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Pacific Northwest
National Laboratory
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# Exposure-Based Health Issues Project Report: Phase I of High-Level Waste Tank Operations, Retrieval, Pretreatment, and Vitrification Exposure-Based Health Issues Analysis

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November 2001

Prepared for the U.S. Department of Energy
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Environment, Safety and Health
Office of Oversight (EH-2)

Pacific Northwest National Laboratory and
Hanford Environmental Health Foundation
Richland, Washington 99352

# Summary

Responding to the need for Hanford tank-farm workers to better understand the full range of potential exposure-related health issues associated with their assignments, the Pacific Northwest National Laboratory (PNNL) and Hanford Environmental Health Foundation (HEHF) have teamed to study current and future operations' potential worker health impacts. In particular, the project studies chemical-exposure-based health issues associated with the Hanford high-level waste (HLW) tank operations and future pretreatment and vitrification operations. In fiscal year 2001, the DOE Office of Oversight (EH-2) funded a seed project (Phase I) to begin to address these concerns. Phase I focused on examining the ongoing tank-farm operations, assembling a technical team to characterize potential exposures, and identifying exposure conditions requiring assessment. This report addresses current monitoring and control practices for tank-farm operations, selected key chemicals (based on their health effects as noted in previous studies or experience), identification and involvement of key organizations, toxicological and clinical information for the selected chemicals, exposure scenarios for the operations of greatest interest, and determination of exposure limits and control values. The report also identifies exposure issues that should be addressed as the project progresses to Phase II and beyond.

# Acknowledgments

The authors gratefully acknowledge the support of $CH_2M$ Hill Hanford Group (CHG), DOE Office of River Protection (ORP), Hanford Environmental Health Foundation (HEHF), and other Pacific Northwest National Laboratory (PNNL) staff in helping put this document together in its final form. Lauri Marquardt, Scott Somers, and Rick Melbihess of CHG provided invaluable technical knowledge and insights into the current operations at the Hanford tank farms and the industrial hygiene challenges involved with protection of the workers. Jim Huckaby of PNNL provided his insight into gas and vapor generation and high-probability release points associated with the single-shell tanks. Our thanks go to Charles Olaiya and Richard Grill of the ORP for their discussions on the important aspects of this work, their guidance for the prioritization of efforts, and for their support of the project. We also want to thank Mary Ann McKinney of HEHF for her excellent job of performing a high-quality and timely technical review of the document.

# Acronyms

| | |
|---|---|
| ACGIH | American Conference for Governmental and Industrial Hygienists |
| AIHA | American Industrial Hygiene Association |
| AMZ | air monitoring zone |
| BEI | biological exposure limit |
| C | ceiling limit |
| CHG | CH2M Hill Hanford Group |
| DRI | direct reading instrument |
| EAPASE | erythrocyte actinide phosphatase |
| EH-2 | DOE Office of Oversight |
| EPA | U.S. Environmental Protection Agency |
| HEHF | Hanford Environmental Health Foundation |
| HIH2 | Hanford Industrial Hygiene 2 database |
| HLW | high-level waste |
| LCLo | lethal concentration low |
| LOEL | lowest observed effect level |
| NIC | Notice of Intended Change |
| NOAEL | no observed adverse effect level |
| NTP | National Toxicology Program |
| ORP | Office of River Protection |
| OSHA | Occupational Safety and Health Administration |
| PEL | permissible exposure limit |
| ppb | parts per billion |
| ppm | parts per million |
| PNNL | Pacific Northwest National Laboratory |
| RfC | reference concentration |
| RfD | reference dose |
| RfDI | reference dose (inhalation) |
| RfDSI | reference dose (subchronic inhalation) |
| SST | single-shell tank |
| STEL | short-term exposure limit |
| TLV | threshold limit value |
| toc | total organic compound |
| TWA | time-weighted average |
| TWINS | Tank Waste Information System |

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# 1.0 Background

Discussions during 2000 - 2001 between staff at the Pacific Northwest National Laboratory (PNNL) and the Hanford Environmental Health Foundation (HEHF) addressed the needs for better understanding of and preparation for health issues involving chemical exposures associated with Hanford high-level waste (HLW) tank operations and future pretreatment and vitrification plant operations. Currently, workers who come to HEHF with illness symptoms and indicate that they may have been exposed to a hazardous chemical usually cannot specifically identify the substance but report that they smelled something unusual or describe the incident in a similar way. HEHF physicians are thus primarily limited to treating the symptoms and watching for clinical signs. PNNL and HEHF proposed to the U.S. Department of Energy (DOE) Office of Oversight (EH-2) a joint effort to remedy the difficulties in making accurate clinical judgments. This effort involves performing a prospective health-issue assessment of both current and potential future worker-exposure scenarios for the current HLW tank and future pretreatment/vitrification plant operations. This effort fits well with the EH-2's Hot Topic #2, which addresses workers' desire to understand the full range of potential health issues associated with their assignments (i.e., to have improved access to information and to medical programs).[(a)]

This effort covers health issues resulting from chemical exposures during the following operations:

- tank-waste maintenance operations - based on selected compounds from a headspace vapor study
- retrieval operations - based on retrieval design
- pretreatment operations - based on pretreatment design
- vitrification operations - based on vitrification plant design
- process waste-handling and disposal - based on current operations, retrieval, pretreatment, and vitrification plant design.

In Fiscal Year 2001, EH-2 had a limited amount of resources available to commit to the idea, so this Phase I project was formulated. Although Phase I addresses only tank-waste maintenance operations, it also serves as a mechanism to begin assembling a team to address all five operations of concern.

(a) "Description of the Office of Independent ES&H Oversight (EH-2)," 12/19/00.

# 2.0 Purpose

EH-2 has the responsibility to understand the "big picture" of worker health and safety, which includes fully recognizing the vulnerabilities and associated programs necessary to protect workers at various sites across the DOE complex. Exposure analysis and medical surveillance are key aspects for understanding this big picture, as is understanding current health and safety practices and how they may need to change to meet future needs. Thus, this exposure-based health issues project assembles all the necessary components to understand potential exposure situations and their medical surveillance and clinical aspects associated with particular operations at a DOE site. Since HEHF and PNNL were already discussing these concerns and needs for future aspects of the Hanford Site HLW operations, this topic was chosen as the pilot for the project.

Phase I focuses only on current Hanford tank-farm operations and serves as a starting point for the overall project. It is also anticipated that once the pilot is fully developed for Hanford HLW (i.e., it covers current operations, retrieval, pretreatment, vitrification, and disposal), the process and analysis methods developed will be available and applicable for other DOE operations and sites.

The purpose of this Phase I project report is to present the health impact information collected regarding ongoing tank-waste maintenance operations, show the various aspects of health and safety involved in protecting workers, and introduce the reader to the kinds of information that will need to be analyzed in order to effectively manage worker safety. When these goals have been accomplished, the assessment process will move into Phase II and beyond.

This report explains the focus of the Phase I assessment (Section 3.0), discusses current tank-farm monitoring and control practices (Section 4.0) and the rationale for selection of chemicals for Phase I analysis (Section 5.0), and describes the exposure scenarios, drawn from current tank-farm operations (Section 6.0). Section 7.0 presents the clinical and toxicological health effects profiles for the chemicals chosen, and Section 8.0 lists worker-exposure limits for each chemical.

# 3.0 Phase I Focus

Phase I focused on understanding current HLW tank-farm operations from the perspective of potential chemical exposures to workers. This focus on existing operations helped establish good coordinated working relationships among the DOE Office of River Protection (ORP), $CH_2M$ Hill Hanford Group (CHG), PNNL, and HEHF. These relationships will be needed to perform a complete analysis of HLW operations including all aspects from current operations through vitrification and final disposal of the vitrified logs and associated wastes. It also provided an opportunity for PNNL and HEHF to establish how best to effectively integrate their toxicological and clinical health assessment capabilities for the larger study.

Focusing on current tank-farm operations has kept Phase I functional for the time and resources available and provided DOE EH-2 with confirmation that current worker health-protection practices are necessary and effective. It also has provided HEHF with valuable insight and information for effectively dealing with potential worker-exposure cases from tank-farm operations at Hanford.

Phase I has focused on current tank-farm operations and associated exposure hazards. Evaluating current tank-farm operations provides an excellent initial focus because it involves current potential exposure hazards and the most near-term exposure hazards that EH is overseeing (i.e., it allows the focus of current EH resources to be on currently recognized potential hazards). Since retrieval, pretreatment, and vitrification operations are not fully established at this time, the exposure hazards associated with these operations can best be addressed in later phases. In the future, we will work closely with the designers of the pretreatment and vitrification plant to ensure that exposure scenarios and additive chemicals considered are realistic and in line with the most current vitrification operation designs.

The following tasks were completed under Phase I:

- evaluated current monitoring and control practices for tank-farm operations and any projected plans for monitoring and controlling retrieval operations
- selected the chemicals to study based on their health effects as noted in a previously conducted study, "Organic Chemical Hazards Found in Single Shell Tank Headspace"[(a)]
- identified, in cooperation with the ORP/CHG safety staff, potential chemical exposure scenarios for the selected chemicals, based on current HLW tank operations and any projected retrieval operations (i.e., those that are currently available)
- conducted both toxicological and clinical health-effects literature reviews/analyses for the selected chemicals

(a) Battelle Memo from James Toth, PE (Chem.), to Kelvin Soldat, June 19, 2001.

- identified the clinical implications/symptoms associated with the selected chemicals
- identified worker-based exposure limits, which were correlated with associated symptom-related levels for the selected chemicals.

# 4.0 Current Tank-Farm Monitoring and Control Practices

From the time the tank farms were first built and operated at Hanford, there have been odors associated with tank-farm operations. However, a significant series of exposures to personnel via vapor emissions were reported from July 1987 to January 1992. In January 1992, the manager of the Richland Field Office directed that a Type B investigation be conducted to evaluate recurring exposures of workers to hazardous vapors at the tank farms (Brown and Coleman 1992). The board of investigation evaluated 16 different events that occurred from 1987 to 1992 and that ranged in severity from no effects to a probable partial disability. The investigation reviewed and evaluated the adequacy of measures to control exposure of personnel to hazardous vapors in the tank farms and attempted to determine why the control measures implemented after the July 1987 exposure incident were not successful.

In response to the investigation, the tank-farms contractor implemented a program to protect employees from hazardous vapor exposures. Because the nature of the vapors was unknown, a decision was made to implement controls for the tank farms similar to those employed at an uncontrolled hazardous waste site. The strategy consisted of the following elements:

- immediately implement tank-farm work controls to prevent employee overexposure to vapors
- develop a tank-farm health and safety plan based on 29 CFR 1910.120 requirements
- conduct vapor monitoring and sampling of employees working in tank farms
- characterize the tank-headspace vapors to determine the potential for employee overexposure to vapors
- based on analysis of worker monitoring and headspace data, revise the control measures to protect employee health without being overly restrictive.

After 4 years of extensive work by the tank-farm contractor and three independent review bodies (i.e., the Occupational Safety and Health Waste Tank Advisory Panel, the Tank Farm Operations Advisory Council, and the Tank Farm Tank Vapor Task Team), a report was issued that concluded that the problems associated with protecting employees from overexposure to vapors during tank-farm work were defined and controlled (Hewitt 1996b). Employee exposure incidents had virtually ceased due to implementing controls around potential vapor-release points and establishing better communications regarding vapor odors and risks. The review bodies and the contractor concluded that worker health and safety considerations caused by the inhalation of potentially hazardous vapors had been resolved.

## 4.1 Exposure Sources

The exposure sources for tank vapors are the double-shell tanks (DSTs), single-shell tanks (SSTs), and miscellaneous underground storage tanks. Vapors from tanks are released during breaks in containment, and from breather filters, pump pits, transfer lines, valves, and saltwell pits. All Hanford tanks have been characterized. The SSTs provide the largest potential sources during routine activities because most of these tanks are passively ventilated. The tank-farms contractor has classified the SSTs into three categories, based on previous monitoring levels of total organic carbon (TOC) and ammonia ($NH_3$):

- Category 1 - TOC < 2 ppm, $NH_3$ < 25 ppm
- Category 2 - TOC >2 ppm and <10 ppm, $NH_3$ > 25 ppm and < 125 ppm
- Category 3 - TOC > 10 ppm, $NH_3$ > 125 ppm

Information is available in Table 1 of the *Ch2MHill Procedures* manual (HNF-IP-0842), vol. 9 ("Safety"), Section 4.4 ("Industrial Hygiene Personal Monitoring Program Plan").

*Tank-Farms Health and Safety Plan* (HNF-SD-WM-HSP-002; Hewitt 1996a) provides a list of the tanks and locations that have demonstrated elevated airborne levels during past sampling and the tanks most likely to result in elevated levels. Based on previous monitoring and evaluations, the primary potential chemical exposure sources in the tanks include ammonia, nitrous oxide, benzene, butanol, acetone, hexane, and xylene. These compounds are target compounds when performing personnel monitoring. Ammonia is a primary contaminant of concern. It and many other inorganic chemicals have characteristic noxious odors. The ammonia odor threshold is much lower than the permissible exposure limit (i.e., 5 ppm compared to 25 ppm).

## 4.2 Exposure Baseline

The tank-farm vapor exposure baseline is composed of several previous evaluations conducted at the tank farms and current tank-farms database sources (listed in Section 7.3 of "Industrial Hygiene Personal Monitoring Program Plan," Section 4.4 of vol. 9, "Safety" of *CH2MHill Procedures*, available at http://aptfpg02.rl.gov/twrsadmin_procedures/volume9.htm):

- "Baseline Hazard Assessment, Hanford Tank Farms 200E/200W Areas"
- "Final Report Exposure Monitoring Data Evaluation for the Hanford High Level Waste Tanks-Tank Farms B, T, and TY"
- Exposure Monitoring Data Evaluation for the Hanford High Level Waste Tanks Stage III: Tank Farms A, AX, BX, BY, C, S, TX, and U"

- Exposure Monitoring Data Evaluation for the Hanford High Level Waste Tanks Stage II: Tank Farms AN, AP, AW, AY, AZ, and SY"

- HNF-SD-TWR-RPT-001, "Tank Waste Remediation System Resolution of Potentially Hazardous Tank Vapor Issue" (Hewitt 1996b)

Other information has been included in the following databases:

- Tank Waste Information System (TWINS)

- Hanford Industrial Hygiene 2 (HIH2) database

- CHG safety and health database.

Hewitt (1996b) provides a summary of the exposure baseline data, which are the basis for the current exposure monitoring plan in the tank farms. Exposure baseline data yielded the following conclusions:

- Area airborne chemical measurements obtained in areas where employees are working near tank vapor-release points were much less than the actual release-point concentrations. Worker area concentrations were generally 2-ppm organic vapors and <25-ppm ammonia. The release point area concentrations were up to 100-ppm organic vapor and up to 500-ppm ammonia. These concentrations demonstrated a 20-times reduction in airborne concentrations between the release points and the work area.

- A review of headspace data indicated that only two compounds (ammonia and nitrous oxide) identified in the tank headspace are routinely present at concentrations greater than 5 times the exposure limit (lower of permissible exposure limit or threshold limit values [TLV]). Potential carcinogens were identified at very low concentrations.

- Over 350 personnel samples are collected from 18 tank farms during all types of work activities, including breaking containment. The highest exposure levels obtained from the personal sampling were about 10% of the allowable 8-hour time-weighted average exposure limit and about 30% of the short-term exposure limit.

- Most of the gases and vapors escaping from the tanks are at known release points and can present a potential hazard to employees working near the tanks. However, barriers have been installed around these release points. Based on the personal sampling and area monitoring results, these control measures are sufficient to prevent any employee overexposures to vapors. Respiratory protection is identified in some of these areas as an added control. Employees are not at risk of vapor overexposure as long as appropriate control measures are continued.

- Ammonia and several other chemicals identified in tank-headspace sampling have odor thresholds that are well below their exposure limits. Thus, even if a failure of control measures were to occur and employees were briefly exposed to an elevated ammonia level, they would be aware of the

condition and would leave the tank farm and request that monitoring be performed. Thus, overexposure would be unlikely.

- The reduction in exposure complaints is likely a result of both additional controls and, perhaps more importantly, better information and worker communication.

## 4.3 Exposure Controls

Exposure controls are described in *Tank Farm Health and Safety Plan* (HNF-SD-WM-HSP-002; Hewitt 1996a), Section 2.9, and include the following:

- proper planning and notification
- identification of tanks with elevated release concentrations
- barriers and postings around areas with elevated release concentrations
- tank and area-specific air-monitoring screening requirements
- air-monitoring screening requirements for containment-breaking activities
- tank, area, and screening level specific personal protective equipment requirements
- actions for incidents and incident recovery.

The exposure control on tank-farms work in the Interim Stabilization Project will typically include an industrial hygiene sampling strategy developed by the interim stabilization industrial hygienist. This strategy will assist project staff in recognizing the sampling and monitoring criteria to be used during the start-up and surveillance of the pumps and equipment. The staff will use the strategy to develop, assess, and provide insight into control measures that will minimize the employee health and safety impacts of the work. This strategy is referenced in the start-up work package documentation.

The strategy will be used to determine and assign the appropriate level of industrial hygiene instrumentation or sorbent tube sampling schemes. This sampling/monitoring scheme will be commensurate with the output of the start-up strategy, in which the objective is to design an approach that will track pre-identified concentrations of hazardous constituents suspected to be liberated during the initiation of pumping. Based on tank vapor chemistries and past practice monitoring activities, the screening for organic and ammonia vapors should offer an excellent insight to the vapor release periods.

The sampling strategy will typically identify total organics and ammonia vapors in addition to a variety of other industrial hygiene instrumentation and sampling media, as necessary. The project industrial hygienist will coordinate industrial hygiene technicians to carry out all field surveillances and data collection, in turn providing the project industrial hygienist with the data necessary to refine, amend,

or suspend start-up criteria. All data collection activities will be recorded on the direct reading instrument (DRI) survey form and entered into the HIH2 database as prescribed in the *CH2MHill Procedures* manual (HNF-IP-0842), vol. 9 ("Safety"), Section 4.27, ("Exposure Monitoring, Reporting, and Records Management"). It will also be entered into the CHG Safety and Health Database.

The sampling strategy will designate surveillance locations for source, area, perimeter, and personal breathing zones. It will also typically be sequenced into phases of the work, e.g., pre-start-up activities, initial pump start-up, and post-start-up activities.

The interim stabilization industrial hygiene sampling strategy is an excellent tool to ensure that workers are not overexposed to hazardous vapors.

## 4.4 Exposure-Control Assessments

There are three types of exposure-control assessments currently used for tank-farm gases and vapors: 1) activity/location-related screening, 2) tank-farm source monitoring, and 3) personnel monitoring.

### 4.4.1 Activity/Location-Related Screening

The activity/location-related screening requirements provided in HNF-SD-WM-HSP-002 (Hewitt 1996a), Paragraph 2.9, identify appropriate barriers, monitoring requirements, and personal protective equipment based on activity performed and location. The levels in Paragraph 2.9, were derived from extensive previous activity/location monitoring and tank-farm source monitoring.

### 4.4.2 Tank-Farm Source Monitoring

Ninety-seven SSTs are currently in Category 1, the lowest exposure potential level. Twenty-six are in Category 2 and twenty-six are in Category 3. Category 3 tanks require the highest control level. Actions based on these Category 3 tanks are defined in HNF-SD-WM-HSP-002 (Hewitt 1996a), Paragraph 2.9, requirements. Double-shell tanks are not categorized because they are all actively ventilated.

Annually, the River Protection Program safety industrial hygienist prepares a source-monitoring schedule to evaluate these tanks. Monitoring methods and frequencies are identified. Category 3 tanks are monitored more frequently to detect changes in the tanks and to help establish a basis for reducing controls.

### 4.4.3 Personnel Monitoring

Personnel monitoring is periodically performed during activities involving tank vapors to evaluate a wider range of chemical contaminants and provide additional information for reducing exposure controls. Personnel monitoring generally includes evaluation of the following target chemicals: ammonia, nitrous oxide, benzene, butanol, acetone, hexane, and xylene. Personal monitoring is collected according to the *CH2MHill Procedures* manual (HNF-IP-0842), vol. 9 ("Safety"), Section 4.4 ("Industrial Hygiene

Personal Monitoring Program Plan"), and is consistent with nationally recognized standards. Samples are analyzed in an American Industrial Hygiene Association certified laboratory.

Personal monitoring results are documented in accordance with the *CH2MHill Procedures* manual (HNF-IP-0842), Vol. 9 ("Safety"), Section 4.27, ("Exposure Monitoring, Reporting, and Records Management"). A centralized, computerized, industrial hygiene exposure database (HIH2) is used to provide rapid access and summary reports of industrial hygiene exposure information.

Although no personnel monitoring has indicated exposures greater than Occupational Safety and Health Administration (OSHA) permissible exposure limits, the monitoring frequencies OSHA often uses for exceeding action level and permissible exposure limits shall be used for tank farms, as indicated in the *CH2MHill Procedures* manual (HNF-IP-0842), vol. 9 ("Safety"), Section 4.4 ("Industrial Hygiene Personal Monitoring Program Plan"), Table 2.

# 5.0 Selected Chemicals for the Analysis

The chemicals selected for the Phase I analysis primarily came from a study of the organic vapors in the headspace of the SSTs at Hanford. These chemicals were selected because they were deemed to pose the highest potential for exposure of workers during HLW operations. Benzene and ammonia were also selected at the suggestion of HEHF, as these are additional common compounds associated with clinical situations that HEHF staff encounter. A number of these compounds are widely used chemicals in U.S. industry, with considerable industrial hygiene, clinical, and toxicological information available on them. Most of these compounds are also known to present ill health effects to humans.

The following chemicals were selected for the Phase I analysis:

- benzene
- ammonia
- biphenyls (highest measured concentration in SSTs and representative example selected, 1,1 biphenyl)
- halo alkanes and alkenes (highest measured concentration in SSTs and representative example selected, trichlorofluoromethane)
- alcohols, phenols and ethers (highest measured concentration in SSTs and representative example selected, 1-butanol)
- nitriles (highest measured concentration in SSTs and representative example selected, acetonitrile)
- hetrocycles (highest measured concentration in SSTs and representative example selected, tetrahydrofuran).

# 6.0 Exposure Scenarios for Current Tank Farm Operations

Organic vapors and other chemical compounds are present in the headspace of waste tanks (both SSTs and DSTs) and in the waste itself. Certain activities performed during tank-farm operations create a higher potential for personnel exposure to chemicals being released from the tanks, transfer lines, valves, or other associated system components. The overall risk to the worker during the activities is related to the types of chemicals stored in the tanks, the amounts of those chemicals, the physical form of the waste, the control mechanisms in place, and the specific activity being performed. The location of the workers with respect to the activity also directly affects the risk to the worker. Workers closer to the activity or downwind of the activity will have a higher potential for exposure to chemicals than those farther away or upwind. The magnitude of the exposure can also be influenced by meteorological conditions such as wind direction, wind velocity, humidity, and temperature (Mahlum and Young 1993). Experience has shown that most reports of odor problems and exposure to chemical vapors and gases occur in the SST farms rather than DST farms. The SSTs are older and are not as well contained. Moreover, they have passive breather filters from which gases can more easily be released to the environment.

Ventilation rates for the SSTs can be significantly different for different tanks. There appears to be an inverse correlation between ventilation rate and ambient temperatures. The ventilation rate decreases as the difference between the headspace temperature and the ambient temperature decreases; the rate approaches and fluctuates around a very low value (Huckaby et al. 1997). It has also been observed that a significant exchange of air occurs between tanks via the underground cascade pipes for those tank systems that have cascade systems (Huckaby et al. 1998). Concentrations of gases and vapors within the waste can build up over time until the surface of the waste is broken through or the gases move to the surface of the waste inside the tank. The probability of a high-level exposure of chemicals to personnel would be decreased if periodic forced ventilations of waste tanks occurred.

Past experience and data on what chemicals are in each tank give the industrial hygienists an idea of the types and levels of exposures that can be expected prior to performing specific activities. The headspaces of most of the SSTs have been sampled (Stock and Huckaby 2000) and the resulting data placed in the Tank Waste Information Network System (TWINS) database, which also contains information on the contents of waste that has been transferred from tank to tank. These sources provide industrial hygienists with initial estimates of the chemicals potentially involved in the exposures. However, these data are just estimates. The measurements were made in static situations. The typical exposure scenarios involve dynamic situations – in some cases, with waste being physically moved or transferred to other tanks or somehow involving intrusive activities. The maximum concentrations for specific compounds and the waste tanks in which those concentrations have been measured have been documented (Stock and Huckaby 2000). Levels greater than the exposure limit for workers for some compounds are present in the headspace of some of the waste tanks.

The constituents of the waste contained in each tank are different. Prior to a specific activity being performed, industrial hygienists routinely develop a sampling strategy. They look at past characterization data to determine the types and levels of chemical exposures that could occur, the work has been recently performed on the tank system, and whether or not specific chemicals were measured to be present. Initial air monitoring zones (AMZs) are established around the area of work. If possible, for a period of

48 hours before initiating the activity, samples are collected and monitoring data obtained to gain insight into possible gas and vapor releases that could be generated by the activity. This initial work provides an estimate and a baseline from which to work. Depending on the activity being performed, the initial levels of gas and vapor concentrations actually measured during the activity can be much higher than baseline (e.g., 10 to 100 times the baseline levels). An example would be a high gaseous concentration of ammonia or organics that has built up beneath the hard surface of the waste. Upon initial intrusion through the surface, the higher concentration of gases could be released, remain at a high level for 5 minutes or so, then decrease to a fairly stable level that is closer to the baseline values seen prior to the work being performed.

Past experience with activities around certain waste tanks provides industrial hygienists with knowledge about the types and levels of chemicals to be expected. For example, high levels of ammonia are expected when work is performed on Tank U-107. Employee complaints and/or concerns are expected when work is performed on Tanks S-102, A-101, C-102, or C-103 because of documented past exposures to odorous or noxious chemicals. This onsite, hands-on knowledge is useful for choosing personal protective equipment that will be needed and for anticipating odors or chemical exposures that may be experienced by workers. If the odor threshold is below the threshold limit value for a chemical, then it is very likely that exposures will be kept below the exposure limit. If, however, the odor threshold is greater than the TLV, then it is more difficult to know that a specific chemical is present during the activity. This latter situation could be the case with nitrous oxide. It must be noted that odor thresholds for specific chemicals differ for individuals. It also has to be noted that exposures do not often consist of single chemicals. Combinations of different chemicals and compounds may produce odors and/or noxious mixtures. It is possible that these mixtures can create a difficulty in the accurate measurement of a specific constituent of the mixture.

Several scenarios have been identified that pose a higher than normal potential for personnel exposures: e.g., breaching of a system, waste intrusion (such as, pump installation, core sampling, etc.), saltwell pumping, transfer of waste, and some maintenance activities. Releases or exposure are more likely when layers are stratified and the task requires breaking through the layers or when the environmental conditions are such that atmospheric stagnation occurs (e.g., temperature inversion). The exposure scenarios discussed below do not cover every possible exposure situation but do cover a cross-section of activities that have higher potential for personnel exposure to chemicals. Personnel can be exposed to odors or to specific chemicals at any time while near the tank farms, but the probability can be low. For example, the waste inside an SST could be in a configuration such that a volume of gas could be released to the atmosphere on its own, not due to any intrusive activity or maintenance procedure. The probability is low, but it happens.

Table 6.1 lists 10 tank-farm activities that could elevate the potential for worker exposures to occur, divided according to 1) types of activities, 2) types of personnel who would be located at “ground zero” (the area closest in proximity to the work being performed) and are considered essential personnel for that activity, 3) estimates of times/week and hours/task for the tank-farm activities, and 4) an estimate of the high-risk exposure time for essential personnel (i.e., the amount of time that the workers would/could be in the area where a chemical exposure could occur).

**Table 6.1**. Potential Exposure Scenarios for Current Tank-Farm Operations

| Activity | Personnel ("Ground Zero") | Estimates for Task | | Approximate High-Risk Exposure Time, h |
|---|---|---|---|---|
| | | Times/ Week | Hours/ Task | |
| Equipment installation (Waste-intrusive) | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Electricians<br>Pipefitters<br>Riggers<br>Truck drivers | 1 | 8 | 3 |
| Saltwell pumping | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Pipefitters | 5 | 12 | 3 |
| Waste transfer | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Pipefitters | 1 | 8 | 4 |
| Valve pit reconfiguration | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Electricians<br>Pipefitters | 1 | 8 | 3 |
| Core sampling | Health Physics and Industrial Hygiene techs<br>Pipefitters<br>Riggers<br>Electricians<br>Instrument techs | 3 | 8 | 2 |
| Maintenance activities (waste-intrusive) | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Electricians<br>Pipefitters<br>Riggers<br>Truck drivers | 1 | 8 | 4 |
| Pressure tests of transfer lines | Health Physics and Industrial Hygiene techs<br>Pipefitters<br>Operations personnel | 1 | 8 | 4 |
| Ventilation testing and maintenance | Vent and balance personnel<br>Health Physics and Industrial Hygiene techs<br>Operations personnel | 2 | 8 | 4 |
| Tank-intrusive activities | Health Physics and Industrial Hygiene techs<br>Operations personnel<br>Electricians<br>Pipefitters | 3 | 8 | 3 |
| Operation routines | Health Physics and Industrial Hygiene techs<br>Power operators<br>Operations personnel | 5 | 12 | 4 |

Notes:
"Ground Zero" is the area at and around the main activity. Personnel listed have the highest probability of exposure to chemicals. For each activity, there would also be a number of support personnel who would be located away from "ground zero."

The estimates for each task are just that – estimates. The number of times/week a task is performed in tank farms is highly variable. The estimated number of hours/task is also highly variable, depending on the job and the requirements for the activity. The high-risk exposure time is the approximate time during an activity that personnel are at a higher risk for chemical exposure.

Of the activities listed in Table 6.1, an example of an equipment installation that is *waste-intrusive* is the removal or installation of a pump located in the waste itself.

*Saltwell pumping* is a continuous activity. The essential personnel normally come back and check on the activity every 2 hours or so to make sure that there are no problems. Sometimes, the line has to be flushed and this may cause a potential for a higher-level chemical exposure.

*Waste transfers* create several opportunities for chemical exposures because there are several locations where personnel could be exposed (e.g., receiving tanks, lift stations [ventilated systems], valve locations).

During *valve pit reconfigurations*, nozzles are being set up for routing waste transfers so that lines are broken open for a short while. This activity may also include some equipment installation. There have been situations where process waste in the lines has gone into the valve pit, exposing personnel.

The highest potential for personnel exposure during *core sampling* would be during the time to set up the sampling because it is waste-intrusive. When the sample is being obtained, the exposure is actually controlled because it is a closed system. The potential for exposure increases again when the sampling equipment is being removed.

*Maintenance activities*, when waste-intrusive, create a higher potential for exposures. Sometimes, these activities can have fairly long associated exposure times; the process may include a number of workers staying at "ground zero" for extended times. An example would be removing equipment that has been in the waste for a long time and is no longer needed or useful.

*Pressure testing of transfer lines* creates a higher exposure potential because the lines are pressurized with water and air (including gas and vapors) that have to be bled off to let the line be filled with water.

*Ventilation testing and maintenance activities* are performed on all tank systems periodically and include positioning workers close to breather filters and exhaust stacks as well as other potential release points.

An example of a *tank-intrusive activity* would be inserting a camera into the dome area of a tank and obtaining pictures of the waste. The exposure to chemicals may not be as high as when waste equipment is installed (because taking photos is not waste-intrusive), but the activity may require the same number or more personnel to perform the work.

*Operation routines* include the acquisition of measurement equipment information, e.g., liquid levels and waste temperature, checks on other monitoring equipment, etc. These routines are performed on all shifts and can put the workers into potential exposure situations, such as getting into areas with known exposure points, to obtain the instrument readings.

# 7.0 Clinical and Toxicological Health Effects Analysis

This section presents toxicological and clinical information about chemicals to which tank-farm workers may be exposed. These chemicals, which were identified in "Organic Chemical Hazards Found in Single Shell Headspace"[(a)] and through consultation with HEHF, include benzene; ammonia; 1,1-biphenyl; tricholorofluoeromethane; 1-butanol; acetonitrile; and tetrahydrofuran.

## 7.1 Benzene

### 7.1.1 Properties

Benzene is a stable, colorless liquid at room temperature and normal atmospheric pressure. It has a characteristic aromatic odor, a relatively low boiling point (80.1° C), and a high vapor pressure (13.3 KPa); thus, it evaporates readily at room temperature and is highly flammable. It is slightly soluble in water but miscible with most other organic solvents. In air, benzene exists primarily in the vapor phase, with residence times varying between a few hours and a few days. Degradation in air is primarily by the reaction with hydroxyl radicals (WHO 1993).

### 7.1.2 Toxicity - Health Effects

Benzene appears to effect a low acute toxicity in various animal species: an LD50 after oral exposure ranging between 3000 and 8100 mg/kg body weight in rats; an LC50 ranging from 1500 $mg/m^3$ (over 8 hours) in mice to 44,000 $mg/m^3$ (over 4 hours) in rats (WHO 1993); or an LD50 of 1-10 g/kg body weight and LC50 of 15-60 $g/m^3$ (over 2-8 hours) (Canton et al. 1991). Benzene is a moderate eye and skin irritant in rabbits. Exposure of mice by inhalation results in a significant lowering of blood parameters (i.e., hematocrit, hemoglobin level, and erythrocyte, leukocyte and platelet counts). Long-term exposure at high doses results in bone marrow aplasia (WHO 1993). Acute exposure to 65 $g/m^3$ may cause death. Exposure to 2275 $mg/m^3$ over a 30-minute period produces signs of disturbances of the central nervous system. Chronic exposure to high but ill-defined concentrations (approximately 400 $mg/m^3$ and higher) causes damage to the hematopoietic system. This damage includes anemia, leucopoenia, and thrombocytopenia, and in severe cases, aplastic anemia.

Anemia and leucopoenia have been observed in workers exposed to 130 to 260 $mg/m^3$. Exposure to 3.25 to 97.5 $mg/m^3$ causes a transient reduction in red blood-cell counts. Enzyme changes within leucocytes have been observed after exposures of 32.5 to 81 $mg/m^3$ over a 3-year period. There is also significant evidence that exposure to concentrations greater than 325 $mg/m^3$ of benzene may eventually cause leukemia. Exposure to benzene and acute myeloid leukemia was found to be correlated, and, to a lesser extent, this has been shown for erythroleukemia and other leukemias and lymphomas (Canton et al. 1991). Metabolism studies have shown that one or more metabolites are responsible for the

(a) Battelle memo from James Toth, PE (Chem.), to Kelvin Soldat, June 19, 2001.

hematological toxicity of benzene, which is exerted primarily on bone marrow precursor and lymphocytic cells. Benzene and alkyl benzene exert similar acute central nervous system effects (Goldstein 1988).

### 7.1.3 Genotoxicity, Mutagenicity, and Carcinogenicity

Benzene is carcinogenic in rats both by oral and inhalation administration and in mice by inhalation (Canton et al. 1991). Benzene has negative results in mutagenicity assays in vitro. In vivo, benzene or its metabolites cause both structural and numerical chromosome aberrations in humans and laboratory animals. Administration of benzene has been shown to produce sister chromatid exchanges and polychromatic erythrocytes with micronuclei (WHO 1993). The clastogenic potential (i.e., ability to break chromosomes) of benzene is thought to be due partly to its hydroxylated metabolites. The mechanism is thought to be that its metabolites interfere with the formation of the mitotic spindle and not by direct interaction with DNA. However, binding of benzene to nucleic acids has been reported (Canton et al. 1991). After intraperitoneal dosing, benzene has been shown to reach germ cells, as shown by the production of abnormalities in sperm head morphology. Benzene can cause the production of several types of neoplasms (i.e., new abnormal tissue growth, such as tumors) in both rats and mice after either oral or inhalation exposures (e.g., Zymbal gland, liver, mammary tissue and nasal cavity neoplasms, and a few lymphomas and leukemias). Inhalation doses showing positive carcinogenic responses were between 100 and 960 $mg/m^3$ for 5-7 days, 5 days/week. Oral doses between 25 and 500 mg/kg body weight in mice and rats produced neoplasms. The length of exposure was usually 1-2 years (WHO 1993).

### 7.1.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

Benzene freely crosses the placental barrier. No data was found showing that it is teratogenic after several experiments in animals, even at maternally toxic doses (WHO 1993; Canton et al. 1991). Benzene has been shown to be fetotoxic following inhalation exposure in mice and rabbits (1600 $\mu g/m^3$, 7 hours/day with gestation days of 6-15) (WHO 1993).

### 7.1.5 Immunotoxicity

Benzene depresses the proliferative ability of B- and T-cell lymphocytes. This effect is evident by host resistance to infection shown in several laboratory species subjected to benzene exposure (WHO 1993).

### 7.1.6 Clinical Symptoms, Indications, and Effects

The most frequently reported health effect of benzene is bone-marrow depression, leading to aplastic anemia. At high levels of exposure, a high incidence of these diseases is probable. Benzene is also a well-established human carcinogen. Epidemiological studies have demonstrated a causal relationship between benzene exposure and the production of myelogenous leukemia. Also, there may be a relationship between benzene exposure and the production of lymphoma and multiple myeoloma, but this relationship has yet to be substantiated (WHO 1993). Benzene concentrations above 10 $mg/m^3$ may cause odor annoyance (Canton et al. 1991). Benzene is an irritant to skin and by its defatting of the keratin layer may cause erythema, vesiculation, and dry/scaly dermatitis (Clayton and Clayton 1993-94).

After a short exposure to high concentrations of benzene by ingestion or inhalation, the major toxic effect is on the central nervous system, with progressive symptoms (depending upon amount of exposure) ranging from mild dizziness, weakness, euphoria, headache, nausea, vomiting, tightness in chest, and staggering. If exposure is severe, symptoms progress to blurred vision, tremors, shallow and rapid respiration, ventricular irregularities, paralysis, and unconsciousness (Hardman et al. 1996).

Long-term exposure to benzene via inhalation or dermal contact results in symptomatic effects on the central nervous system and the gastrointestinal tract, with symptoms such as headache, loss of appetite, drowsiness, nervousness, and pallor. However, the major manifestation is aplastic anemia. Bone marrow cells in early stages of development are most sensitive (Hardman et al. 1996). Ellenhorn et al. (1997) list the following symptoms and toxicities associated with the inhalation of benzene: irritation of conjunctiva and visual blurring, irritation of mucous membranes, dizziness, headache, unconsciousness, convulsions, tremors, ataxia, delirium, tightness in chest, irreversible brain damage with cerebral atrophy, fatigue, vertigo, dyspnea, respiratory arrest, cardiac failure and ventricular arrhythmias, leucopoenia, anemia, thrombocytopenia, petechiae, blood dyscrasia, leukemia, bone marrow aplasia, fatty degeneration and necrosis of heart, liver, and adrenal glands. Obviously, these would be graded depending upon dose and duration of exposure.

Single exposures to concentrations of 66,000 mg/$m^3$ (20,000 ppm) have been reported fatal in man within 5-10 minutes (IARC 1982). In general, acute symptoms are dependent on both the concentration and duration of exposure. Exposure to 7500 ppm for 30 minutes is life-threatening, 1500 ppm for 60 minutes produces significant symptoms, 50-150 ppm for 5 hours results in headache and weakness, and exposure to 25 ppm or less for 8 hours results in no demonstrable acute effect (Sullivan and Krieger 1992).

### 7.1.7 Interactive Effects

Exposure to toluene with benzene appears to lower the clastogenic effects of benzene and protect against the formation of chromosomal aberrations in male mice. Co-exposure with toluene also reduced benzene metabolite levels in urine by 60 to 70% and improved red cell iron intake in benzene-treated mice, which suggests that benzene metabolism is closely related to its hematotoxicity. It also suggests that the toluene protection may stem from its inhibition of benzene metabolism. The toluene-induced suppression of benzene metabolism was also confirmed by a co-exposure human study, which showed a reduction in urine levels of phenol and hydroquinone in male workers.

These human and animal studies indicate that metabolite levels may be a more sensitive indicator of interactive effects of benzene and other solvents than blood or tissue levels of benzene alone. This was also confirmed by the observation that increased metabolism of benzene induced by co-administration of ethanol increased the hematotoxicity of benzene, because interactions between benzene and its metabolites may have affected the benzene metabolism and toxicity. Benzene displayed a dose-dependent metabolism, where high benzene exposures were found to inhibit oxidation of phenol, the primary product of benzene oxidation, to hydroquinone (Medinsky et al. 1994).

### 7.1.8 Risk Assessment

Benzene is classified as a known human carcinogen (Category A) under U.S. Environmental Protection Agency (EPA) Risk Assessment Guidelines. It is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies (IRIS 2000). Two risk assessments conducted by the EPA have predicted a unit risk of 7 deaths per million for a lifetime exposure of 0.3-ppm benzene exposure. OSHA has estimated 10 excess leukemia deaths per 1000 workers exposed for a working lifetime exposure to 1 ppm. An assessment considered reasonably acceptable suggests that 1000 men exposed to 10-ppm benzene for a working lifetime of 30 years would incur about 50 excess deaths due to leukemia in addition to the baseline expectation of 7 deaths (Austin et al. 1988).

The EPA lists in IRIS a cancer oral risk value of 1.8E-4 to 6.7E-4 mg/kg-day (IRIS 2000). Health Canada lists a cancer inhalation risk value of 1.5E+1 $mg/m^3$, which translates into a 1-in-100,000 risk level of 3E-3 $mg/m^3$, with the target organ listed as leukemia (Hughes et al. 1994). Health Canada's value is computed directly from the dose-response curve within or close to the experimental range, while EPA's risk estimate is the upper 95% confidence limit on the low-dose extrapolation.

### 7.1.9 Medical Surveillance

A recommended monitoring program for benzene consists of a complete blood count, including a white cell differential and platelet count, every 6 months. The first count should include a reticulocyte count and serum iron and total iron binding capacity as a baseline (Goldstein 1988). Medical surveillance should include blood pressure check, lung functions, blood chemistry, hematology, urinalysis, and skin examination (Clayton et al. 1993-94).

### 7.1.10 Body Burden

Benzene was detected in all 8 samples of mothers' milk from women living in four U.S. urban areas (Pellizzari et al. 1982). Breath samples from persons without specific exposure to benzene ranged from 8 to 20 parts per billion (ppb) (IARC 1982). Whole blood samples from 250 subjects (121 males, 129 females) ranged from not detectable to 5.9 ppb, with mean of 0.8 ppb (Antoine et al. 1986). The National Human Adipose Tissue Survey found that in 46 composite specimen samples, 96% tested positive to benzene (concentrations were greater than 4 ppb for wet tissue) with a maximum concentration of 97 ppb (Stanley 1986). In a 1980 study, smokers had an average benzene body burden about 6 to 10 times higher than that of nonsmokers, and received about 90% of their benzene exposure from smoking. The mean benzene concentrations found in the breath and blood of 1683 individuals was 13.1 and 131 ng/L, respectively (Wallace et al. 1996).

## 7.2 Ammonia

### 7.2.1 Properties

Ammonia is normally present in all tissues, and it constitutes a dynamic pool from which absorbed ammonia is distributed. Once absorbed, ammonia is converted to the ammonium ion as hydroxide and as salts, especially carbonates. Ammonium salts are rapidly converted to urea. Excretion of ammonia is primarily via the kidneys and some through the sweat glands. It may also be excreted through expired air (Basilico and Garlanda 1993).

The World Health Organization (WHO) has estimated that exposure to 25 ppm would increase blood ammonia concentrations by only 10% over fasting levels, and such a small increase is not considered likely to cause any harm (Swotinsky and Chase 1990). Ammonia in the environment is a part of the nitrogen cycle. It volatilizes into the atmosphere where it undergoes a variety of reactions. Photolytic reactions destroy some of the ammonia and reactions with sulfur dioxide or ozone produce aerosols, such as ammonium sulfate or nitrate, which return to the earth's surface as wet or dry deposition (WHO 1986).

Ammonia has a molecular weight of 17.03. It is a colorless gas with a sharp, cloying, repellent, pungent, intensely irritating odor, characteristic of drying urine. It will attack some forms of plastics, rubber, and coatings (Merck 1996; NIOSH 1997 and 1981; Booth and McDonald 1982). It is 47% soluble in water at 0° C and 18% in water at 50° C (Merck 1996). It has a vapor density of 0.59 compared to air of 1 (CRC 1987-8) and a vapor pressure of 7510-mm Hg at 25° C (Daubert and Danner 1989). Odor recognition of pure ammonia in air is 4.68E1 ppm (Fazzalari 1978).

### 7.2.2 Toxicity - Health Effects

The main route of exposure to ammonia is inhalation (Basilico and Garlanda 1993). The lowest observed effect level (LOEL) observed in rats is calculated by multiplying 105 $mg/m^3$, the exposure concentration from the selected study, by the reference rat inhalation rate of 0.223 $m^3$/day and by dividing by 0.35 kg, the reference rat weight, to obtain 66.9 mg/kg/day as a LOEL. Incorporating an uncertainty factor of 1000 (factors of 10 for interspecies extrapolation, 10 for individual variability, and 10 for calculating an interim inhalation reference dose [RfDI] from a LOEL), an estimated interim subchronic reference dose (RfDSI) for ammonia is 0.07 mg/kg/day and 4.9 mg/day for a 70-kg human, which is slightly less than the RfDI of 7.0 mg/day calculated from the odor threshold value. Since the odor threshold value reflects inadequacies associated with animal toxicity studies, the RfDI of 0.1 mg/kg/day or 7.0 mg/day (for a 70-kg human) was adopted as the RfDSI for ammonia. Since this has an odor threshold basis, it is most appropriately expressed as 0.36 $mg/m^3$ (EPA 1987).

An odor threshold of 3.6 $mg/m^3$ as an upper bound of the range of concern is recommended (EPA 1987). Applying an uncertainty factor of 10 gives a recommended lower bound limit of 0.36 $mg/m^3$. In contrast, the WHO (1986) indicated that the best estimate for an odor threshold is 35 $mg/m^3$, with sensitive individuals able to detect about 3.5 $mg/m^3$. The air concentration of 3.6 $mg/m^3$ is substantially lower that the threshold limit value of 25 ppm (i.e., approximately 18 $mg/m^3$) recommended by the American Conference for Governmental and Industrial Hygienists (ACGIH)

(ACGIH 1986). An estimated short-term exposure limit (STEL) of 22 mg/m$^3$ (32 ppm) was considered reasonable by Basilico and Garlanda (1993). Environment Canada has established an inhalation lethal concentration low (LCLo) of 7000 mg/m$^3$/3 hours (Environment Canada 1981).

The primary mechanism of ammonia toxicosis appears to be the inhibition of the citric acid cycle (i.e., the Kreb cycle). Usually, there is an increase in anaerobic glycolysis, blood glucose, and blood lactate associated with an exposure. Acidosis is also manifested (Jones et al. 1977).

### 7.2.3 Genotoxicity, Mutagenicity, and Carcinogenicity

Ammonia has not been shown to be carcinogenic by either the oral or inhalation routes of exposure (EPA 1987). Ammonia was reported mutagenic in *in vitro* studies at toxic levels in *E. coli*, and it may affect mutagenic responses to other agents. Mutagenic effects were also found in Drosophila, which were minimal or observed only at toxic levels. There is no evidence that ammonia is mutagenic in mammals (Basilico and Garlanda 1993).

### 7.2.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

No data were found on the reproductive or embryo toxicity or teratogenicity of ammonia.

### 7.2.5 Immunotoxicity

No data were found on immunotoxicity of ammonia.

### 7.2.6 Clinical Symptoms, Indications, and Effects

Ammonia vapors cause irritation of eyes and the respiratory tract. High concentrations cause conjunctivitis, laryngitis, pulmonary edema, or pneumonitis. At high concentrations, there is a sensation of suffocation induced by spasm of glottis or laryngeal edema (Gosselin et al. 1984). Contact of the liquid with skin freezes the tissue and can cause caustic burns and blistering (vesication) (U.S. Coast Guard 1984-5; Gosselin et al. 1984). If ammonia is splashed directly into the eyes, a rise in intraocular pressure may mimic narrow-angle glaucoma.

Corneal edema and semidilated fixed pupils are typical (Gosselin et al. 1984). High gas or liquid concentration exposures to the eye may cause temporary blindness and severe eye damage (Braker and Mossman 1980). If systemic absorption becomes extensive, the patient may become comatose, which may be preceded by hypertonus and convulsions (Gosselin et al. 1984).

Inhalation of ammonia often causes secretion of saliva and retention of urine (Braker and Mossman 1980). Changes in the adrenocortical system were seen from inhalation exposures at concentrations of 5 mg/m$^3$ (Kalandarov et al. 1984). Generally, concentrations between 1 and 10 mg/dL of ammonia will effect the viability and mitogenic responsiveness of all lymphocytes (Klucinski and Targowski 1984).

Clear indications of irritation of the skin, eyes and upper respiratory tract were reported with exposures to 50-55 ppm for periods of between 10 minutes and 6 hours. Signs of slight irritation to the skin and eye were reported for concentrations of 25-30 ppm for exposure times ranging between 10 minutes and 2 hours (Basilico and Garlanda 1993). Acute exposure to ammonia causes eye and respiratory tract irritation, airway obstruction, pulmonary edema, and, in some persistent cases, irreversible pulmonary damage.

Experimental studies have shown that exposures of 50 to 100 ppm cause moderate eye, nose, and throat irritation; however, acclimation to these effects usually occurs within 1 to 2 weeks. Short-term exposures to ammonia at concentrations up to 500 ppm do not appear to increase blood ammonia or ammonia metabolite concentrations. Exposure at concentrations below 50 ppm for extended periods is unlikely to cause adverse health effects (Swotinsky and Chase 1990). Eye irritation results at 700 ppm, and permanent injury may result if prompt medical measures are not taken. Exposures to concentrations of 5000 ppm can cause immediate death from spasm, inflammation, or edema of the larynx (U.S. Coast Guard 1984-5). Irritation to mucous membranes becomes noticeable at about 100 ppm. Concentrations above 400 ppm may destroy mucous surfaces upon prolonged exposure, by dissolving or emulsifying keratin, fat, and cholesterol (Clayton and Clayton 1981-2).

### 7.2.7 Interactive Effects

The eyes of volunteers were exposed to a range of concentrations of ammonia, sulfur dioxide, butan-2-one, pentan-2-one, formaldehyde, 3-methyl-butan-2-one, and acrolein for up to 15 seconds inside close-fitting goggles, in addition to receiving 10 breaths of 1 liter of each agent, with the result of increased eye irritancy and bronchoconstriction. The bronchoconstrictive response occurred at concentrations below the threshold for eye irritation. Their lung sensitivity was estimated to be 1.5 times greater than that of the eye (Douglas and Coe 1987). The combined effects of ammonia and carbon particles inhaled by rats in a study were reportedly much greater that those from ammonia or carbon particles alone, suggesting synergism (ACGIH 1991).

Ammonia and methanethiol acted synergistically to accentuate respiratory paralysis and coma in a study (Clayton and Clayton 1981-2). On the other hand, sodium benzoate lowers serum ammonia concentrations by the activation of a non-urea cycle pathway for ammonia removal. Sodium benzoate potentiation of ammonia toxicity and inhibition of urea synthesis *in vivo* has been confirmed. Urea production and N-acetylglutamate levels were decreased by sodium benzoate. Pretreatment of mice with L-carnitine suppressed mortality following ammonium acetate plus sodium benzoate administration. The L-carintine lowered blood concentrations of ammonia and increased urea production and N-acetylglutamate levels (O'Connor et al. 1987).

### 7.2.8 Risk Assessment

The EPA has an ammonia non-cancer inhalation risk value of 1E-1, based on lung as the target organ (IRIS 1998). The U.S. Agency for Toxic Substances and Disease Registry has a non-cancer inhalation risk value of 2E-1 (0.3 ppm), also based on the lung as the target organ (ATSDR 1990).

### 7.2.9 Medical Surveillance

A complete medical history and physical examination should be completed to detect existing conditions that might place the individual at higher risk and to establish a baseline for future health monitoring. Examination of the eyes and respiratory tract is essential. The skin should be examined for evidence of chronic disorders. Chest radiographs should be taken. Periodic surveillance of the lungs is indicated. Medical examinations should be repeated on an annual basis, except that an x-ray is only necessary when indicated by the results of pulmonary function testing or by signs and symptoms of respiratory disease (Mackison et al. 1981).

### 7.2.10 Body Burden

Therapeutic or normal blood levels are in the range of 0.05 to 0.17 mg% or 0.5 to 1.7 μg/mL.

## 7.3 1,1-Biphenyl

### 7.3.1 Properties

Biphenyl is an aromatic hydrocarbon that is a colorless solid at room temperature. It is used as an intermediate in the production of several compounds (e.g., emulsifiers, optical brighteners, crop protection products, plastics), as a heat-transfer medium in heating fluids, as a dyestuff carrier for textiles and copying paper, as a solvent in pharmaceutical production, and in the preservation of citrus fruits (CICAD 2000).

The molecular weight of biphenyl is 154.2 (Budavari 1989). Pure biphenyl is a white crystalline solid that separates from solvents as plates or monoclinic prismatic crystals. Commercial samples are often slightly yellow or tan in color (Kirk-Othmer 1991). Biphenyl has a pleasant but peculiar odor, often described as butter-like (Cain et al. 1993). It has a boiling point of 254-255º C and a melting point of 69-71º C (Budavari 1989). The density (specific gravity) of biphenyl is 1.041 at 20º C (Lide 1995). The octanol/water partition coefficient (logKow) of biphenyl is 4.01 (Hansch et al. 1995). Biphenyl is soluble in most organic solvents including alcohol, ether, and benzene (Lide 1995); it is also soluble in oxygenated and chlorinated solvents (Ashford 1994). Its water solubility is 7.48 mg/L at 25º C (Yalkowsky and Dannenfelser 1992). It has a vapor density of 5.31 (compared to 1.0 for air) (Sax 1984). The odor threshold for biphenyl is 0.0062 $mg/m^3$ (low) and 0.3 $mg/m^3$ (high) (Ruth 1986).

### 7.3.2 Toxicity - Health Effects

Biphenyls are well absorbed through the gastrointestinal tract and through the lung and skin. In some species examined, the metabolites of biphenyl (i.e., mainly 4-hydroxybiphenyl) are excreted rapidly and almost exclusively in the urine. Subchronic exposure by inhalation causes bronchopulmonary changes. Effects on the urinary system are often reported. An increase in the incidence of morphological effects (e.g., calculi formation) and histopathalogical effects (e.g., hyperplasia and desquamation) has been observed within the urinary tract of male rats administered diets containing greater than

2500-mg biphenyl/kg. An increase in the occurrence of calculi and squamous metaplasia within the urinary bladder of female rats have been observed, but at lower incidence than in males. Effects on blood chemistry and hematological parameters have also been observed in animals. For non-neoplastic effects, the LOEL was 38 mg/kg-body-weight/day (oral), based upon the development of alterations in hematological parameters (i.e., decreased hemoglobin concentration and hematocrit) in rats fed diets containing 0, 500, 1500, or 4500 mg/kg (i.e., intakes of 0, 39, 113, or 338 mg/kg body weight per day, respectively) for two years (CICAD 2000).

Prolonged exposure to vapor concentrations greater than 0.005 mg/L are considered dangerous (Worthing and Walker 1987).

### 7.3.3 Genotoxicity, Mutagenicity, and Carcinogenicity

*In vitro* studies with bacteria have provided no evidence of mutagenic potential for biphenyl (CICAD 2000). Genetic toxicology testing in mammalian cells has produced positive results in the presence of metabolic activation and negative results in the absence of metabolic activation (CICAD 2000). Oral doses of 2.5 to 64 mg/kg/day were not found to be tumorigenic in mice (Hayes 1975).

The mutagenicity of biphenyl was evaluated in salmonella (Ames Test), both in the presence and absence of added rat liver S9 metabolic activation. Concentrations up to 1.54 mg/plate, using the plate incorporation technique, did not cause a positive response in any of the tester strains with or without metabolic activation (Westinghouse 1977).

Biphenyl has a classification of D (not classifiable as to human carcinogenicity) (IRIS 2000).

### 7.3.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

Administration of 125 to 500 mg/kg by esophageal intubation in rats on days 6-15 of gestation was not shown to be teratogenic and caused no maternal effects. At 1000 mg/kg, it produced fetal and maternal toxicity (Khera et al. 1979). In a one-generation test at dietary levels of 1000 and 5000 ppm fed to male and female rats for 11 to 60 days before mating, there was no observed effect on fertility, lactation, viability, or the number of pups per liter brought into weaning (Hayes 1982).

### 7.3.5 Immunotoxicity

No information was found regarding the immunotoxicity of biphenyl.

### 7.3.6 Clinical Symptoms, Indications, and Effects

A worker exposed to repeated concentrations as high as 123 $mg/m^3$ for 10 years reportedly developed neurological and gastric symptoms, severe ascites, and massive edema in the legs. Serum transaminase levels were high, and coma and death ensued after 1 month. Autopsy revealed necrosis in the liver and kidney, with regions of cirrhosis in the liver. There were degenerative changes in heart tissue. Brain

tissue was edematous and degeneration of ganglion cells was observed. Also, bone marrow appeared hyperactive with large numbers of immature white and red blood cell precursors (Gosselin et al. 1984).

Workers exposed for 10 years to approximately 123 $mg/m^3$ complained of headache, fatigue, abdominal pain with nausea or diarrhea and various symptoms of polyneuropathy. Damage to the central and peripheral nervous system was seen after 2 years, with further neural degeneration following (Gosselin et al. 1984). A French study describes transient nausea, vomiting, and bronchitis in workers exposed to biphenyl vapors during paper impregnation. The clinical picture of biphenyl poisoning was characterized by central and peripheral nerve damage and liver injury. The cause of death was acute yellow atrophy of the liver (ACGIH 1991).

Chronic human exposure is characterized by fatigue, headache, insomnia, sensory impairment, and mood changes, accompanied by clinical findings of cardiac and hepatic impairment, irregularities of the peripheral and central nervous systems, and possibly some brain lesions. Repeated skin contact may produce sensitization or dermatitis (Clayton and Clayton 1981-2).

Physiologic response to biphenyl via inhalation (chronic) in concentrations less than 1.6 ppm (less than 1 $mg/m^3$) resulted in no observable symptoms and deviations of cardiac or hepatic function (Clayton and Clayton 1981-2). However, chronic inhalation exposure to concentrations of 4.4 to 128 ppm (28 to 800 $mg/m^3$) for 5 to 15 years resulted in the observance of abdominal pain, headache, cardiac, hepatic, and renal effects, peripheral and central nervous system abnormalities, and one death (Clayton and Clayton 1981-2).

A case of reversible hepatotoxicity induced by occupational exposure to biphenyl was observed in a 46-year-old female. She worked for 25 years in a citrus-packing factory. Clinical examination revealed a soft non-tender abdomen and moderate hepatomegaly that was confirmed by ultrasound. Significant elevations in serum transaminase, alkaline phosphatase and gamma-glutamyl-transpeptidase, and neutrophilic leukocytes were observed. A liver biopsy revealed polymorphic inflammatory infiltrate with eosinophils in the portal and lobular regions, which are consistent with chronic persistent hepatitis. In the past, the patient had experienced episodes of asthenia that were accompanied by increases in serum transaminase activities to two or three times normal levels. She stopped working in citrus packaging and her asthenia gradually disappeared, which suggested the chronic persistent hepatitis seen in the patient was related to biphenyl exposure. The hepatotoxicity likely resulted from a combination of dermal and oral exposure (Carella and Bettolo 1994).

Biphenyl is an irritant of the eyes, nose, throat, mucous membranes, and respiratory tract. It is a powerful lung irritant by inhalation. Repeated dermal contact can result in sensitization dermatitis. Eye exposure produces redness and pain (MICROMEDEX 1998).

Acute exposure effects include cough, headache, flaccid paralysis, anorexia, nausea, vomiting or diarrhea, bronchitis, insomnia, depression, memory loss, facial paralysis, vertigo, numbness and aching of the extremities, and fatigue. Acute and chronic exposures result in central and peripheral nerve damage and severe liver injury. Chronic exposure can produces symptoms of fatigue, headaches, tremor,

insomnia, sensory impairment, and mood changes. Animal studies have shown central nervous system depression, paralysis and convulsions, as well as kidney damage (MICROMEDEX 1998).

### 7.3.7 Interactive Effects

Comparative effects of biphenyl on hepatic drug metabolizing enzymes in rat 2-hydroxybiphenyl had a greater inducing effect on the activity of aniline hydroxylase and aminopyrine N-demethylase than did 4-hydroxybiphenyl (Miller and Bajaj 1972).

### 7.3.8 Risk Assessment

The oral LD50 for biphenyl in rat is 3280 mg/kg (Worthing and Walker 1987), the oral LD50 for rabbit is 2400 mg/kg (ACGIH 1991), and the skin LD50 for rabbit is 2500 mg/kg (Kirk-Othmer 1984).

The 8-hour time-weighted average (TWA) for biphenyl is 0.2 ppm. Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded (ACGIH 1998). The NIOSH 10-hour time-weighted average is 0.2 ppm (1 $mg/m^3$), and 100 $mg/m^3$ is considered dangerous to life or health (NIOSH 1997).

### 7.3.9 Medical Surveillance

The most probable route of human exposure to biphenyl is inhalation. This is indicated by extensive workplace air monitoring, non-workplace indoor monitoring, and personal air sampling (Lesage et al. 1987); thus, adequate workplace monitoring is indicated. Monitoring of kidney and liver function is suggested.

### 7.3.10 Body Burden

In a study of 387 expired air samples from 54 normal, healthy, non-smoking urban U.S. subjects, biphenyl was detected in 28.7% of the samples as a mean concentration of 0.032 ng/L (Krotoszynski et al. 1979).

## 7.4 Trichlorofluoromethane

### 7.4.1 Properties

The molecular weight of trichlorofluoromethane is 137.37. It is a liquid at temperatures below 23.7º C (Budavari 1996), and is colorless and, in concentrations of less than 20% (by volume in air), is odorless. In higher concentrations, it has a mild, somewhat ethereal odor (Matheson 1980). Its odor is characteristically sweet, from pleasant to unpleasant (Verschueren 1966). It has a boiling point of 23.7º C at 760-mm Hg. It has a melting point of –111º C, and a density (specific gravity) of 1.494 at 17.2º C (Budavari 1996). The octanol/water partition coefficient (logKow) is 2.53 (Hansch et al. 1995). It is

soluble in alcohol, ether, and other organic solvents (Budavari 1996), and soluble in water at 1100 mg/L at 25º C (DuPont 1980) and 0.0036 g/100 g at 0º C (Gerhartz 1985). Its vapor density is 5.04 at 25º C (with air being 1.0) (Budavari 1996).

Trichlorofluoromethane has an odor threshold of 28.0 mg/$m^3$ (low) and 1170 mg/$m^3$ (high) (Ruth 1986). It is immediately dangerous to life or health at concentrations of 2000 ppm (NIOSH 1997).

All fluorocarbons will undergo thermal decomposition when exposed to flame or red-hot metal. Decomposition products of the chlorofluorocarbons will include hydrofluoric and hydrochloric acid, along with smaller amounts of phosgene and carbonyl fluoride, which is very unstable to hydrolysis and quickly changes to hydrofluoric acid and carbon dioxide in the presence of moisture (International Labour Office 1998).

### 7.4.2 Toxicity - Health Effects

The toxicity of chlorofluorocarbons had been considered to be low; they are absorbed via the lungs and undergoes little subsequent biotransformation. However, prolonged exposure to trichlorofluoromethane may result in damage to several organ systems. Clinical problems include cardiac arrhythmias, bone marrow depression, cerebral degeneration, and damage to liver, kidney, and peripheral nerves. Death occasionally has been attributed to inhalation of high concentrations, probably via the mechanisms of cardiac arrhythmias, especially accompanying exercise or upper airway obstruction (Hardman et al. 1996). High concentrations cause narcosis and anesthesia in humans. Human systemic effects associated with exposure to high concentrations are conjunctiva irritation, fibrosing alveolitis, and liver changes (Lewis 1996).

Large acute inhalation doses have resulted in cardiac sensitization (arrhythmia) or bronchial constriction, leading to death (NRC 1977). Human exposures to 1000 ppm, 8 hours/day, 5 days/week for a total of 18 exposures produced no untoward subjective effects and there were no changes in electrocardiogram or pulmonary function tests. Venous blood levels after 8 hours were as high as 4.69 μg/mL, with the gradual attainment of this level representing a low uptake (Clayton and Clayton 1993-94).

In a controlled study, volunteers were exposed to concentration of 250, 500, or 1000 ppm for periods of 1 minute to 8 hours. Volunteers were exposed for 8 hours/day, 5 days/week for 2 to 4 weeks at concentrations of 1000 ppm. The acute exposures did not produce any untoward physiological effects as determined by a number of biological endpoints, including clinical hematology and chemistry, EKG, EEG, neurological parameters, pulmonary function, and cognitive tests. The repetitive exposure at 1000 ppm was without measurable untoward physiological effect except for a minor decrement in several cognitive tests (ACGIH 1991).

Bradycardia is the usual response in humans inhaling 10% of a chlorofluorocarbon. It is suggested that bradycardia in man originates from irritation of the upper respiratory tract and that cardiac effects can be initiated prior to absorption of the chlorofluorocarbon in the lungs (Clayton and Clayton 1993-94).

Chlorofluorocarbon inhaled at 5% concentration sensitizes the myocardium to epinephrine, a 6% concentration results in apnea and areflexia, and a 10% concentration produces cardiac arrhythmias (Ellenhorn et al. 1988).

Studies of neurological effects have focused on refrigeration workers. In these studies, there were no cases of peripheral neuropathy, nor significant differences in mean nerve conduction velocities (ulnar, median, peroneal, sural, tibial) between study and reference subjects. Lightheadedness and palpitations were reported significantly more often in the exposed subjects (Campbell et al. 1986). Chlorofluorocarbons are anesthetic and cardiotoxic and can produce hallucinogenic effects and (rarely) contact dermatitis (Ellenhorn et al. 1988).

Phosgene poisoning can occur from the disintegration of chlorofluorocarbons in open flame (Clayton and Clayton 1981-82). Also, chlorofluorocarbon vapors are 4 to 5 times heavier than air, with high concentrations tending to accumulate in low-lying areas, resulting in inhalation hazards (Clayton and Clayton 1993-94).

### 7.4.3 Genotoxicity, Mutagenicity, and Carcinogenicity

The hydrochlorofluorocarbons HCFC-225a and HCFC-225cb were not mutagenic in the Ames reverse mutation assay, or clastogenic in a chromosomal aberration assay with Chinese hamster lung cells. Neither induced unscheduled DNA synthesis in liver cells. Both of these agents were clastogenic in the chromosomal aberration assay with human lymphocytes (MICROMEDEX 1998).

Trichlorofluoromethane was tested for mutagenicity in a salmonella/microsome preincubation assay using a protocol approved by the National Toxicology Program. It was tested at doses of 0, 100, 333, 1000, 3333, and 10,000 μg/plate in four salmonella typhimurium strains in the presence and absence of Aroclor-induced rat and/or hamster liver cells. Trichlorofluoromethane was negative in these tests (Zeiger et al. 1987).

Trichlorofluoromethane exposure to rats caused no carcinogenic effects. Exposures to mice caused increased numbers of total tumors in females, which were dose-related mammary tumors at 5000 ppm. Also, lung adenomas and leukemia in females were reported and they were also dose-related (Maltoni et al. 1988).

### 7.4.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

Dichlorodifluoromethane was not teratogenic in rats and rabbits. A 1,1,1,2-tetrafluoroethane study showed no adverse effect on reproductive performance or on the development, maturation or reproductive performance of up to two successive generations (MICROMEDEX 1998).

### 7.4.5 Immunotoxicity

No information was found regarding the immunotoxicity of trichlorofluoromethane.

### 7.4.6 Clinical Symptoms, Indications, and Effects

Acute exposure to inhalation of trichlorofluoromethane at low concentrations can result in transient eye, nose, and throat irritation. Palpitations, lightheadedness, and headaches can also be seen. At high concentrations, the potential effects are ventricular arrhythmias, pulmonary edema, and sudden death. Acute exposures to the eyes can cause irritation and possibly frostbite of the eye lids. Ocular instillation has resulted in corneal burns in exposures to rabbits. Nasal irritation can also occur, as well as throat irritation and possible frostbite of the lips, tongue, buccal mucosa and hard palate, if the exposure concentrations are high enough.

The inhalation of high concentrations can be associated with the development of refractory ventricular arrhythmias and sudden death, believed to be secondary to myocardial sensitization to endogenous catecholamines. Certain individuals may be more susceptible to arrhythmogenic effects at lower concentrations. Pulmonary irritation, bronchial constriction, cough, dyspnea, and chest tightness may develop after inhalation. Chronic pulmonary hyperreactivity has occurred.

Adult respiratory distress syndrome has been reported following acute inhalation exposures. Pulmonary edema is an autopsy finding in fatal cases; cerebral edema has also been found on autopsy. Neurologic symptoms such as headache, dizziness, and disorientation are common after acute exposures.

A syndrome of impaired psychomotor speed, impaired memory and learning, and emotional lability has occurred in workers with chronic occupational exposure. Nausea may develop from oral exposures. Acute inhalation or ingestion exposure has resulted in jaundice and mild elevations in transaminases. Hepatocellular coagulative necrosis has been observed on liver biopsy for high-level exposures. Dermal contact may result in defatting, irritation, or contact dermatitis. Severe frostbite has been reported as an effect from dermal exposure (MICROMEDEX 1998).

Workers involved in a spill of a large volume of chlorofluorocarbon, who were exposed to high concentrations, developed central nervous system depressant effects. In one case, unconsciousness occurred and, in another, potentiation of the endogenous adrenaline effect and tachycardia occurred (WHO 1990).

Allergic contact eczema was reported in patch tests performed on three patients who had a prior history of skin reactions to deodorant sprays. All three patients showed mild to strong positive reactions to chlorofluorocarbon exposure. These results suggest that individuals may become sensitized to certain chlorofluorocarbon dermal exposures (WHO 1990).

Significant interpatient variation has made it difficult to predict which symptoms a patient will exhibit following exposure (MICROMEDEX 2001).

Trichlorofluoromethane, one of the most toxic fluorocarbons, sensitized dogs to epinephrine at a concentration of 0.3%, and such effects have also occurred in humans (Amdur et al. 1991).

### 7.4.7 Interactive Effects

Mixtures of chlorofluorocarbons (e.g., CFC-11, CFC-12, CFC-114) resulted in significant acute reduction of ventilatory lung capacity on exposure to each chlorofluorocarbon, as well as bradycardia and increased variability in heart rate. Negative T-waves were reported in two subjects, and atrioventricular block was reported in one subject. Mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure (WHO 1990). In humans, a 10 and 90% mixture of CFC-11 and CFC-12, respectively, caused more severe respiratory effects than either fluorocarbon inhaled singularly (Clayton and Clayton 1981-82).

If inhalation of chlorofluorocarbons occurs, epinephrine or another sympathomimetic amine and adrenergic activator should not be administered since they will further sensitize the heart to the development of arrhythmias. The combination of chlorofluorocarbon exposure with a sympathomimetic bronchodilator is potentially dangerous for the treatment of bronchial asthma. Symphathomimetic drugs are also contraindicated in cardiac resuscitation of patients suffering from chlorofluorocarbon poisoning (Clayton and Clayton 1993-94).

Trichlorofluoromethane is chemically active with metals such as sodium, potassium, calcium, powdered aluminum, zinc, magnesium and lithium shavings, and granular barium (NIOSH 1997). Granular barium in contact with trichlorofluoromethane is susceptible to detonation. Mixtures of lithium shavings and several halocarbon derivatives, including trichlorofluoromethane, are impact-sensitive and will explode, sometimes violently (Bretherick 1990). It is also dangerous on contact with acid or acid fumes, as they emit highly toxic chloride fumes (Lewis 1996).

### 7.4.8 Risk Assessment

The Guinea pig inhalation LD50 for trichlorofluoromethane is 250,000 ppm/30 min, the rat inhalation LD50 is 100,000 ppm/30 min, and the rabbit inhalation LD50 is 250,000 ppm/30 min (Verschueren 1983). The mouse intraperitoneal LD50 is 1743 mg/kg and the mouse inhalant LC50 is 10,000 ppm/30 min (Lewis 1996); the rat oral LD50 is 3725 mg/kg (ACGIH 1991); the hamster inhalation LC50 is 571g/$m^3$/4 h (WHO 1990).

The EPA has established a non-cancer oral risk value, reference dose (RfD), of 3E-1 mg/kg-day based on a 1978 National Cancer Institute study, with the critical organ/effect listed as survival (IRIS 1998).

### 7.4.9 Medical Surveillance

Employees should be screened for history of certain medial conditions, which might place them at increased risk from chlorofluorocarbon exposures. In persons with impaired cardiovascular function, especially those with a history of cardiac arrhythmias, the inhalation of chlorofluorocarbons might cause exacerbation of disorders of the conduction mechanism due to its sensitizing effects on the myocardium. Any employee developing these conditions should be referred for further medical examination; employees with cardiovascular disease are increased risk (Mackison et al. 1981).

Measurements to determine employee exposure are best taken so that the average 8-hour exposure is based on a single 8-hour sample or two 4-hour samples. Several short time-interval samples (up to 30 minutes) may also be used to determine the average exposure level. Air samples should be taken in an employee's breathing zone (Mackison et al. 1981).

### 7.4.10 Body Burden

Mother's milk from four urban U.S. sites was positive for trichlorofluoromethane. It was detected in four of eight samples of respired air at a range of 0.007 to 0.041 μg/h in subjects having previous occupational exposure, e.g., laboratory technicians (Pellizzari et al. 1982).

## 7.5 1-Butanol

### 7.5.1 Properties

1-butanol is a flammable colorless liquid with a rancid sweet odor. It has a molecular weight of 74.12 and a boiling point of 118° C, a water solubility of 77 g/L, and its octanol/water partition coefficient (logKow) is 0.88. It is miscible with many organic solvents, has a vapor density of 2.6 (with air being 1.0), and occurs naturally as a product of fermentation of carbohydrates. Human exposure is mainly occupational (WHO 1987). It has an odor threshold in air of approximately 2.8 ppm, with a recognition in air of as low as 1.8 ppm (Fazzalari 1978).

### 7.5.2 Toxicity - Health Effects

In animals, 1-butanol is readily absorbed through the skin, lungs, and gastrointestinal tract. It is rapidly metabolized by alcohol dehydrogenase to the corresponding acid, via the aldehyde, and then on to carbon dioxide, which is the major metabolite of 1-butanol (WHO 1987).

It is slightly toxic and is irritating to the eyes and moderately irritating to the skin. The primary effects from exposure to 1-butanol vapor for short periods are various degrees of irritation of the mucous membranes and central nervous system depression. Its potency for intoxication is approximately 6 times that of ethanol. Effects of repeated inhalation exposure in animals include pathological changes in the lungs, degenerative lesions in the liver and kidneys, and narcosis (WHO 1987).

The most prominent effects in humans are alcoholic intoxication and narcosis. Signs of excessive exposure may include irritation of the eyes, nose, throat, and skin, headache, and drowsiness. Vertigo has been reported under conditions of severe or prolonged exposure (WHO 1987).

Alcohol exposure produced a dose-dependent elevation and then decline in specific prolactin binding in membrane preparations from ventral prostate glands in rats. 1-butanol produced a maximal 37-42% increase in prolactin binding at concentrations of 1%. The value of the microviscosity parameter decreased by 10-13% after a 15-minute exposure of prostatic membranes to 1% butanol, indicating that *in vitro* fluidization of the prostatic membrane modifies prolactin-binding capacity (Dave and Witorsch

1983). The effects of n-butanol on the respiration of electrically stimulated and unstimulated slices of rat brain cortical tissue, at concentrations of 9 mM, reduced the respiration of stimulated tissue by about 11.5% and depressed respiration of unstimulated tissue, suggesting that it acts primarily by interfering with mechanisms closely related to the excitation cycle in conducting membranes (Lindbohm and Wallgren 1962).

In a study using male Sprague-Dawley rats exposed to 2000 ppm, the most pronounced effect was on cytochrome P-450 (hepatic), which was elevated 28% (Aarstad et al. 1985).

### 7.5.3 Genotoxicity, Mutagenicity, and Carcinogenicity

1-butanol has been found to be nonmutagenic (WHO 1987). It is classified as "D" (not classifiable as to human carcinogenicity), based on non-human or animal cancer data (IRIS 2000).

### 7.5.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

No information was found regarding reproductive toxicity, embryotoxicity, or teratogencity of 1-butanol.

### 7.5.5 Immunotoxicity

No information was found regarding the immunotoxicity of 1-butanol.

### 7.5.6 Clinical Symptoms, Indications, and Effects

Central nervous system symptoms include headache, muscle weakness, giddiness, ataxia, confusion, delirium, and coma, which are progressively dose-dependent. Gastrointestinal symptoms include nausea, vomiting, and diarrhea (with odor of alcohol in excreta). Irritation symptoms include skin, eyes, and throat irritation from inhalation of the vapors or liquid, cough, and dyspnea. In severe cases, death will result from respiratory failure. It can also produce disturbances in cardiac rhythm. More rare complications include gastrointestinal hemorrhage, renal damage with glycosuria, liver damage, cardiac failure, and pulmonary edema (Gosselin et al. 1984). In some circumstances, there is evidence of it causing vacuolar keratitis and, in some patients, vacuolar keratopathy. Although in cases of vacuolar keratopathy, there are usually no complaints, it can result in associated pain and tearing, usually most marked on the first opening of the eyes in the morning (Grant 1986).

Acute exposure can result in central nervous system depression, hypotension, nausea, vomiting, and diarrhea. It is also an irritant. If aspirated, hemorrhagic pneumonitis may occur. Vapor or splash contact exposure may cause burning, lacrimation, blurring of vision, and vacuolar keratopathy. It can cause hypotension and cardiac arrhythmias. Inhalation causes pulmonary tract irritation and rarely pulmonary edema. Headache, dizziness, giddiness, ataxia, sedation, and coma may result. Liver injury may occur but is probably rare. Dermatitis of varying severity may be noted. Following chronic exposure, drying and fissuring of the skin may occur. Hypoglycemia may also occur (MICROMEDEX 1998).

### 7.5.7 Interactive Effects

N-butanol exerts a potentiating effect on the acute inhalation toxicity of carbon tetrachloride. The potentiation seems to be due to the presence of the unmetabolized alcohol (Doull et al. 1986). Biotransformation of chloral hydrate to trichloroethanol in rat-liver slices was found to be enhanced more effectively by n-butanol than by ethanol (Chemical Society 1971). Ethyl alcohol does not protect against toxicity of n-butanol, which is likely due to the fact that n-butanol is an excellent substrate for alcohol dehydrogenase or that the metabolic products of n-butanol are not a major cause of toxicity (Doull et al. 1980).

The activity of partially purified human erythrocyte actinide phosphatase (EAPASE) was enhanced four-fold by n-butanol. EAPASE activation was noncompetitive (Sawada et al. 1980).

### 7.5.8 Risk Assessment

As extrapolated from rat data, a reasonable mean lethal dose in man is 3 to 7 oz. (Gosselin et al. 1984). The rat LD50 ranges from 0.7 to 2.1 g/kg body weight. The rat oral LD50 is 790 mg/kg (Kirk-Othmer 1984).

Inhalation and skin absorption represent the main routes of workplace exposure. Inhalation of humans results in 49 to 60% retention in the body, which increases with exercise. 1-butanol has been shown to cause eye irritation in occupationally exposed individuals at levels between 60 and 195 $mg/m^3$. The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit of 45 $mg/m^3$ (15 ppm) averaged over an 8-hour work day.

The noncancer oral risk RfD is 1E-1 mg/kg/day. It is based on a NOEL of 125 mg/kg/day, with hypoactivity and ataxia as the critical effect (IRIS 1998).

### 7.5.9 Medical Surveillance

Employees should be screened for history of certain medical conditions (i.e., skin, liver, kidney, eye, chronic respiratory diseases, central and peripheral nervous system) that might place them at increased risk to 1-butanol exposure (Mackison et al. 1981). Blood n-butanol concentrations should not exceed 0.08 mg/L during exposure at the threshold limit value of 50 ppm (Baselt 1988).

### 7.5.10 Body Burden

N-butanol was detected but not quantified over time in a total of 12 human milk samples. The concentration of n-butanol in expired air from eight individuals ranged from 1.3 to 35.0 μg/h, and the n-butanol was said to be of metabolic origins. It was also detected in a range of 0.02 to 0.08 ng/L in the expired air of 54 individuals (Pellizzari 1982).

## 7.6 Acetonitrile

### 7.6.1 Properties

Acetonitrile has a molecular weight of 41.05 and a boiling point of 81.6º C at 760-mm Hg. Its density (specific gravity) is 0.78745 at 15º C (Budavari 1989). It is a colorless, aromatic liquid (NIOSH 1994; Sax and Lewis 1987). Its octanol/water partition coefficient (logKow) is –0.34 (Hanch 1995). Acetonitrile is miscible with water, methanol, methyl acetate, acetone, ethyl acetate, ether, acetamide solutions, chloroform, carbon tetrachloride, ethylene chloride, and many other unsaturated hydrocarbons. It is also miscible with saturated hydrocarbons and dissolves somewhat in inorganic salts such as silver nitrate, lithium nitrate, and magnesium bromide (Budavari 1989). It has a vapor density of 1.42 (with air being 1.0) (Clayton and Clayton 1981-82), and its odor threshold is 70.0 $mg/m^3$ (low) and 70.0 $mg/m^3$ (high), being irritating at 875 $mg/m^3$ (Ruth 1986).

### 7.6.2 Toxicity - Health Effects

Based on observations of systemic toxic effects in animals and humans, acetonitrile can be readily absorbed from the lungs, in the gastrointestinal tract, and through the skin. It is metabolized to inorganic cyanide, which is further oxidized to thiocyanates and acetaldehyde. Signs of toxicity produced by acetonitrile are those of cyanide and thiocyanate poisoning. Acetonitrile and its metabolites are eliminated primarily in the urine. It does not appear to bioaccumulate in mammalian tissues (Santodonato et al. 1985).

After systemic absorption, acetonitrile is first converted to a hydroxyl intermediate by liver cytochrome P450 and then on to cyanide via catalase. Systemic cyanide toxicity has been reported following ingestion and inhalation exposures to acetonitrile. Dermal exposure could also result in system cyanide toxicity.

The onset of signs and symptoms depends on the route, quantity, and duration of exposure, but is typically over 2 to 13 hours post-exposure because of the slow conversion to cyanide. Nausea and vomiting are common initial presenting signs and symptoms. Splash contact may cause a superficial injury similar to that caused by acetone. Tachycardia, bradycardia, palpitations, hypotension, and cardiac arrest have been reported. Hyperpnoea, respiratory insufficiency, Kussmaul respirations, and chest tightness have been reported. Headache, dizziness, confusion, agitation, weakness, seizures, and coma have also been reported.

Anorexia may be noted in patients exposed chronically, while nausea and vomiting are seen in acute exposures. Vomiting has preceded serious toxicity within several hours in most cases of ingestion. Elevated anion gap metabolic acidosis and lactic acidosis are common after ingestion. Splash contact with the liquid may cause faint erythema of short duration. Chronic exposure may produce maculopapular vesicular dermatitis (MICROMEDEX 1998).

Acetonitrile concentrations up to 500 ppm cause irritation of mucous membranes. Higher concentrations produce weakness, nausea, convulsions, and death. Urine thiocyanate concentrations were not significantly elevated after an exposure of 160 ppm for 4 hours (Tietz 1983).

It should be noted that acetonitrile has insufficient warning properties to prevent workers from working in atmospheres that may cause death. High concentrations cause rapid death (NFPA 1986).

Several cases of accidental poisoning were caused by inhalation of acetonitrile in different work places. Signs of toxicity include bronchial tightness, gastric distress, respiratory distress, hypotension, hypersecretion of saliva, conjunctivitis, skin discoloration, tachypnea, general weakness, absence of deep reflexes, coma, and, in some cases, death. Postmortem analysis for cyanide and thiocyanate revealed that of all tissues examined, the spleen contained the largest amount of cyanide. While levels of thiocyanate were found in the lungs, the largest amounts of acetonitrile were found in the liver and kidneys (Snyder 1990).

### 7.6.3 Genotoxicity, Mutagenicity, and Carcinogenicity

Acetonitrile is assigned a carcinogen class "D" (not classifiable as to human carcinogenicity). There is absence of human evidence and the animal evidence is equivocal (IRIS 2000). The National Toxicology Program (NTP) concluded that the evidence for carcinogenicity via inhalation of acetonitrile in the F344/N rat was equivocal based on a positive trend of hepatocellular tumors in male rats. Although there was a statistically significant positive trend in the incidence of hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas combined in male rats only, the incidences were not statistically significant by pairwise comparison or by life-table analysis. The incidence of adenomas and carcinomas combined in the 400-ppm group was only slightly higher than the historical range for inhalation study controls. Male rats exhibited an increased incidence of basophilic foci in liver that was statistically significant in the 200- and 400-ppm groups. These foci were not atypical in appearance, as those more closely related to the carcinogenic process, altered hepatocellular foci, are generally considered to be pre-neoplastic. The NTP concluded that a causal relationship between acetonitrile exposure and liver neoplasia in male rats was uncertain. There was no evidence of carcinogenicity in female rats or in either male or female B6C3Fi mice (IRIS 2000).

Mutagenicity assays indicate that acetonitrile does not cause point mutations. It was negative in assays with five strains of *S. typhimurium* in the absence of S9 as well as in the presence of rat or hamster S9 induced with Aroclor 1254. Acetonitrile does have the potential to interfere with chromosome segregation, possibly leading to aneuploidy, as evidence in experiments with *D. melanogaster* (IRIS 2000).

### 7.6.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

Acetonitrile was evaluated for embryotoxic and teratogenic potential in rats. Mated Sprague-Dawley rats were administered acetonitrile by gavage on gestation days 6-19. Daily dosage levels were 0, 125, 190, and 275 mg/kg. There was evidence of maternal toxicity in each of the high-dose groups. Embryotoxic effects were observed at the highest dosage tested. No teratogenic effects were observed at

any dosage level (Johannsen et al. 1986). Inhalation of acetonitrile by pregnant animals may produce malformations in the offspring such as axial skeletal disorders at maternally toxic levels (Hashimoto 1991).

### 7.6.5 Immunotoxicity

No information was found regarding the immunotoxicity of acetonitrile.

### 7.6.6 Clinical Symptoms, Indications, and Effects

Massive doses may produce, without warning, sudden loss of consciousness and prompt death from respiratory arrest. With smaller but still lethal doses, the illness may be prolonged for 1 or more hours. Upon ingestion, a bitter, acrid, burning taste is often noted. This is followed by a feeling of constriction or numbness in the throat. Salivation, nausea, and vomiting are common. Anxiety, confusion, vertigo, giddiness, and often a sensation of stiffness in the lower jaw occur. Hyperpnea and dyspnea also occur. Respirations become very rapid and then slow and irregular. Inspiration is characteristically short while expiration is greatly prolonged. The odor of bitter almonds may be noted on the breath or vomit.

In the early phases of poisoning, an increase in vasoconstrictor tone causes a rise in blood pressure and reflex slowing of the heart rate. Thereafter, the pulse becomes rapid, weak, and sometimes irregular. A bright pink coloration of the skin due to high concentrations of oxyhemoglobin in the venous return may be confused with that of carbon monoxide poisoning. Unconsciousness occurs, followed promptly by violent convulsions, epileptiform or tonic, sometimes localized but usually generalized. Opisthotonos and trismus may develop. Involuntary micturition and defecation occur. Paralysis follows the convulsive stage. The skin is usually covered with sweat. The eyeballs protrude, and the pupils are dilated and unreactive. The mouth is covered with foam, which is sometimes bloodstained. The skin color may be brick red. Cyanosis is not prominent in spite of weak and irregular gasping. In the unconscious patient, bradycardia and the absence of cyanosis may be key diagnostic signs. Death from respiratory arrest occurs. As long as the heart beat continues, prompt and vigorous treatment offers some promise of survival (Gosselin et al. 1984).

In a study of exposures of 40-, 80-, and 160-ppm acetonitrile, none of the subjects reported adverse response during the 40-ppm exposure. One subject experienced a slight tightness of the chest a few hours later, and a cooling sensation in the lung the next morning and the rest of the day. The experience was reported to be similar to that of inhaling menthol. All subjects detected the odor at 40 ppm for the first 2 to 3 hours, then experienced some olfactory fatigue. No detectable cyanide was found in blood specimens, but one subject showed a slightly elevated urinary thiocyanate level (ACGIH 1986).

A fatal exposure of a photographic laboratory worker was reported. After a massive exposure, he left work, ate his evening meal, and began experiencing gastric distress and nausea about 4 hours after exposure. He vomited during the night. The next morning he was sweating profusely and alternately

crying out sharply and lapsing into a comatose state. Other symptoms were hypersalivation, conjunctivitis, very low urine output, low blood pressure, and albumin in urine and cerebrospinal fluid. He experienced cardiac and respiratory arrest, from which he was resuscitated. He died six days later (Clayton and Clayton 1981-82).

Two men who were occupationally exposed to acetonitrile vapor were hospitalized with severe symptoms consisting of nausea and vomiting, respiratory depression, extreme weakness, and semi-comatose state. One developed transient weakness of flexor muscles of arms and wrists. Both developed urinary frequency, associated in one instance with albuminuria and in another with the passage of small oxalate-type urinary calculi. Both showed elevated blood cyanide levels and somewhat increased serum thiocyanate levels. All other exposed workers were evaluated, with incremental blood cyanide and thiocyanate values occasionally found. The symptoms were also found in other exposed workers but to lesser degrees. None of the individuals developed any enlargement of thyroid or alteration in thyroid function (Clayton and Clayton 1981-82).

Patients with potential ingestion or inhalation exposure should be admitted to intensive care for at least 24 to 48 hours for observation. Toxicity may be prolonged, with clinical deterioration following initial response to antidote treatment reported for as long as 3 days after ingestion. Signs and symptoms typically develop over time and include nausea, vomiting, hematemesis, hyperpnea, tachypnea, respiratory insufficiency, bronchial tightness, headache, dizziness, agitation, confusion, weakness, seizures, coma, metabolic acidosis, tachycardia, bradychardia, cardiac arrhythmias and conduction defects, hypotension, cardiac arrest, and death (MICROMEDEX 1998).

### 7.6.7 Interactive Effects

The nature and mechanism of toxicological interaction between acetonitrile and acetone in oral dose-response studies showed that acetone potentiated acute acetonitrile toxicity three- to four-fold in rats. The onset of severe toxicity (manifested by tremors and convulsions) was delayed in the groups dosed with both solvents. Blood cyanide and serum acetonitrile and acetone concentrations were measured. Concentrations of cyanide in the blood of rats given both solvents remained near baseline, in contrast to the high blood cyanide concentrations found in rats dosed with acetonitrile alone. At 34 to 36 hours, high blood cyanide concentrations were found in rats dosed with both solvents. This delayed onset of elevation of blood cyanide coincided with the occurrence of clinical signs and the disappearance of serum acetone.

In pharmacokinetic studies, blood cyanide concentrations were measured. Peak cyanide concentrations were significantly greater in rats given both acetonitrile and acetone than in rats given only acetonitrile. Administration of sodium thiosulfate or a second dose of acetone prevented the toxicity associated with exposure to both solvents. It is believed that the effects of acetone on acetonitrile toxicity are due to a biphasic effect on the metabolism of acetonitrile to cyanide (i.e., initial inhibition followed by a stimulation of this metabolism upon acetone elimination) (Freeman 1985).

The toxic mechanism of acetonitrile and the effect of metabolic modifiers in mice were studied in relation to their physiochemical properties. Cyanide was liberated *in vivo* and *in vitro*. Acute toxicity was greatly reduced by carbon tetrachloride pretreatment. The amount of cyanide was higher at death in

the brains, with the level being comparable to that found in mice killed by dosing with potassium cyanide. When mice were dosed with ethyl alcohol, metabolic enhancement was seen compared with the control. However, ethyl alcohol inhibited the *in vitro* metabolism (Tanii 1985).

### 7.6.8 Risk Assessment

The rat inhalation LC50 is 7500 ppm/8 h and 330 ppm/90 days (Verschueren 1983); the rat oral LD50 is 3800 mg/kg (Budavari 1989); the Guinea pig oral LD50 is 140 mg/kg (Snyder 1990); the rabbit dermal LD50 is 980 mg/kg (Snyder 1990); the rabbit inhalation LC50 is 2825 ppm/4 h (Snyder 1990).

The noncancer oral risk RfD was withdrawn in 1999. It has a cancer oral risk classification of "D" (nonclassifiable as to human carcinogenicity). Acetonitrile has a noncancer inhalation risk reference concentration (RfC) of 6E-2 based on a "no observed adverse effect level" (NOAEL) of 336 $mg/m^3$ and mortality as the critical effect basis (IRIS 1998).

### 7.6.9 Medical Surveillance

Determination of blood cyanide or urinary thiocyanate should not be relied on as evidence for brief inhalation of lower concentrations of acetonitrile vapor (Clayton and Clayton 1981-82). In biological monitoring, pre-exposure levels should be established, since smokers show elevated concentrations of metabolites (Tietz 1983). The skin, respiratory tract, heart, central nervous system, and renal and liver functions should be considered during placement and periodic examination (Sittig 1985).

Medical procedures should be made available to each employee who is exposed to acetonitrile at potentially hazardous levels. A complete history and physical examination should be conducted to detect pre-existing conditions that might place the exposed employee to increased risk and to establish a baseline for future health monitoring. Examination of the kidneys, liver, cardiovascular system, and central nervous system should be stressed. The skin should also be examined for evidence of chronic disorders. These examinations should be repeated on an annual basis (Mackison et al. 1981).

### 7.6.10 Body Burden

A standard second puff of cigarette smoke contains 0.31-mg acetonitrile. A smoker may absorb between 73 and 82% of this 0.31 mg in post-smoking habits (EPA 1980). An individual who died about 2 hours after a 12-hour exposure had the following cyanide concentrations detected in his tissues at autopsy. The blood had 8 mg/L of cyanide, lung 1.3 mg/kg, liver 0.0 mg/kg, kidney 2.0 mg/kg, and urine 2.2 mg/L (Baselt 1980). Blood cyanide concentrations exceeding 0.1 mg/L or plasma or urine thiocyanate concentrations exceeding 20 mg/L in workers potentially exposed to acetonitrile are indicative of excessive exposure (Baselt 1980).

## 7.7 Tetrahydrofuran

### 7.7.1 Properties

The molecular weight of tetrahydrofuran is 72.11 (Lide 1995). It is a colorless mobile liquid (Sax 1984) with an ether-like odor and a boiling point of 66º C at 760-mm Hg. Its density (specific gravity) is 0.8892 at 20º C (Budavari 1989). Its octanol/water partition coefficient (logKow) is 0.46 (Hansch and Hoekman 1995). Tetrahydrofuran is 30% soluble in water at 25º C (ILO 1983) and is miscible with alcohols, ketones, esters, hydrocarbons, and ethers (Budavari 1989). It has an odor threshold of 20-50 ppm (CHRIS 1984) and is recognizable in air at 7.3 to 10.2 $mg/m^3$ (Verschueren 1983).

### 7.7.2 Toxicity - Health Effects

Data pertaining to the toxicity of tetrahydrofuran in humans is quite limited. The probable oral lethal dose in humans is 50 to 500 mg/kg. Severe occipital headaches were reported in the testing for pharmacological properties of tetrahydrofuran and among technicians performing animal experiments (Gosselin et al. 1984). Animals studies indicate that tetrahydrofuran is only moderately toxic from acute exposure, with the lowest reported LD50 of 1900 to 2900 mg/kg by oral route. Median lethal concentrations by inhalation varied with the duration of exposure but were greater than 20,000 ppm with all exposures of 1 hour or less. It can cause irritation of the skin and mucous membranes, including the eyes, nose, and upper respiratory tract, as the predominant effect from lower exposures such as 100 to 200 ppm. High acute doses (25,000 ppm) produced anesthesia with delayed induction and recovery periods, accompanied by a fall in blood pressure and strong respiratory stimulation. The margin of safety between anesthesia and death is small. Other effects recorded are damage to the liver, kidneys, and lung after prolonged exposures to levels greater than 1000 ppm (MICROMEDEX 1998).

A single 4-hour inhalation of tetrahydrofuran in rabbits in the range of 100 to 12,000 ppm resulted in transient dose-related decrease of tracheal ciliary activity. Single or repeated exposures have been associated with cytolytic hepatitis and fatty degeneration of the liver (ACGIH 1991). Concentrations greater than 25,000 ppm were required to produce anesthesia. The anesthetic properties were rather poor in that onset was delayed and recovery poor. This was accompanied by pronounced hypotension and marked respiratory hyperpnea. There was a narrow margin of safety between anesthesia and death in dogs and mice studies. When dogs inhaled 200 ppm of tetrahydrofuran 6 h/day for 3 to 4 weeks, an observable effect on pulse pressure was recorded. No demonstrable histopathologic changes were found despite extended exposure of 9 weeks, followed by an additional 3-week exposure at up to 400 ppm (ACGIH 1991).

Acute oral administration of tetrahydrofuran to cats was found to cause inflammation, necrosis, and hemorrhage of the gastrointestinal tract. The kidneys showed injury to the tubules, and there was inflammation of the liver as well as congestion and edema in the lung (Browning 1965).

Male rats that inhaled more than 5000 ppm for 12 weeks at 4 h/day showed signs of systemic intoxication, skin and respiratory tract irritation, liver function disturbance, and abnormalities in glucose

metabolism. The systemic effects were not observed after similar exposures at lower concentrations, but slight respiratory tract irritation occurred in some of the rats that inhaled less than 200 ppm (ACGIH 1991).

Rabbits exposed to tetrahydrofuran at 12,000 ppm for 4 hours had paralysis of the nasal ciliary function due to the absence of ciliary beating, while morphological damage of ciliated cells was not so severe (Ohashi et al. 1982).

### 7.7.3 Genotoxicity, Mutagenicity, and Carcinogenicity

No carcinogenic effects were observed in a test of skin tumors in which tetrahydrofuran was applied to the skin of mice twice per week for 25 exposures with an observation period of 17.5 months. It was negative when tested for mutagenicity using the Ames test. However, it did appear to enhance the mutagenicity of certain tryptophan-pyrolysate substances (MICROMEDEX 1998). Tetrahydrofuran caused DNA damage in mammalian cells. It was mutagenic in *E. coli*, but not in the Ames salmonella/ microsome assay. It did not increase DNA repair in human cells and was inactive for producing sex-linked recessive lethal mutations in fruit flies, sperm abnormalities in mice, and dominant lethal mutations in male rats. It strongly enhanced the mutagenicity of pyrolysis products of trypophane in salmonella (MICROMEDEX 1998).

Tetrahydrofuran tested negative for sex-linked recessive lethal heritable genetic effects in Drosophila. In test results for cytogenetic effects in Chinese hamster ovary cells, it tested positive for chromosomal aberrations and negative for sister chromatid exchanges (NTP 1984).

Tetrahydrofuran was tested for mutagenicity in the salmonella/microsome preincubation assay using the standard protocol approved by NTP. It tested negative at doses of 0.1, 0.33, 1.0, 3.3 and 10 mg/plate in as many as five salmonella typhimurium strains, in the presence and absence of rat or hamster liver S-9. The highest ineffective dose tested in any salmonella typhimurium strain was 10 mg/plate (Mortelmans et al. 1986).

Under the conditions of a 2-year inhalation study, there was some evidence of carcinogenic activity in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female F344/N rats or male B6C3F1 mice when either were exposed to 200, 600, or 1800 ppm. There was clear evidence of carcinogenic activity in female B6C3F1 mice based on increased incidences of hepatocellular neoplasms (NTP 1998).

### 7.7.4 Reproductive Toxicity, Embryotoxicity, and Teratogenicity

Tests in Sprague-Dawley rats and Swiss CD-1 mice suggest that tetrahydrofuran may be embryotoxic in mice, but if the conceptus survives, development as assessed by the experimental design continued in a normal fashion. Fetuses exposed to 1800 ppm exhibited a significantly increased incidence of reduced sternebral ossification sites. The NOAEL for maternal toxicity was 1800 ppm in both rats and mice. The NOAEL for developmental toxicity was 1800 ppm in rats and 600 ppm in mice (Mast et al. 1992).

### 7.7.5 Immunotoxicity

No information was found regarding the immunotoxicity of tetrahydrofuran.

### 7.7.6 Clinical Symptoms, Indications, and Effects

Ingestion of tetrahydrofuran may cause nausea, dizziness, headache, and central nervous system depression. Its vapors may be a respiratory tract irritant, or produce nausea, dizziness, and central nervous system depression with general anesthesia. It is an eye irritant and will cause burning and dermatitis on prolonged exposure to the skin. Clinical symptoms are accompanied by a marked decrease in the number of white blood cells in chronic occupational exposures. Profuse salivation and irritation of the eyes and mucous membranes often occurred with exposure to tetrahydrofuran. Hypotension may be noted, as well as upper respiratory irritation or stimulation. Occipital headache and dizziness are common. Nausea and gastrointestinal irritation may be noted. Liver damage can result from tetrahydrofuran exposures. It is irritating in concentrations of 20% or greater (MICROMEDEX 1998).

Signs and symptoms accompanied by a marked decrease in the number of white blood cells were observed in researchers engaged in experimental spinning of synthetic fibers, which were thought due to poisoning by tetrahydrofuran. The researchers recovered after 2 years of treatment with cystin, liver preparate, vitamin B1 and 2, and vitamin C (Horiguchi 1981). Tetrahydrofuran can cause dermatitis on prolonged exposures (Mackison et al. 1981). Exposure to tetrahydrofuran has been reported to be irritating to the skin, eyes, and mucous membranes, and individuals exposed to high concentrations have elevated circulating enzymes, in addition to complaints of nausea, tinnitus, and occipital headache. Liver biopsy from an occupationally exposed male has confirmed fatty degeneration and siderosis along with elevated gamma glutamyl transferase and alanine aminotransferase (ACGIH 1991).

There were two cases of occupational exposure where the symptoms included irritation of mucous membranes, nausea, headache, dizziness, and possible cytolytic hepatitis. The effects on mucous membranes and the central nervous system resolved within a few hours after cessation of the exposure (ACGIH 1991).

### 7.7.7 Interactive Effects

A polyvinyl chloride pipe insulator, whose most recent exposure to tetrahydrofuran occurred over 2 weeks prior in a poorly ventilated confined space, developed cerebral convulsions after hospitalization for acute appendicitis with the administration of enflurane anesthesia. It was thought that the interaction of the anesthetic and the occupational exposure to tetrahydrofuran contributed to the onset of convulsions (ACGIH 1991).

### 7.7.8 Risk Assessment

The rat inhalation LC50 is 80,975 ppm/1 h, 62,000 ppm/2 h, and 18,000 ppm/4 h (Verschueren 1983). The rat oral LD50 is 3.2 mL/kg in older rats, 2.3 mL/kg in old male rats, and 3.6 mL/kg in young adult rats (ACGIH 1991).

A noncancer oral risk RfD of 1E-3 was established based on a NOAEL of 2.0 mg/kg-day, with the liver being the critical organ (IRIS 1998).

### 7.7.9 Medical Surveillance

In preplacement and periodic physical examinations, it is important to consider the points of attack, which are the eyes, skin, respiratory system, and central nervous system (Sittig 1985).

Medical procedures should be made available to each employee who is exposed to tetrahydrofuran at potentially hazardous levels. These procedures should include initial medical screening, which should include screening for history of medical conditions that might place them at increased risk. Medical histories related to skin, liver, kidney and chronic respiratory disorders should be screened. Periodic medical examinations should take place (Mackison et al. 1981).

### 7.7.10 Body Burden

Tetrahydrofuran has been found in 1 out of 12 samples of mother's milk in a four urban areas of sampling (Pellizzari 1982).

# 8.0 Worker Exposure Limits

In Table 8.1, exposure limits are listed for specific chemicals under evaluation. Each compound class is represented by one compound identified in the table. For each compound, the threshold limit (TLV) is listed in ppm for an 8-hour time-weighted average (TWA) and/or a short-term exposure limit (STEL) or ceiling limit (C). These values were obtained from the ACGIH (2001). Also noted in the table for two of the compounds (1-butanol and acetonitrile) are new (proposed) exposure limits. These are identified as "NIC-Notice of Intended Change" in the comments column. These new levels would take effect when the 2002 booklet is published unless specific concerns over changing the levels have been identified and substantiated. Permissible exposure limits (PELs) are also listed from 29 CFR 1910.100 (OSHA). Also listed in Table 8.1 are maximum concentrations that have been measured along with the specific waste tanks that had those maximum concentrations (Stock and Huckaby 2000) so that they can be compared to the worker exposure limits.

**Table 8.1**. Exposure Limits for Chemicals under Evaluation and Maximum Concentrations Measured in the Headspaces of Single-Shell Tanks

| Compound Class | Compound | Exposure Limits | | | | | Maximum Concentration Observed[c] | Tank with Maximum Concentration[c] |
|---|---|---|---|---|---|---|---|---|
| | | ACGIH TLV Booklet [a] | | | | OSHA [b] | | |
| | | TLV, ppm | | | | | | |
| | | 8-h TWA | STEL/C | Notation | Comments | PEL, ppm | | |
| Benzene and alkyl benzenes | Benzene | 0.5 | 2.5 | Skin; A1; BEI | | 10 (TWA) 25 (C) | 2 | BY-104 |
| Ammonia | Ammonia | 25 | 35 | | | 50 (TWA) | 1043 | BY-108 |
| Biphenyls | Biphenyl | 0.2 | -- | | | 0.2 (TWA) | 2 | C-103 |
| Halo alkanes and halo alkenes | Tricholoro-fluoromethane | -- | C 1000 | A4 | | 1000 (TWA) | 29 | BY-104 |
| Alcohols, phenols, and ethers | 1-Butanol | -- | C 50 | Skin | | 100 (TWA) | 58 | BY-108 |
| | | 20 | | | NIC for 2001 | | | |
| Nitriles | Acetonitrile | 40 | 60 | A4 | | 40 (TWA) | 13 | C-103 |
| | | 20 | -- | Skin, A4 | NIC for 2001 | | | |
| Heterocycles | Tetrahydrofuran | 200 | 250 | BEI | | 200 (TWA) | 5 | C-103 |

- A1 – Confirmed human carcinogen
- A4 – Not classified as a human carcinogen
- BEI – A biological exposure indice (BEI) is also recommended for the substance listed.
- TLV – Threshold limit value
- TWA – Time-weighted average
- STEL – Short-term exposure limit
- C – Ceiling limit
- NIC – Notice of Intended Change
- Skin – Notation refers to the potential significant contribution to the overall exposure by the cutaneous route.
- PEL – Permissible exposure limit

(a) ACGIH 2001.
(b) 29 CFR 1910.1000, Table Z-1 or Z-2 (2000).
(c) Stock and Huckaby 2000.

# 9.0 Conclusions

The primary purpose of the Phase I work was to begin establishing an exposure-based health assessment team and working relationships, drawing from ORP, CHG, HEHF, and PNNL. Following-up Phase I work, the team should collectively review the toxicological and clinical data presented in this Phase I report and compare the detectable human-effect levels with those of the worker exposure limits and standards. The goal is to look for odor or minor-effect levels where it might make sense to establish warning or working levels. If such levels are identified, the reviewers should then look for areas where current tank-farm monitoring and control practices could be modified to more effectively manage tank-farm health and safety.

Also, a database should now be developed at HEHF to manage the exposure, toxicological, and clinical data, so it would be readily available for both planning and responding to worker exposure situations and complaints. The overall goal would be to effectively manage these data so they could be readily coupled with health monitoring capabilities (both current and expanded field/clinical, mobile laboratory, and health-monitoring capabilities).

In Phase II and beyond, the goal is to begin looking forward to retrieval, pretreatment, nitrification, and disposal operations. These relationships will help prepare health and safety and medical staff for potential worker exposure situations that might arise. This effort will need to be coordinated with ongoing HLW disposition planning and design activities and divided into the appropriate phases that match the progress of the ongoing technology design and development work within the ORP and its contractors. The team will need to address future operations, develop realistic exposure scenarios associated with such operations, and establish ways to include HEHF physicians more actively in protecting employee health, preventing future ill health effects, and managing exposure events. Thus, Phase II will focus on using preliminary design information on retrieval, pretreatment, and vitrification operations, tailored to coincide with current ORP planning and design activities and needs, to develop comparable exposure–based health-issue analyses similar to those developed under Phase I for the current HLW operations.

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