergency events. In addition, the shorter duration for acute exposures indicated in Sax’s Dangerous Properties of Industrial Materials (Lewis 2004), lack of sub-acute health code numbers (HCNs), and the indication time (sometimes months) for chronic exposures led to this definition (Lewis 1998, 2004; NIOSH 2008). Consequently, chronic exposure is defined as any toxic effects longer than 7 days. A period of 14 days is the threshold chosen by other agencies.

The CMM assumes that impacts on different target-organ groups are independent of each other unless there is evidence to the contrary. This approach allows the CMM to separately consider the impact on organ systems from each chemical in a mixture and then add the effects of all chemicals to yield a cumulative impact for each target-organ group. This approach yields more realistic results for cumulative health impact than two other commonly applied alternatives, namely:

- Treating all chemicals in a mixture independently and assuming that there is no cumulative impact on the exposed individual (i.e., the human health impact is estimated by the exposure to the chemical that would do the most harm). This non-conservative approach tends to underestimate human health impacts.
- Adding the exposures to all of the chemicals, regardless of the different target organs affected by the chemicals. This conservative approach tends to overestimate cumulative health effects.

The HCN values assigned to each chemical indicate which target-organ groups are affected by exposure to that chemical. HCNs offer a convenient way of categorizing identical or similar target-organ effects. HCNs are similar to medical diagnostic codes in that they are code numbers and identify specific acute or chronic toxic effects on individual target organs. Currently, 63 different HCNs are available for characterizing the potential target-organ or health effects caused by exposure to a chemical (Yu et al. 2010). Table A.2 lists the HCNs, their associated target-organ effects, and their rank for emergency planning and response applications.

Hazardous health effects from irritants are evaluated by different target organs using the CMM. Depending on the severity of the health effects (i.e., severe, moderate, or mild), weighting factors are applied to more properly represent potential health effects (Yu et al. 2013a, 2013b).

Table A.2. Health Code Numbers Used to Classify Toxic Effects by Target Organ. Health Care Numbers are listed in the order adapted from Craig et al. (1999). Rank indicates the importance in terms of a health effect and its impact on a person's ability to respond in an unplanned incident.

Rank	HCN	Target-Organ Effect
30	1.00	OSHA carcinogen (29 CFR 1910.1000) – chronic effect
31	1.01	Bladder carcinogen – chronic effect
32	1.02	Liver carcinogen – chronic effect
33	2.00	Suspect carcinogen or mutagen – chronic effect
34	2.01	Kidney carcinogen – chronic effect
35	2.02	Liver carcinogen – chronic effect
56	3.00	Systemic toxin – chronic effects
46	3.01	Bladder – chronic effects
42	3.02	Hematological effects – chronic, unspecified
47	3.03	Bone – chronic effects
43	3.04	Bone marrow – chronic blood-forming system and other chronic effects
36	3.05	Brain – chronic effects
48	3.06	Eye – chronic ocular effects
45	3.07	Gastrointestinal tract – chronic effects
29	3.08	Heart, Cardiovascular system – chronic effects
41	3.09	Kidney – chronic effects
44	3.10	Liver – chronic effects
53	3.11	Skin – chronic effects including dermatitis and sensitization
55	3.12	Skin perforation – nasal septum perforation and other chronic effects other than skin absorption
14	4.00	Systemic toxin – acute short-term high hazard effects
9	4.01	Eye – acute, other than irritation
21	4.02	Nose – acute effects other than irritation
27	4.03	Bladder – acute effects
24	4.04	Bone marrow – acute blood-forming system and other acute effects
16	4.05	Brain – acute effects
23	4.06	Hematological effects – acute, unspecified
26	4.07	Gastrointestinal tract – acute effects
15	4.08	Heart, Cardiovascular system – acute effects
22	4.09	Kidney – acute effects
25	4.10	Liver – acute effects
52	4.11	Skin – acute effects other than irritation
54	4.12	Skin perforation – acute effects other than skin absorption
28	4.13	Bone – acute effects
50	5.00	Reproductive toxin – acute effects
51	5.10	Reproductive toxin – chronic effects
4	6.00	Cholinesterase toxin – acute effect
19	7.00	Nervous system toxin – acute effects
17	7.01	Central nervous system – acute effects
38	7.10	Nervous system toxin – chronic effects
37	7.11	Central nervous system – chronic effects
18	8.00	Narcotic – acute effect
40	9.00	Respiratory sensitizer – chronic effect
39	10.00	Respiratory toxin – chronic effects
20	11.00	Respiratory toxin – acute effects other than irritation
10	11.01	Respiratory irritant – acute severe or moderate but not mild irritant effects
11	11.02	Respiratory irritant – acute moderate
58	11.03	Respiratory irritant – mild

Rank	HCN	Target-Organ Effect
49	12.00	Blood toxin, anemia – chronic effect
3	13.00	Blood toxin, methemoglobinemia – acute effect
6	14.00	Severe irritant
5	14.01	Eye irritant – severe
12	14.02	Skin irritant – severe
8	15.00	Moderate irritant
7	15.01	Eye irritant – moderate
13	15.02	Skin irritant – moderate
59	16.00	Mild irritant
57	16.01	Eye irritant – mild
60	16.02	Skin irritant – mild
1	17.00	Asphyxiants, anoxiants – acute effect
2	18.00	Explosive, flammable safety (no adverse effects with good housekeeping)
61	19.00	Generally low-risk health effects – nuisance particles, vapors or gases
62	20.00	Generally low-risk health effects – odor

The TVAT report (SRNL 2014) indicated that mixture interactions associated with similar health effects are a real potential (i.e., irritation); hence, under tank conditions capable of producing a transient vapor/gas plume, acute interactions between COPCs with common modes of action (e.g., respiratory tract irritation) are highly plausible. Of particular concern are interactions in transient plumes in which combinations of relative high (but transient) concentrations of chemicals can overwhelm protective detoxification metabolic pathways, resulting in greater than additive effects (i.e., potentiation). To address this issue, the following approaches should be further considered:

- For COPCs at their respective OEL-?, identify which chemicals are anticipated to have similar toxicological effects (i.e., respiratory irritation) based on the Quantitative Structure-Activity Relationships and known MOAs.
- Evaluate published literature for all toxicity interaction studies for the grouping of chemicals.
- Consider interactions that are not based on quantitative structure-activity relationship or MOA, such as COPCs that might modify metabolism, bioactivation, and/or detoxification of other COPCs.
- Where feasible, consider exploiting computational modeling approaches to evaluate dose-dependent mixture interactions (see Corley et al. 2015).
- Consider in vitro and/or in vivo toxicological studies to assess interactions for COPC mixtures at OEL concentrations.

Evaluating and prioritizing COPC mixtures for tank headspace constituents should focus on the following specific actions (TVAT recommendations):

- Evaluate tank vapor mixture toxicological interactions at concentrations associated with transient plume exposures to modify OELs to accommodate mixture effects (**DR-7**).
- Use the OEL–C from analysis or subsequent toxicological testing to characterize the hazard index and risk from the tank vapor mixtures, and control to 10% of the value (**RCH-3**).

A.6 Odor Threshold and Sensory Irritation

As noted in the TVAT report (SRNL 2014), many of the identified tank vapor chemical constituents are respiratory irritants, but the term irritation is generally used without any discrimination between pathophysiological or sensory irritation (Paustenbach 2000). Pathological irritation involves local redness, swelling, pruritus, or pain. Chemosensory effects produce temporary but undesirable consequences on the eyes, nose, or throat that involve trigeminal nerve stimulations (Arts et al. 2006). Odors can stimulate olfactory receptors; hence, it is particularly challenging to differentiate MOA based on symptomology, particularly when dealing with complex mixture interactions within the respiratory system (SRNL 2014).

Odors are routinely noted in the vicinity of the tank farms (SRNL 2014). Although it is reasonable to equate smell with a chemical exposure, exposure intensity cannot be determined based on odor (Greenberg et al. 2014; Paustenbach and Gaffney 2006; Arts et al. 2006), and odor alone cannot imply a medically significant exposure. In addition, the identification of a particular odor (e.g., pungent) may not be construed to be an indication of exposure to a specific chemical constituent in a complex mixture such as tank headspace vapors. Nonetheless, ~33% of the nearly 1000 chemicals for which OELs have been established have odor/irritation as their most sensitive effect (Paustenbach 2000); hence, exposure to tank waste chemicals is anticipated to involve a range of odors and produce a range of respiratory irritations.

When evaluating COPCs and establishing OEL and TEC levels, efforts should consider establishing odor thresholds and the relationship between odor detection and OEL/TEC atmospheric concentrations. Efforts to establish the dose relationship between odor detection and irritation response for both individual tank farm vapors and relevant COPC mixtures should be considered. Many chemicals produce both odors and sensory or pathological irritation, making it extremely challenging to differentiate biological responses particularly when dealing with mixtures. Therefore, engaging researchers who have specific expertise in odor/irritant response may be warranted to help identify strategies for differentiating between odor detection and sensory/pathological irritation.

Respiratory irritants are important in evaluating potential adverse health effects of sporadic tank farm releases. Using the revised CMM, respiratory irritants are categorized as mild, moderate, or severe according to their toxic effects on the respiratory tract. Weighting factors that correspond to each severity level (similar to how skin, eye, and other irritants are treated in the CMM) are used. Implementing the revised CMM can provide more accurate assessment of the acute pulmonary health effects of COPC mixtures.⁶

Evaluating and prioritizing odor and sensory/irritation response for tank headspace constituents should focus on the following specific actions (TVAT recommendations):

1. Conduct additional evaluations of COPC toxicological studies to provide insight into the sensory and pathophysiological irritation response, including the role of mixture interactions and the potential need for additional toxicological evaluation (**DR-3**).
2. Perform a comprehensive evaluation of acute odor thresholds and toxicity effects for all COPCs to facilitate the establishment of action levels based on the relationship between odor and toxicity threshold (**DR-4**).

⁶ Yao, J, X-Y Yu, CS Glantz, CE Nix, HM Dixon, JM Jablonski, ER Griffin, HE Fournier, SM Folkens, JM Datri, and RE Komorek. 2016. *Testing and Analysis of the Chemical Mixture Methodology (CMM) – Part III: Refining the Acute Respiratory Irritant Health Code Number*. PNNL-25867, Pacific Northwest National Laboratory, Richland, Washington. Not published.

3. Perform a comprehensive evaluation of respiratory health effects for all COPCs to facilitate the assessment of chemical mixture toxicity based on the respiratory irritant severity (**DR-4**).

A.7 Odor Threshold and Sensory Irritation

A.7.1 Tank Headspace and Emissions Data

Previously, the primary data source for identifying COPC was the Tank Characterization Database (TCD) within the TWINS. The TCD included analytical characterization of both single- and double-shell tank headspace and waste sampling (TWINS 2005). Although the TCD within TWINS will remain an important data source for identifying priority COPCs, efforts also will focus on obtaining the most up-to-date headspace characterizations particularly under tank-disturbing conditions consistent with the recommendations (DR-1) of the TVAT (SRNL 2014). This is of particular importance because, as noted by the TVAT, static tank measurements may not reflect the maximum chemical headspace concentration, particularly under transient conditions when vapor/gas plumes may be generated. More recent headspace, area, and personal monitoring data is available from the Site-Wide Industrial Hygiene Database (DOE Undated). Assessment of the both historic TWINS and more recent Site-Wide Industrial Hygiene Database tank vapor data allows for evaluation of the potential dynamic changes in tank headspace constituents and their concentrations over time, as well as stack sampling and personal monitoring data, which were not a component of the original strategy for prioritization of COPCs.

A.7.2 Available Environmental and Toxicology Literature

The assessment of the toxicology literature will use a strategy similar to the one used to establish initial screening values of tank vapor constituents (Poet et al. 2006). Table A.3 lists a number of key databases that will be used to assess relevant literature concerning health effects of COPCs. The analysis will consider all relevant human exposure, epidemiology as well as toxicology (human/animal/in vitro) DR data when conducting these reviews. Internet databases include TOXNET[®], TOMES[®], PubMed[®], and international databases such as that of IARC. These databases contain information applicable to the toxicological assessment of chemicals. Both TOXNET[®] and TOMES contain the RTECS[®] and HSDB[®] files. If information found from any of the above sources is incomplete, conflicting, or considered insufficient, other sources such as the National Institute of Environmental Health Sciences National Toxicology Program, IARC, EPA, and the Agency for Toxic Substances and Disease Registry Monographs will be exploited.

Table A.3. Key Databases Used to Assess Relevant Literature Concerning the Health Effects of COPCs

TOXNET [®]	The Toxicology Data Network, a set of databases covering toxicology, hazardous chemicals, and related areas; it is maintained by the National Library of Medicine (NLM). (http://toxnet.nlm.nih.gov/)
HSDB [®]	Hazardous Substances Data Bank. Accessible through TOXNET. Provided by the NLM.
PUBMED [®]	PubMed, provided by the NLM, contains citations for biomedical articles back to the 1950's; sources include MEDLINE and additional life science journals. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed).
RTECS [®]	Registry of Toxic Effects of Chemical Substances, provided by Thomson Micromedex, Inc. Accessed through TOMES [®] , which has the same provider.
STN [®]	STN is the Scientific & Technical Information Network, provided by FIZ Karlsruhe, the American Chemical Society, and the Japan Science and Technology Corporation. It links to published research in the world's journal and patent literature back to the beginning of the 20th century.
TOMES [®]	RTECS [®] , provided by Thomson Micromedex, Inc.

A.7.3 Available Exposure Guidelines

For each chemical of potential interest and current COPCs, available databases will be systematically evaluated to identify published OELs and threshold values for inhalation and carcinogenicity ranking as previously described (Burgeson et al. 2004). The types of inhalation OELs and chronic exposure levels will include Permissible Exposure Limits, TLVs, Reference Concentrations for Chronic Inhalation Exposure, Recommended Exposure Limits, and short-term exposure limits among others. To accommodate a more comprehensive evaluation of acute-transient exposure concerns, a number of databases focused on acute exposures will likewise be evaluated, including NAS AEGLs, Spacecraft Maximum Allowable Concentration for Airborne Contaminants, Workplace Environmental Exposure Limits, the ERPG series from the AIHA, TEELs, and Submarine Escape Action Levels, etc. In the absence of available exposure guidelines, quantitative structure-activity relationship analysis can be implemented to predict the toxicological properties of a specific chemical (or class of chemical) based on structural similarities to known chemical toxicants. The subsequent classification (i.e., COPCs, needing further evaluation or of low concern) will be based on predicted toxicological significance using available OELs/model simulations versus measured or simulated tank maximum tank vapor concentrations as previously described (Burgeson et al. 2004).



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