California Environmental Protection Agency

Air Resources Board

Recommendations to the California Public Utilities Commission

Regarding Health Protective Standards for the

Injection of Biomethane into the Common Carrier Pipeline

May 15, 2013

Prepared by Staff of the

California Air Resources Board and the

Office of Health Hazard Assessment

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EXECUTIVE SUMMARY

Biogas is created when organic waste decomposes anaerobically (without oxygen). This can occur in landfills, covered lagoons, or enclosed vessels, where access to oxygen is limited. The decomposition (or "digestion") process involves a series of steps in which microorganisms break down the organic waste, ultimately producing primarily methane and carbon dioxide. The raw (unprocessed) mixture of methane and carbon dioxide is referred to as biogas. Biogas can be processed or upgraded to increase the percentage of methane in the gas by removing carbon dioxide and other trace components. When biogas is upgraded to pipeline quality, it is referred to as biomethane. Biomethane is interchangeable with natural gas. In addition, biomethane offers several benefits including:

- Supporting energy diversity as a renewable energy source,
- Reducing greenhouse gas emissions,
- Promoting sustainable waste management practices, and
- Creating new jobs in California.

AB 1900, authored by Assemblyman Mike Gatto and chaptered into law on September 27, 2012 (Chapter 602, Statutes of 2012), requires the California Public Utilities Commission (CPUC) to develop standards for constituents in biogas to protect human health and pipeline integrity and safety, identify impediments that limit procurement of biomethane in California, and adopt policies and programs that promote the in-state production and distribution of biomethane. To support CPUC's standards development efforts, the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB), in consultation with other State agencies, are to undertake certain actions.

Specifically, OEHHA is tasked with compiling a list of constituents of concern found in biogas that could pose a health risk and that are at levels that significantly exceed the concentrations of those constituents found in natural gas. OEHHA is also to determine health protective levels for these constituents. ARB is tasked with developing realistic exposure scenarios and identifying the associated health risk to utility workers and gas end users; determining the concentrations of these constituents in biogas necessary to protect public health; and identifying monitoring, testing, reporting, and recordkeeping requirements necessary to ensure that health protective standards are maintained. These tasks are to be completed on or before May 15, 2013. Per AB 1900, ARB and OEHHA are not to consider pipeline integrity and safety aspects that may be associated with the use of biogas; the CPUC will address these aspects during its rulemaking process.

ARB and OEHHA staff worked together to fulfill the AB 1900 requirements and develop recommendations to inform the CPUC rulemaking process. For the evaluation and identification of the constituents of concern in biogas, ARB and OEHHA staff focused on the larger sources of biogas – landfills, dairies, and sewage treatment plants (POTWs). For each of these three sources, data is available regarding the constituents present in the biogas. Further, these three sources have the greatest potential to economically

inject biogas into the natural gas pipeline in California. ARB and OEHHA staff will address other sources of biogas i.e., crop residuals, food waste, woody biomass, energy crops, etc., in future updates as additional data becomes available regarding constituents present in these sources of biogas. Briefly summarized below are our findings and recommendations. Additional details can be found in the chapters that follow this executive summary.

Findings and Recommendations

Based on the available data, and depending on the biogas source, there are up to 12 constituents of concern that can potentially be present in raw biogas that if not sufficiently removed during the cleaning and upgrading processes may present health concerns.[1] These constituents are listed in Table ES-1, and as shown, not all of the constituents are found in each source of biogas. All 12 constituents of concern were present in landfill biogas, 6 were present in dairy biogas and 5 in POTW biogas.

Table ES-1: Constituents of Concern in Biogas

Constituents of Concern	Biogas Source		
	Landfills	**Dairies**	**POTWs**
Antimony	✓		
Arsenic	✓		
Copper[1]	✓		
p-Dichlorobenzene	✓		✓[2]
Ethylbenzene	✓	✓	✓
Hydrogen Sulfide	✓	✓	✓
Lead	✓		
Methacrolein	✓		
n-Nitroso-di-n-propylamine	✓	✓	
Mercaptans (Alkyl Thiols)	✓	✓	✓
Toluene	✓	✓	✓
Vinyl Chloride	✓		✓

OEHHA has recommended health protective levels for these constituents of concern consistent with OEHHA health risk assessment methodologies. In our review of the available data, the majority of the constituents of concern in the biogas were either not detected or reduced to concentrations below the OEHHA recommended health

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[1] Copper was not detected in any of the raw biogas but was detected in some samples of landfill biomethane, raising the possibility that it was introduced in either the upgrading equipment or the sampling apparatus used for testing. As discussed in Chapter V, we recommend that the status of copper be further evaluated by ARB staff during the CPUC rulemaking process to determine whether it is appropriate to require monitoring of this compound, or if the risk management approach needs to be adjusted.

[2] Errata: An error in the report released on May 15, 2013 resulted in p-Dichlorobenzene being checked as a constituent of concern for dairies instead of for POTWs. This error was corrected on May 23, 2013 and is reflected in this document.

protective levels during the upgrading process to biomethane indicating that from a public health perspective, the injection of biomethane does not present additional health risk as compared to natural gas.

ARB staff has recommended a risk management strategy based on the approach outlined in ARB's Risk Management Guidelines for New and Modified Sources of Toxic Air Pollutants (ARB, 1993) wherein trigger levels and lower and upper action levels for potential cancer risk and total non-cancer hazard indexes are identified and evaluated to ensure that health protective levels are adequately maintained.

Briefly, the trigger level is set at the OEHHA health protective level for each constituent of concern and operators are required to routinely monitor (quarterly or annually) the levels of compounds above the trigger levels to verify that the total potential cancer and non-cancer risks for the constituents of concern continue to stay within the trigger level and the lower and upper action levels.[3] The constituents of concern that must be measured depend on the biogas source and the frequency of monitoring is dependent on the concentration level of a constituent of concern measured during an initial pre-injection screening evaluation. A facility must be shut-off (stop injecting into the pipeline) and repaired if the lower action level is exceeded three times in a 12 month period or at any time the levels exceed the upper action level. The recommended risk management levels for the constituents of concern are presented in Table ES-2. Additional details on the recommendations are provided in Chapter V of this report.

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[3] Both hydrogen sulfide and mercaptans are typically addressed by natural gas tariffs. In the event there is a natural gas or other tariff for these compounds that is lower than the OEHHA health protective level (trigger) then compliance with the tariff is sufficient for demonstrating compliance with the health protective standards recommended.

Table ES-2: Recommended Risk Management Levels for Constituents of Concern

Constituent of Concern	Risk Management Levels (Health Based Standards) mg/m^3 (ppmv)		
	Trigger Level	Lower Action Level	Upper Action Level
Carcinogenic Constituents of Concern			
Arsenic	0.019 (0.006)	0.19 (0.06)	0.48 (0.15)
p-Dichlorobenzene	5.7 (0.95)	57 (9.5)	140 (24)
Ethylbenzene	26 (6.0)	260 (60)	650 (150)
n-Nitroso-di-n-propylamine	0.033 (0.006)	0.33 (0.06)	0.81 (0.15)
Vinyl Chloride	0.84 (0.33)	8.4 (3.3)	21 (8.3)
Non-carcinogenic Constituents of Concern			
Antimony	0.60 (0.12)	6.0 (1.2)	30 (6.1)
Copper	0.060 (0.02)	0.60 (0.23)	3.0 (1.2)
Hydrogen Sulfide	30 (22)	300 (216)	1,500 (1,080)
Lead	0.075 (0.009)	0.75 (0.09)	3.8 (0.44)
Methacrolein	1.1 (0.37)	11 (3.7)	53 (18)
Alkyl Thiols (Mercaptans)	N/A (12)	N/A (120)	N/A (610)
Toluene	904 (240)	9,000 (2,400)	45,000 (12,000)

ARB and OEHHA staff will continue to work with CPUC staff as they adopt standards for constituents in biomethane and address any issues pertaining to incorporating health based standards with standards to maintain pipeline integrity and safety as required by AB 1900. Staff will also work to encourage incorporation of a streamlined pathway in the regulations to allow introduction of new sources of biomethane such as crop residuals, food waste, woody biomass, etc., in the event data becomes available and it is analyzed by OEHHA and ARB staff pursuant to AB 1900. In addition, ARB and OEHHA staff will continue to evaluate available data on constituents in biogas. As required by AB 1900 we will update the list of constituents of concerns, the health protective levels, and the monitoring, testing, reporting, and recordkeeping requirements at least every five years if data warrant.

ARB staff also recommends that the CPUC consider the cost of testing for constituents of concern as they identify impediments that limit procurement of biomethane in California and adopt policies and programs that promote the in-state production and distribution of biomethane pursuant to AB 1900. During the development of the risk management strategy, concerns were raised that the cost of testing for the constituents of concern may impede the economic viability of some biomethane production facilities. In response, ARB staff developed a monitoring approach that balanced the need to demonstrate the removal efficiency of a conditioning process in the early stages of operation and to reduce testing once the functionality of a system was verified. Even so, if all the costs for testing that may be required for monitoring of the health based

standards and any additional tests required when CPUC develops requirements to maintain pipeline integrity and safety are placed on the biomethane producer, it may limit the number of biomethane production facilities that will be viable. Given the broader public benefits from the increased use of biomethane, we recommend that the CPUC explore ways to minimize the testing cost burden to the biomethane producer, while at the same time ensuring that reasonable and prudent testing is conducted to protect both public health and pipeline integrity and safety.

References

(ARB, 1993) "Risk Management Guidelines for New and Modified Sources of Toxic Air Pollutants," California Air Resources Board, July 1993.
http://www.arb.ca.gov/diesel/documents/rmg793.pdf

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I. INTRODUCTION

In this chapter, we provide a brief description of biogas and biomethane and Assembly Bill 1900 (AB 1900). In addition, we discuss the scope of the Air Resources Board (ARB) staff recommendations to the California Public Utilities Commission (CPUC) and provide a brief overview of the information collected by ARB and the Office of Environmental Health Hazard Assessment (OEHHA) and the process used to develop the recommendations.

A. Biogas and Biomethane

Biogas is generated from the anaerobic digestion of organic materials.[4] This can occur in landfills, covered lagoons, or enclosed vessels, where access to oxygen is limited. The chemical composition of biogas varies and is dependent on the source material (e.g. municipal waste water, livestock manure, food wastes, or municipal solid wastes), and the environmental conditions. Raw biogas consists primarily of methane (the main component in natural gas), carbon dioxide (CO_2), and smaller amounts of nitrogen, oxygen, and hydrogen. Depending on the waste stream, several trace gases can also be produced, including hydrogen sulfide, ammonia, and various volatile organic compounds. Particulates and biological components, such as bacteria, can also be present.

Biogas can be processed or upgraded to increase the percentage of methane in the gas by removing CO_2 and other trace components. When biogas is upgraded to pipeline quality, it is referred to as biomethane. Conversion of biogas into biomethane typically requires water removal, CO_2 separation (using adsorption, absorption, membrane separation, or cryogenic distillation technology), and compression. (DOE, 2009) During biogas upgrading, trace constituents are removed to levels comparable to or below those in traditional pipeline natural gas. (NG, 2010) This is done with the same equipment (adsorption, absorption, membrane separation, or cryogenic distillation technology) that is needed to upgrade the biogas to meet pipeline quality (tariff) specifications. (AGL, 2013) According to the Coalition for Renewable Natural Gas, if a clean-up system is removing CO_2, it is also removing trace organic and particulate compounds in the gas stream. (RNG, 2013)

Biomethane is interchangeable with natural gas, and it offers several additional benefits. It is a renewable energy source that supports energy diversity, it has the potential to reduce greenhouse gas emissions, it promotes sustainable waste management practices, and its production and use creates jobs.

There are numerous biomethane projects in the United States that inject into the natural gas pipeline. According to the American Biogas Council (ABC), there are about 60 such projects nationwide. (ABC, 2013) Specifically, the ABC reported 33 landfill projects, one

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[4] Biogas can also be generated by thermal gasification systems, where waste is exposed to very high temperatures (greater than 700° C) within a reactor vessel to produce synthesis gases ("syngas"), such as carbon monoxide, carbon dioxide, methane, and hydrogen. Thermal gasification systems are not as prevalent as anaerobic digestion processes and were not evaluated by ARB and OEHHA staff.

farm-based project, and at least 25 POTWs (sewage treatment facilities). The United States Environmental Protection Agency's (U.S. EPA) Landfill Methane Outreach Program (LMOP) maintains a data base of landfill methane projects that provides further information on the 33 projects. The LMOP database indicates that the 33 projects that upgrade landfill biogas to pipeline quality ("high BTU") biomethane are located in 13 states. (U.S. EPA, 2013) Most of these projects began operation within the last ten years, but a couple of projects (Fresh Kills, NY; Rumpke, OH) have been in operation since the 1980s.

In California, there is currently one project where biomethane is injected into the common-carrier natural gas pipeline. The project is located at the San Diego Point Loma wastewater treatment plant. The project upgrades biogas (that was previously flared) to pipeline quality gas that meets Rule 30[5] biomethane specifications. The gas is injected into the San Diego Gas and Electric pipeline for distribution to local customers. In addition, Pacific Gas and Electric (PG&E) worked with Bioenergy Solutions in 2006-2009 to develop a biomethane injection project at Vintage Dairy, located near Fresno. PG&E received delivery of biomethane from the project from October 2008 through December 2009. However, according to PG&E, the volumes of gas being delivered were not substantial enough to sustain the project as the economy deteriorated in 2009. The project subsequently ceased operations. Regarding landfill-derived biogas in California, there are a numerous landfill gas-to-energy projects, such as those that burn landfill gas in a boiler to power a steam turbine and generate electricity. However, none of these projects currently inject biomethane into the natural gas common carrier pipeline system due to utility tariffs prohibiting this.

In California, the primary potential sources of biogas are landfills, POTWs, and diaries/animal waste operations. Of these, landfills offer the greatest potential for generation. (NREL, 2010, http://www.nrel.gov/docs/fy10osti/48057.pdf)

B. AB 1900

AB 1900, authored by Assemblyman Mike Gatto and chaptered into law on September 27, 2012 (Chapter 602, Statutes of 2012), establishes a process to promote and facilitate the injection and use of cleaned biogas (biomethane) in common carrier pipelines. Under AB 1900, the CPUC is tasked with multiple duties including adopting standards for constituents in biogas to protect human health and pipeline integrity and safety. In adopting these standards, the CPUC is to give due deference to recommendations from ARB and OEHHA regarding health protective concentrations and monitoring, testing, reporting, and recordkeeping requirements for constituents of concern in each source of biogas. A copy of AB 1900 is provided in Appendix A to this report.

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[5] Rule 30 created by the Sothern California Gas Company (SoCalGas) is a guideline meant to demonstrate how biomethane suppliers can meet their obligation to provide merchantable gas to SoCalGas. (SoCalGas, 2013)

As noted, in support of the CPUC standards development efforts, OEHHA and ARB are to develop recommended health protective standards and identify reasonable and prudent monitoring, testing, reporting, and recordkeeping requirements for each source of biogas. More specifically, AB 1900 requires the following actions be taken and completed on or before May 15, 2013:

OEHHA Actions

- In consultation with ARB, the Department of Toxic Substances Control (DTSC), the Department of Resources Recycling and Recovery (CalRecycle), and the California Environmental Protection Agency (Cal-EPA), compile a list of constituents of concern that could pose risks to human health and that are found in biogas, as defined, at concentrations that significantly exceed the concentrations of those constituents in natural gas.
- Determine the health protective levels for the list of constituents of concern.

ARB Actions

- Identify realistic exposure scenarios and in consultation with OEHHA, identify any health risks associated with the exposure scenarios for the constituents of concern identified.
- Determine the appropriate concentrations for constituents of concern.
- Identify reasonable and prudent monitoring, testing, reporting, and recordkeeping requirements, separately for each source of biogas, that are sufficient to ensure compliance with the health protective standards.

In addition, AB 1900 requires that ARB and OEHHA update the constituents of concern and health protective levels, exposure scenarios, and the health risks associated with the exposure scenarios, at least every five years.

AB 1900 provides that actions taken pursuant to the described requirements do not constitute regulations and are exempt from the Administrative Procedure Act.

C. Development Process and Scope of Recommendations

There are many types of organic materials that can be anaerobically digested to produce biogas. For this evaluation and identification of the constituents of concern in biogas, ARB and OEHHA staff focused on the larger sources of biogas – landfills, dairies, and POTWs. These are the sources with the greatest potential to economically inject into the natural gas pipeline in California and for which data is available regarding the constituents present in the biogas. ARB and OEHHA staff will address other sources of biogas (i.e., crop residuals, food waste, woody biomass, energy crops) in future updates as additional data becomes available regarding constituents present in these sources of biogas.

Staff analyzed the constituents in both raw (untreated) biogas and upgraded biogas (or biomethane) to determine what compounds may be present, the concentration of these compounds, and the potential for control technologies to reduce or remove these

compounds. The analysis focused on potential exposure to compounds in uncombusted biogas/biomethane and not on combustion products produced when the gas is burned. This is because staff expects most of the constituents of concern to be destroyed during combustion, and there is limited information available on potential combustion products. In Table I-1 below, we provide a brief overview of the tasks undertaken to develop the recommendations to the CPUC.

Table I-1: Overview of ARB and OEHHA Tasks

Task	Actions
Identify List of Constituents and Measured Concentrations	ARB and OEHHA staff reviewed available data on the composition of natural gas and biogas/biomethane and compiled a list of constituent data (chemical name and measured concentration). For each data set, the maximum concentration measured for each constituent was identified. Data was collected for natural gas, landfill, dairy, and POTWs. Approximately 270 chemicals and chemical groups were identified in biogas.
Develop Health Values for Constituents	OEHHA staff used four main sources of toxicity data and risk values for risk evaluation: OEHHA Reference Exposure Levels (RELs) for non-carcinogens, and Cancer Slope Factors for carcinogens, U.S. EPA Reference Concentrations and Cancer Slope Factors, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), and worker protection values from Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), or American Conference of Industrial Hygienists (ACGIH). Risk-screening values were identified for 180 constituents, defined surrogate screening values for 25 chemicals and groups.
Develop Realistic Exposure Scenarios	ARB staff developed 4 scenarios: 2 residential and 2 worker exposure scenarios. The residential scenarios consist of a household leak and the pre-ignition phase of stove use. The worker scenarios consist of a biogas worksite leak and utility worker that is exposed to an indoor leak on a service call.
Model Exposure Scenarios	ARB staff developed assumptions for each scenario to determine appropriate exposure adjustment ratios. A simple box model with a given air exchange rate was used to calculated the dilution of the gas in the household or worksite.
Conduct Health Risk Screen (HRS)	Using the model derived developed exposure adjustment factors, OEHHA staff conducted a HRS using standard calculations to find the cancer, chronic, and acute risk from each constituent.
Identify Constituents of Concern Based on HRS	Constituents were identified as a constituent of concern if, based on the HRS, it was determined that the constituent: 1) had a potential cancer risk greater than one in a million for a residential scenario or 30 in million for a worker scenario or 2) had a potential acute or chronic hazard quotient greater than 0.01 for a residential scenario and 0.3 for a worker scenario. If a constituent was observed in both natural gas and biogas and the concentration in natural gas was significantly higher than that in biogas, the constituent was removed from the list.
Determine Health Protective Levels	Health protective levels were identified by OEHHA staff for each constituent of concern and were set at the concentrations that would result in a potential cancer risk of 1 in a million for the resident or 30 in a million for the worker for the cancer risk. OEHHA staff also calculated the health protective levels for the acute and chronic constituents using 0.1 and 3.0 as limits for the hazard quotient limit for the resident and worker, respectively.
Identify Risk Management Action Concentrations for Constituents of Concern	ARB staff established recommended risk management concentrations for constituents of concern similar with the framework outlined in ARB's Risk Management Guidelines for New and Modified Sources of Toxic Air Pollutants. (ARB,1993) wherein trigger levels and lower and upper action levels for potential cancer risk and total non-cancer hazard indexes are identified and evaluated to ensure that health protective levels are adequately maintained.
Identify Monitoring, Reporting and Recordkeeping Requirements	ARB staff recommended monitoring (testing) procedures based on the risk management guidelines above. Initial pre-injection testing would need to be performed on biomethane prior to its introduction into the pipeline to demonstrate that it is pipeline quality. After injection, periodic testing would be required, with the testing frequency based on the concentrations of the constituents of concern. ARB staff also recommended recordkeeping and reporting requirements. These include reporting startup testing results for new projects, a three year records retention requirement for test data of constituents of concern, and an annual report to the CPUC on test results.

ARB and OEHHA staff worked together to fulfill the AB 1900 requirements and develop recommendations to inform the CPUC rulemaking process. As noted earlier, existing sources of information were relied upon to develop the underlying technical foundation for the recommendations. To provide relevant information to interested stakeholders, a website and list serve were created. In December 2012, ARB and OEHHA staff posted an update on the website, inviting interested parties to provide comments or information that would assist with completion of the tasks under AB 1900. ARB and OEHHA staff met or consulted with several interested stakeholders including public utility representatives, representatives of the biogas industry, analytical equipment providers, Gas Technology Institute staff, U.S. EPA staff, landfill operators, biogas treatment manufacturers, and existing operators of biomethane production facilities where the biomethane is being injected into a common carrier pipeline. ARB and OEHHA staff also consulted with other State agencies including the California Energy Commission (CEC), DTSC, CalRecycle, and Cal-EPA. In addition, ARB and OEHHA staff participated in two public workshops hosted by the CPUC in support of the CPUC rulemaking activities. At each workshop, ARB and OEHHA staff provided updates on activities and presented preliminary information on the work conducted to date by ARB and OEHHA staff such as the list of constituents of concern, exposure scenarios, modeling results and monitoring, recordkeeping and reporting. One workshop was held in San Francisco on March 19, 2013 and the second was held in Sacramento on May 2, 2013. Informal discussion sessions open to all parties were held on April 10th and April 25th in Sacramento and notice of the discussion sessions were sent to the AB 1900 list serve.

References

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(U.S. EPA, 2013) "Current Landfill Methane Outreach Program (LMOP) List of Operational Projects," http://www.epa.gov/lmop/projects-candidates/operational.html

II. IDENTIFICATION OF BIOGAS CONSTITUENTS

Per AB 1900, OEHHA was tasked with developing a list of constituents of concern that could pose risks to human health and that are found in biogas[6] at concentrations exceeding those found in natural gas, and to define health protective levels for these constituents. In this chapter, we summarize the primary sources of data used to identify constituents in biogas and provide the list of the constituents identified.

A. Data Sources for Constituents in Biogas

OEHHA and ARB staff compiled a list of constituents that have been identified in biogas derived mainly from landfills, dairies, and POTWs. A search was completed to identify studies published in the literature and reports from government agencies or industry groups. Staff also consulted with representatives from the Gas Technology Institute (GTI), biogas-related businesses, and California POTWs and landfills to obtain additional biogas and natural gas constituent data. Briefly summarized below are the sources of information used to identify biogas constituents:

- Five recent studies completed by GTI that identify and quantitate the constituents present in biogas derived from municipal landfills, dairies, POTWs, and natural gas in the United States and California. (GTI 2009 a, b, c, d; and GTI, 2012)[7]

- Biogas sampling data and other information for municipal landfills and POTWs in Southern California. (LACSD, 2012; SCAQMD, 2012; JWPCP, 2011)

- Reports on municipal landfill biogas constituents published by the U.S. EPA. (U. S. EPA, 2008) and the Environment Agency of the United Kingdom (UKEA, 2002)

- Emission testing results of a natural gas sample was obtained from *Air Liquide* Advanced Technologies U.S. LLC. (*Air Liquide,* 2012) A volatile fatty acid analysis of two dairy farm biomethane samples was also obtained from Pacific Gas & Electric Company. (PG&E, 2008)

- Several literature reports on specific constituents in biogases from municipal wastes and sewage sludge digestion. (Glindemann, et al. 2005; Grumping, et al. 1999; Hensel, et al. 2000; Hirner, et al. 1994; Rasi, 2009)

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[6] In this chapter we use the term biogas generally to refer to both raw biogas and upgraded biogas (i.e., biomethane).

[7] According to GTI (GTI, 2013), Tables 23-30 were mislabeled in the GTI report titled "Pipeline Quality Biogas: Guidance Document for Dairy Waste, Wastewater Treatment Sludge and Landfill Conversion" DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736, December 31, 2009. The units should be reported as ppb, corresponding to the data in the appendix.

Of the available data sources, the GTI reports and additional Southern California landfill and POTW data provided the most recent quantitative constituent data for landfill, dairy, POTW biogas, and natural gas, and were chosen as the primary source of constituent concentration data for the biogas evaluation. (We will refer to these studies together as the "GTI dataset.") The GTI dataset was developed using defined and consistent analytical methodologies. The U.S. EPA and UKEA landfill gas reports and the academic papers on biogas constituents were used in a complementary way, mainly to identify additional constituents that were not analyzed or detected in the GTI dataset. The U.S. EPA and UKEA reports were particularly useful in identifying a long list of trace constituents, many of which are likely to be formed from the decomposition of biological materials present in municipal wastes. Although the number of these chemicals is large, their total content in raw landfill gas appears to be less than 0.1% (measured as non-methane organic carbon). The academic biogas studies were useful in helping to confirm the presence of volatile metallic compounds in biogas (e.g., methylated arsenic and antimony).

Although the GTI dataset was used to carry out the bulk of the risk evaluation, concentrations from the U.S. EPA landfill report (or "AP-42 update") were used in a few instances where the primary dataset did not provide adequate coverage. In particular, we used the AP-42 update to help screen out several groups of toxicologically similar chemicals (see Section IV for details), and we used the GTI dataset together with AP-42 and *Air Liquide* data on benzene in comparing concentrations in biogas to natural gas (See Section IV).[8]

The decision to use the AP-42 concentration data in only a supplementary fashion was based upon the fact that its samples were collected mainly between 1996 and 2000. Staff judged that the AP-42 data was likely to be representative of current concentrations with regard to constituents that arise mainly from biological materials (e.g., green wastes, woody wastes, and food wastes), and would also be somewhat representative of BTEX compounds (benzene, toluene, ethylbenzene, xylene) since some Class II landfills accept petroleum-contaminated soils. However, the AP-42 data is expected to be less representative of California landfills for chemicals that have been increasingly regulated over the last two decades, for example many of the chlorinated solvents. An added reason for not using the AP-42 update as a general reference for concentration data was its variable data quality, with sample sizes ranging from 78 to 1 (landfills sampled) for any particular chemical listed.

B.   Constituents in Biogas

Through this process we identified more than 300 individual constituents likely to be present in landfill, dairy, and POTW biogas, representing a broad range of chemical groups. The biogas constituents and chemical groups identified through this review process were compiled into 3 lists which are provided in Appendix B, Tables B-1

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[8] In our group risk evaluation we also used supplemental concentration data from UKEA 2002 and PG&E 2008 (See Section IV).

through B-3. Table B-1 contains constituents identified from the GTI dataset, B-2 contains a list of constituents that were found in landfill gas samples reported in the AP-42 update and the UKEA landfill report. Table B-3 contains chemicals reported in academic studies. Risk screening values were developed for as many of the chemicals on these three lists as was possible (these constituents and their screening values are listed in Chapter IV, Tables IV-1 and IV-2). In some cases, specific chemicals in the three tables of Appendix B were grouped together for the risk screening process (see Table IV-3). Further details of the risk evaluation (including the evaluation of chemical groups) are described in Section IV.

Concentrations of constituents in biogas, biomethane and natural gas from the GTI datasets are provided in Table B-4 of Appendix B. This is an Excel workbook containing individual worksheets for each set of gas data used in the health risk screening of the individual constituents. Specifically, there are 13 datasets: 3 for natural gas, 4 for landfill, 4 for POTW and 2 for dairy. Each worksheet contains data for individual constituent maximum concentrations from the specified data source and is separated by gas type (e.g. natural gas, raw dairy, clean dairy, etc.). Also included in the workbook are 3 additional worksheets summarizing the maximum concentrations for each constituent in natural gas, raw biogas, and cleaned (upgraded) biomethane.

It should be noted, that not all the constituents that have been identified in this evaluation process and listed in Appendix B could be quantitatively screened in the risk evaluation. In some cases, this was due to a lack of toxicity information (see Chapter IV Table IV-4 for a list of chemicals without criteria) and in some cases it was due to a lack of representative concentration data (in particular, this was a problem with respect to biogas combustion products, some of which we tentatively identify in Table B-3). In order to address these and other unavoidable uncertainties in our risk evaluation, we will continue to work with the CPUC in the rule-making process, and will also refine our risk analysis as more information becomes available for an update of these recommendations (which, depending upon circumstances could occur earlier than the 5-year statutory deadline for review).

Biological agents (biologicals) can also be found in both biogas and natural gas. For example, a recent report by GTI found levels of biologicals in landfill biomethane to be similar to those in natural gas. (GTI, 2012)

Based on a staff review of the available literature, there does not appear to be a significant health risk associated with biologicals in biomethane. A report prepared for the European Parliament examined the available literature and did not find any recorded examples of health problems associated with biological agents in biomethane that was injected into the natural gas pipeline. (Marcogaz, 2006) One of the studies they examined, conducted by the Swedish Institute for Veterinary Medicine (SIVM, 2005), measured biogas from four biogas plants, two sewage treatment plants and two co-digestion plants, before and after treatment. The results were compared with similar analyses of natural gas and air. The results showed very low levels of micro-organisms in biogas, similar in amount and type to natural gas. The amount of micro-organisms was found to be much lower than the levels in ambient air. Similar conclusions were

reached in a research paper that examined potential hazards in biogas. The authors concluded, based on the currently available data, that no microbial risk could be identified from the biogas injection into a gas pipeline network. (Naja et al., 2011)

In addition, the Pacific Gas and Electric Company conducted an analysis to address concerns associated with the 2008 introduction of dairy-based biomethane in the natural gas pipeline. The analysis of microbiological pathogens looked at concentrations of cells or cysts in the gas, and compared the results to minimum infectious dose levels. Based on their analysis, it was concluded that the levels found did not represent a risk of infection through exposure. (PG&E, undated)

Based on the available data, we concluded that biologicals in biomethane do not present additional health risks and did not conduct further analyses. However, we will continue to monitor for any new data and revisit biologicals in future AB 1900 updates if warranted.

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III. EXPOSURE SCENARIOS

In this chapter, we provide a description of the exposure scenarios developed and the approach used to assess the potential health risks associated with exposures to the constituents in biogas/biomethane.

A. Overview of Approach

ARB and OEHHA staff conducted a health risk assessment to assist in determining the constituents of concern present in biogas/biomethane from various sources (landfills, dairies, and POTWs). The health risk assessment consisted of two parts. First realistic exposure scenarios are defined for both residential and worker exposures. The exposure scenarios use mathematical models to estimate the concentrations of the chemical constituents to which a resident or worker could be exposed. Because the gas concentration decreases as the gas expands and is mixed with room air when it is emitted into a residence or a warehouse, these models provide exposure adjustment factors that are much less than one.

Second, established OEHHA guidelines and recommended health values are used to estimate the potential cancer risks and non-cancer health impacts (acute and chronic) for each constituent in the biogas/biomethane. The potential cancer risk is the potential for the chemical to cause cancer and is expressed as excess potential cancers in a population of one million, for a specified exposure duration (for example, 30 years for a resident and 25 years for a worker). For the chronic and acute impacts, we determined a hazard quotient (HQ), which is the ratio of the exposure concentration of the individual compound divided by its reference exposure level (REL). Only the trace components were evaluated in the assessment. The major components of the gas (methane, carbon dioxide, nitrogen, and oxygen) were not addressed and the rationale for this is discussed in Chapter IV.

In this chapter, we provide a description of the exposure scenarios and the development of exposure adjustment factors for each scenario. In Chapter IV, the exposure adjustment factors will be applied to the component concentrations and used to estimate cancer and non-cancer risks.

AB 1900 requires that we "identify realistic exposure scenarios" in evaluating the health risk. In our evaluation, we investigated four different exposure scenarios: two residential scenarios, two worker scenarios – one a biomethane production worker scenario and one utility worker scenario.[9] A summary of the scenarios evaluated is provided in Table III-1.

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[9] On April 9, 2013 Southern California Gas Company representatives provided five additional utility worker scenarios, these scenarios are addressed qualitatively in this report.

Table III-1: Exposure Scenarios Evaluated

Scenario		Gas Streams Evaluated	Exposure Duration
Residential	Leak in home	Natural gas, 100% biogas from 3 different sources: landfill, dairy, and POTWs	24 hours a day for one year
Residential	Stovetop cooking (kitchen)		Two 2 hour cook periods per day for 30 years (24 hours per day exposure with 4 hours in kitchen and 20 hours in remainder of house)
Biomethane Production Worker	Biogas processing facility		8 hours per day, 261 days per year, working for 25 years
Utility Worker	Service call		8 hours per day, 261 days per year, working for 25 years

For all the scenarios, we modeled our approach using U.S. EPA –Indoor Air Modeling guidelines for the box model mass balance equations. (U.S. EPA, 1991) And, in each case, we applied the same models, scenarios and assumptions for evaluating each gas type, including natural gas. In our evaluation, we also relied on conservative concentration assumptions. For example, in each scenario, we assumed that there would be 100% concentration of the biogas, biomethane or natural gas in the delivery pipe and when multiple sources were included in a data set for a particular source, we used the highest measured concentrations for each compound.

B. Residential Exposure Scenarios

For residential exposures, it was assumed that an individual could potentially be exposed to biogas/biomethane indoors from an undetected leak or during cooking with a gas range.[10] While there are other appliances that are typically gas fed – (i.e., furnace or hot water heater), – these appliances are typically vented to the outside air and are not expected to be a significant source of residential exposures to biogas/biomethane. The two exposure scenarios developed to represent realistic residential indoor exposures to biogas/biomethane emissions are presented below.

Residential Leak Exposure Scenario

In the residential leak scenario, the indoor exposure concentrations were modeled for residential exposure to unburned gas constituents due to a small constant gas leak. In this scenario, the indoor concentration was modeled based on a general mass balance

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[10] About 55% of California homes have gas stovetops. (CEC, 2005)

equation (U.S. EPA, 1991) where the steady state concentration is estimated as a function of the indoor source generation rate, the residential air exchange rate and the indoor volume. Exposure adjustment factors were estimated for a maximum 1-hour period (1 hr Max) and annual average concentrations[11] using the following equation:

$$Ci\left(\frac{\mu g}{m^3}\right) = Co\left(\frac{\mu g}{m^3}\right) + \frac{S\left(\frac{ug}{hour}\right)}{v\left(\frac{l}{hour}\right)kV(m^3)}$$

Eq. R1

Where

Ci = indoor source concentration (mass/volume) for each individual constituent
Co = outdoor source concentration (mass/volume)
v = air exchange rate (l/time)
S = indoor source generation rate (mass/time)
kV = effective indoor volume where k is a dimensionless fraction (k=1)
LR = gas leak rate (volume/time)
DF = modeled exposure adjustment factor (unitless)
$C_{constituent}$ = the measured concentration of the individual constituent

Only the concentration due to indoor source generation (gas stovetop or leak) was included in the model and the outside source concentration, Co, was set to zero in this scenario. To determine the concentration of each individual constituent in the gas, the indoor source generation rate, S, is calculated as the measured concentration of the individual constituent in the gas multiplied by the gas leak rate as follows:

$$S\left(\frac{ug}{hour}\right) = Cconstiuent\left(\frac{\mu g}{m^3}\right) X\ LR\left(\frac{m^3}{hour}\right)$$

Eq. R2

And the indoor concentration for each individual constituent becomes

$$Ci\left(\frac{\mu g}{m^3}\right) = Cconstiuent\left(\frac{\mu g}{m^3}\right) X \frac{LR\left(\frac{m^3}{hour}\right)}{v\left(\frac{l}{hour}\right)kV(m^3)}$$

Eq. R3

Using the following formula, an exposure adjustment factor, DF was developed.

$$Ci\left(\frac{\mu g}{m^3}\right) = Cconstiuent\left(\frac{\mu g}{m^3}\right) x\ DF$$

Eq. R4

Where the unit less exposure adjustment factor, is defined as follows:

$$DF = \frac{LR\left(\frac{m^3}{hour}\right)}{v\left(\frac{1}{hour}\right)kV(m^3)}$$

Eq. R5

For the residential leak exposure scenario, exposure adjustment factors for both an annual average and maximum 1-hour were calculated. In Chapter IV, the annual average exposure adjustment factor was used to calculate potential cancer and chronic

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[11] For both the residential leak scenario and the residential stovetop scenario, the annual average exposure and calculated adjustment factor, is the same as the average 24 hour exposure since it was assumed that each day in the year had the same exposure.

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non-cancer exposures and the 1-hour maximum exposure adjustment factor was used to calculate acute exposure.

The annual average was based on a 4-hour exposure to a higher concentration within the kitchen where the leak was located and a 20-hour exposure to the lower concentration within the total volume of the residence for each day.

$$DF\ (annual\ average) = \frac{4\ hours\ x\ DF(room) + 20\ hours\ x\ DF(residence)}{24\ hours}$$ Eq. R6

The maximum 1-hour exposure adjustment factor was based on the highest exposure adjustment factor, calculated using the volume of the room.

For the residual leak scenario, mid-range inputs were selected for residence size, room size, and air exchange rate and are shown in Table III-2.

Table III-2: Inputs and Calculated Exposure Adjustment Factors for the Residential Leak Exposure Scenario

Input	Value	Comment
Residence Volume	396.43 m^3	1750 sq ft residence by 8 ft ceiling height
Room Volume	44.4 m^3	Room size 14 ft x 14 ft X 8 ft ceiling height or 1 room out of 9 rooms in the residence
Air Exchange Rate (ACH)	0.53 /hr	(U.S.EPA, 2002)
Leak Rate	0.003 m^3/hr	0.75% of 122,000 ft^3 per year (0.4 m^3/hr) consumption (1 million BTUs per year)
1-hour Maximum Exposure Adjustment Factor	1.275E-04	1-Hour maximum for acute evaluation
Annual Average Exposure Adjustment Factor	4.258E-05	Annual average for cancer and chronic evaluation

Since there was very limited data available on the possible ranges of residential leak rates, ARB staff used published values of gas losses in the natural gas delivery system to estimate leak rates. The leak rate[12] (0.003 m^3/hr) was estimated based on a system wide gas loss rate of 0.75%[13] of consumption applied to an estimated 1 million BTU per year consumption rate for a California residential consumer. While the 0.75% loss

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[12] The ARB estimated leak rate of 0.003 m^3/hour corresponds very well to the leak rate (0.0047 m^3/hr) used in a study of allowable concentrations of renewable gas trace constituents done by IRIS Environmental for Southern California Gas Company. (IRIS, 2013)

[13] 0.75 percent leakage rate estimate is a mid-range value between published loss rates of 0.1% (Wennberg, 2012) and 1.4% (EIA, 2012)

value also includes losses within the natural gas system prior to the consumer meter, staff felt that without more precise data, this estimate was a realistic value for a residential leak rate. Since residences can contain a large number of valves and fittings, it is possible that gas losses may be on the same magnitude as the system wide losses. A recent report on the sources of methane in the Los Angeles atmosphere provides an estimate somewhat similar to that used by ARB staff: approximately 2% loss occurring post-consumer metering (i.e. on the residential side of the gas meter) in the Los Angeles Basin. (Wennberg, 2012)

According to PG&E, the highest residential leak rate will be approximately 2.5 cubic feet per hour (0.07 m^3/hr) as measured on the gas meter. (PG&E, 2013)   If at this rate, the gas service worker cannot identify the leak source, then the gas service to the home must be shut off.   As listed in Table III-3, a leak rate of 0.07 m^3/hr would correspond to a maximum 1-hour exposure adjustment factor of 2.97E-03, about 18 times higher than the residential leak rate 1-hour maximum exposure adjustment factor presented in Table III-2.

As a further comparison to the calculated exposure adjustment factors provided in Table III-2, natural gas is federally required (CFR 192.625) to be odorized so that is detectable to a person with a normal sense of smell at a concentration of 1/5th of the lower explosive limit (LEL). For methane, the LEL is approximately 5% methane to air, by volume. Therefore, odorized methane should be detectable at concentration levels above 1%. A concentration of 1% methane to air, by volume, corresponds to a exposure adjustment factor of 0.01, which is about 60 times higher than the maximum 1-hour exposure adjustment factor provided in Table III-2. In studies done by one utility, the actual odor threshold for a resident may be as low as about 40 parts per million by volume (ppmv) (SCG, 2013). At 40 ppmv, the exposure adjustment factor would be about 4.00E-05, which is in the same range as the calculated residential exposure adjustment factor ARB staff is using.

Table III-3: Comparison of Residential Concentration Exposure Adjustment Factors to Estimated Concentrations for Gas Leak Shut Off Criteria and Odor Thresholds

Concentration or Leak Rate Assumption	Exposure Adjustment Factors
Residential leak rate scenario (leak rate at 0.003 m^3/hr)	1.275E-04 (1-hr maximum)* 4.258E-05 (annual average)
PG&E Maximum leak rate of 0.07 m^3/hr	2.97E-03 (1-hr maximum)* 7.73E-4 (annual average)
Odorized Concentration at 1/5th methane lower explosive limit (CFR 192.625)	1.00E-02**
Odor threshold concentration at 40 ppmv of gas in air (0.004% gas in air). (SCG, 2013)	4.00E-05**

*We assumed that the concentration in the kitchen is higher than the concentration in the remainder of the home. Therefore, the higher 1-hour maximum adjustment factor reflects the higher exposure concentration while the resident is in the kitchen.
**1-hour maximum and annual average are the same since we assumed that the exposure concentrations were the same in all parts of the home.

<u>Stovetop Cooking Exposure Scenario</u>

For the stovetop scenario, we developed a model to represent typical cooking on a kitchen gas stovetop. Exposures to unburned gas constituents would occur during the pre-ignition period, in this case we assumed 5 seconds after the stove is turned on and before the automatic pilot ignites the flame. [14] We assumed there would be two cooking activities per day, and that a volume of gas is emitted only during the pre-ignition phase with the concentration decaying over time due to mixing with air in the kitchen and outside air exchange. The modeling approach for this scenario is similar to the methodology used by the French Agency for Health and Safety in the Environment and Workplace. (Afsset, 2008) The key model inputs are provided in Table III-4.

Table III-4: Inputs for the Residential Kitchen Scenario

Kitchen Scenario Inputs	Values
Daily Time Spent in Kitchen	4 hours/day
Daily Time Spent in the Remainder of the House	20 hours/day
Pre-Ignition Time	5 seconds[*]/ignition event
Hours Between Cooking Periods	7 hours[*]/day
Emission Rate	0.5 m^3/hour per burner[*]
Number of Burners Used	3
Air Exchange Rate (ACH)	0.54/hr
Kitchen Room Volume	44.4 m^3
Residence Volume	396.43 m^3

* (Afsset, 2008)

The following equation was used to determine the decay rate of the biogas in the kitchen and in the rest of the house. (U.S. EPA 1991)

$$C_f = C_0 + (C_i - C_0) \times e^{-v(t-t_0)}$$

Eq. S1

Where:

Cf = concentration at time t

C_0 = constant outdoor concentration. Only the concentration due to indoor source generation was included in the model and the outside source concentration, Co, was set to zero in this scenario

C_i = initial indoor concentration

v = air exchange rate

t = time (hours)

t_0 = initial time (hours)

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[14] In all scenarios, only the unburned gas constituents and emission rates were used. The potential combustion emission rates and combustion products were not included in the evaluation since there was limited data available on the combustion products of the trace constituents in biogas/biomethane. The major combustion components of both treated biomethane and natural gas, such as nitrogen dioxide (NO$_2$), carbon monoxide (CO), is likely to be similar.

In Figure III-1, we show the two concentration peaks from cooking and concentration decay after the pre-ignition phase over a 24-hour period.

Figure III-1: Concentration Decay in 24-hour Period
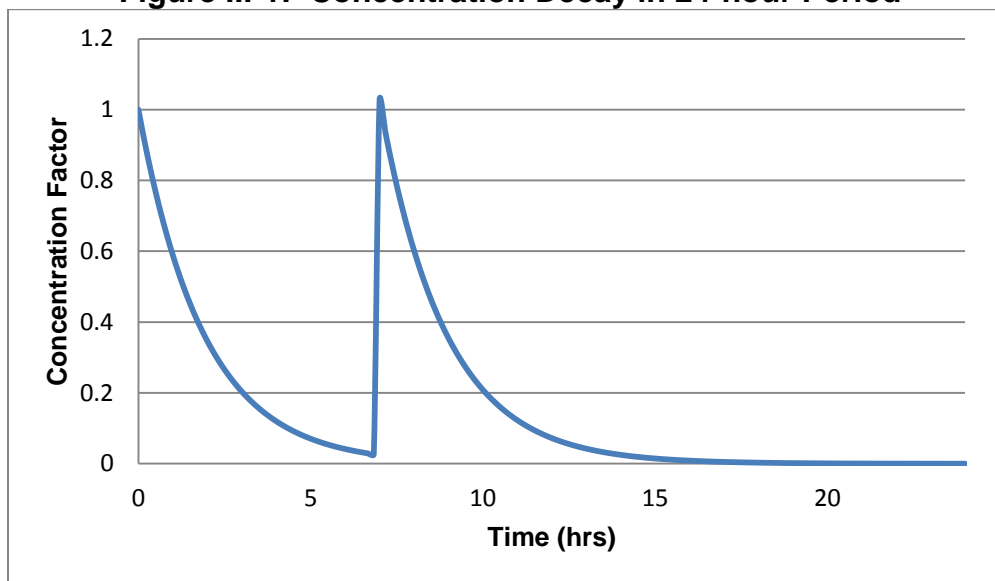
It was assumed that a resident would use the stovetop two times a day with 7-hours between use. The small remaining concentration from the first use is added to the second use. To determine the daily average emission factor to represent the 4 hours spent in the kitchen and 20 hours in the remainder of the house, equation S1 was integrated to find the area under the curve. The area under the curve (hours 1-2 and 7-8 spent in the kitchen) was divided by the time spent in the kitchen (4 hours) and the remaining area under the curve (hours 3-6 and 9-24 spent in the remainder of the house) was divided by the time spent in the remainder of the house (20 hours). Table III-5 below shows the average concentration factors (C_f/C_i) calculated for the stovetop scenario. In the potential cancer health risk evaluation in Chapter IV, we assumed that the resident would be exposed to the stovetop gas emissions for a maximum of 30 years.

Table III-5: Concentration Factors for Time Spent in the Kitchen and in the Remainder of the Residence

Exposure Location	Concentration Factor (EF)
Average Kitchen Concentration Factor (4 Hours)	EF_k=0.629
Average Residence Concentration Factor (20 Hours)	EF_h=0.081
Maximum Concentration Factor (at beginning of second cooking activity) (1 Hour)	EF_{max}=1.02

ARB staff used the average concentration factors to determine the final exposure adjustment factor for cancer risk and the chronic and acute hazard index. The equations for the cancer risk and chronic hazard index exposure adjustment factors are listed below in equations S2 - S4.

$$D_k = \frac{EF_k \times T_k \times ER \times T_i}{V_k}$$ Eq. S2

Where

D_k = exposure adjustment factor in the kitchen
EF_k = concentration factor in the kitchen
T_k = time spent in kitchen (hours)
ER = emission rate of stovetop
T_i = time of pre-ignition phase
V_k = volume of the kitchen

$$D_h = \frac{EF_H \times T_h \times ER \times T_i}{V_h}$$ Eq. S3

Where

D_h = exposure adjustment factor in the residence
EF_H = concentration factor in the residence
T_h = time spent in remainder of house (hours)
ER = emission rate of stovetop
T_i = time of pre-ignition phase
V_h = volume of the residence

$$D_T = \frac{D_k + D_h}{24 \; hours}$$ Eq. S4

Where

D_T = annual average exposure adjustment factor

For the acute hazard index, ARB staff used the maximum 1-hour concentration factor which occurs at the start of the second use of the stovetop. The equation to find the 1-hour maximum exposure adjustment factor is listed in equation S5 as follows:

$$D_A = \frac{EF_{max} \times ER \times T_i}{V_k}$$ Eq. S5

Where

D_A = exposure adjustment factor in the kitchen for the 1-hour maximum acute analysis
EF_{max} = maximum concentration factor in the kitchen

ER = emission rate of stovetop
T_i = time of pre-ignition phase
V_k = Volume of the kitchen

The exposure adjustment factors based on these equations are listed in Table III-6. As discussed in Chapter IV, OEHHA staff used the exposure adjustment factors and the biogas concentrations from the GTI datasets to calculate a modeled concentration factor for the stovetop scenario.

Table III-6: Exposure Adjustment Factor for the Kitchen Scenario

Kitchen Scenario Exposure Adjustment Factor	Value
1-Hour Maximum (Acute Exposure Adjustment Factor)	4.81E-05
Annual Average (Cancer and Chronic Exposure Adjustment Factors)	5.27E-06

C. Utility/Biogas Production Worker Scenarios

For workers, two scenarios were evaluated; one for a biogas production worker and one for a utility worker. These are described below. In addition, we briefly describe additional outdoor utility worker scenarios that were identified by Southern California Gas staff. While these scenarios are discussed here they were not quantitatively analyzed due to the fact that the resultant exposures would be less than the two indoor scenarios analyzed and described below.

Biomethane Production Facility Worker Leak Exposure Scenario

In the biomethane production facility worker leak scenario (biomethane worker scenario), the indoor (warehouse) exposure concentrations were determined similar to the residential leak scenario. In the biomethane worker scenario, the worker is exposed to unburned gas constituents due to a constant gas leak in the processing equipment. In this scenario, the indoor concentration was modeled based on a general mass balance, using equations R1-R5 (U.S. EPA, 1991) where the steady state concentration is estimated as a function of the indoor source generation rate (leak rate), the warehouse air exchange rate and the warehouse volume. Concentration exposure adjustment factors were calculated for a 1-hour maximum and an annual average.

In Chapter IV, the annual average exposure adjustment factor is used to calculate potential cancer risk and the chronic exposure and the 1-hour maximum exposure adjustment factor is used to calculate acute exposure. In the biomethane worker scenario, the leak concentration, the gas exposure concentration, warehouse volume and air exchange rate remain constant, therefore, the 1-hour maximum and the annual average are the same.

For the biomethane worker scenario, mid-range inputs were selected for warehouse size and air exchange rate as shown in Table III-6. Since there was no data available on the possible ranges of production facility leak rates, ARB staff estimated the leak rate as a percentage (0.1%) of a typical biogas production rate.

Table III-7: Inputs and Calculated Exposure Adjustment Factors for the Biomethane Worker Scenario

Input	Value	Comment
Warehouse volume	1417 m^3	2500 sq ft warehouse with 20 ft ceiling height
Air Exchange Rate (ACH)	1.4 /hr	(EPA, 2002)
Leak Rate	0.89 m^3/hr	0.1% of 750000 ft^3 per day biomethane production rate (SEMPRA, 2013)
Calculated Exposure Adjustment Factors (1-hour maximum)	4.46E-04	1-hour maximum for acute evaluation
Calculated Exposure Adjustment Factors (average)	4.46E-04	Average for cancer and chronic evaluation

Utility Worker Service Call Exposure Scenario

In the utility worker service call exposure scenario (utility service worker scenario), the utility employee exposure is due to service calls to customers' residences to repair an appliance (range or stove) with a gas leak. This scenario was detailed as a realistic worker scenario in a presentation from Southern California Gas Company to ARB. (SCG, 2013) For this scenario, the worker is repeatedly exposed to unburned gas during short service calls as part of the employee's typical duties. Southern California Gas Company staff provided estimates of the number of services calls per day (3 calls per day on average) and duration of service calls (13 minutes per call) to ARB staff. In this scenario, the indoor concentration was modeled based on a general mass balance, using equations R1-R5 (U.S. EPA, 1991) where the steady state concentration is estimated as a function of the indoor source generation rate (leak rate), the residential air exchange rate and the volume of the kitchen. For consistency, ARB staff used the same leak rate (0.003 m^3/hr) as was used in the residential leak rate scenario. Exposure adjustment factors were calculated for a 1-hour maximum and an annual average.

The annual average was based on 3 calls per day, each lasting 13 minutes as shown in equation U1.

$$DF\ (average) = \frac{13\ minutes\ per\ call\ x\ 3\ calls\ per\ day\ x\ DF(kitchen)}{24\ hours\ x\ 60\ minutes/hour} \quad \boxed{Eq.\ U1}$$

The 1-hour maximum exposure adjustment factor was based on the highest 1-hour exposure as shown in equation U2.

$$DF\ (1\ hour\ max) = \frac{13\ minutes\ per\ call\ x\ DF(kitchen)}{60\ minutes/hour}$$

Eq. U2

For the utility service worker scenario making service call to customers' residences, the inputs were the same as the residential leak scenario and are summarized in Table III-8.

Table III-8: Inputs and Calculated Exposure Adjustment Factors for the Utility Worker Service Call Exposure Scenario

Input	Value	Comment
Room Volume (kitchen)	44.4 m^3	Room size 14 ft x 14 ft X 8 ft ceiling height or 1 room out of 9 rooms in the residence
Air Exchange Rate (ACH)	0.53 /hr	(U.S. EPA, 2002)
Leak Rate	0.003 m^3/hr	0.75% of 122,000 ft^3 per year (0.4 m^3/hr) consumption
Calculated Exposure Adjustment Factor (1-hour maximum)	2.76E-05	Maximum 1-hour concentration used in acute risk analysis
Calculated Exposure Adjustment Factors (average)	3.45E-06	Average concentration used in cancer and chronic risk analysis

<u>Other Potential Utility Worker Scenarios</u>

In a presentation to ARB and OEHHA staff, Southern California Gas staff provided five scenarios, in addition to the utility service call worker scenario modeled above. The additional scenarios included two processing/treatment operations, two transmission operations and one leak repair operation. (SCG, 2013) In all five of these scenarios, the utility worker exposure to unburned gas would occur outdoors. In outdoor exposure, the concentration of gas dilutes more rapidly, compared to an indoor exposure in a confined space. The indoor exposure scenarios developed by staff provide higher, more conservative, exposure concentrations. Therefore, the five additional outdoor exposure scenarios provided by Southern California Gas staff were not modeled in the exposure scenario evaluation.

D. Exposure Adjustment Factors

In our evaluation, we identified four realistic exposure scenarios: two residential scenarios, one biogas worker scenario and one utility worker scenario. A mass balance box model evaluation was performed for each of the scenarios to estimate the 1-hour maximum and the average exposure adjustment factor, as listed in Table III-9.

Table III-9: Calculated Exposure Adjustment Factors for the Residential and Worker Scenarios

Scenario	Annual Average Exposure Adjustment Factors	1-Hour Maximum Acute Exposure Adjustment Factors
Residential Leak Scenario	4.26E-05	1.28E-04
Residential Stovetop Scenario	5.27E-06	4.81E-05
Biomethane Production Facility Worker Leak Exposure Scenario	4.46E-04	4.46E-04
Utility Worker Service Call Exposure Scenario	3.45E-06	2.76E-05

For the two residential scenarios, the residential leak scenario has the larger factors (i.e., exposure concentrations will be higher). Therefore, in Chapter IV, the residential potential cancer and non-cancer risks are calculated using the residential leak rate scenario exposure adjustment factors. For the two worker scenario, the biomethane production facility worker scenario had the larger factors (i.e., exposure concentrations will be higher). For workers, potential cancer and non-cancer risk exposures are calculated using the biomethane production facility worker exposure adjustment factors.

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IV. CONSTITUENTS OF CONCERN AND HEALTH PROTECTIVE LEVELS

As discussed in Chapter II, we used readily available sources of information to identify more than 300 individual constituents likely to be present in biogas from landfills, dairies, and POTWs. Some of these constituents were substances of low toxicity that were judged at the outset to be of little health concern and therefore not further considered in the evaluation. One group of low-toxicity constituents was the atmospheric components: oxygen, nitrogen, hydrogen, and carbon dioxide. The second group was the low molecular weight alkanes: methane, ethane, and propane. In addition, although not considered to be low-toxicity, manganese and chromium were eliminated from further consideration since each was detected only once in all the sampling data that we reviewed. We therefore determined that these two constituents were not reliably detected in biogas.

After this initial screening process, the number of remaining biogas constituents was still quite large. However, as noted above, they are present in relatively small quantities; for instance, considered together they typically make up less than 0.1 percent of the carbon content of landfill biogas. In addition, many of the identified constituents appear to be derivatives of natural substances present in the biological materials from which the biogases originated. Examples of these types of chemicals are the groups of fatty acid esters and alkyl dienes and terpenes that have been found at trace levels in various studies (see Appendix B, Table B-2, Groups 5, 7 and 13 for specific examples of these chemicals). While toxicity information for many of these biologically-derived constituents is sparse, most of them are expected to be of relatively low concern from the perspective of health risk. In order to quantitatively evaluate as many biogas trace constituents as possible, staff carried out risk calculations for both individual chemicals where screening criteria were available, as well as for groups of chemicals likely to be toxicologically similar, and for which a suitable screening value could be developed. This process is described in more detail below.

A. Development of Health Values

OEHHA staff compiled inhalation health risk screening criteria for as many of the identified biogas, biomethane, and natural gas constituents as possible. Table IV-1 provides criteria for constituents with previously established values. Four sources of health criteria, listed in order of preference, were judged to be of sufficient quality to be included in this table and used for the biogas risk evaluation:

- OEHHA-derived toxicity criteria—e.g., Reference Exposure Levels (RELs) for non-carcinogenic toxicants and Inhalation Slope Factors (SFs) for carcinogens (including both published and proposed criteria)

- U.S. EPA toxicity criteria, which are similar to the OEHHA criteria in both form and method of derivation. U.S. EPA develops Inhalation Reference Concentrations (RfCs) for non-carcinogens and SFs for carcinogens. (In several cases, draft U.S. EPA values are used, based upon a preliminary independent

review and concurrence with the methodology upon which the criteria have been developed).

- Agency for Toxic Substances and Disease Registry (ATSDR) Acute and Chronic Minimal Risk Levels (MRLs), also similar to the OEHHA values.

- Occupational health criteria compiled by the U.S. Occupational Safety and Health Administration (OSHA) or the National Institute for Occupational Safety and Health (NIOSH). For chronic exposures, these are either OSHA Permissible Exposure Limits (PELs) for average exposures over a typical work shift, or similarly defined NIOSH Recommended Exposure Limits (RELs). Both agencies also define Short Term Exposure Limits (STELs) to protect against acute exposures. For some chemicals, NIOSH exposure limits or those recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) are more health-protective than the OSHA standards. In these cases, OEHHA used the most health-protective value available. We then applied an additional uncertainty factor (UFH) of 30 to these limits to protect sensitive members of the general population, as occupational standards are not based solely on health criteria but include cost and technical feasibility considerations. Further, they are developed for healthy working adults. An additional conversion factor was included in developing the chronic exposure criteria. This adjustment was made to account for the fact that occupational exposure guidelines are based upon an assumption of less-than-continuous workplace exposure.

Table IV-2 contains screening criteria for chemicals lacking established inhalation values, but for which surrogate values could be defined. Surrogates were based on established values for toxicologically similar chemicals, or in other cases, by route-to-route extrapolation of oral toxicity criteria for the chemicals in question. Table IV-3 contains 15 groups of chemicals whose toxicological properties are likely to be similar. Health screening criteria for total air concentrations of chemicals in these groups were defined by choosing a surrogate chemical within each group with the most restrictive individual screening value.

Table IV-4 lists chemicals and groups for which OEHHA has not identified screening criteria in the current recommendations. We propose to further evaluate these for future document updates. The development of additional toxicity information related to the biogas constituents will involve additional literature review, use of physiologically-based pharmacokinetic (PBPK) modeling, and dose-response modeling.

Conversion Calculations

The health risk criteria for inhalation exposures in Tables IV-1 are reported in units of microgram per cubic meter ($\mu g/m^3$) for non-carcinogens, and reciprocal milligrams per kilogram-day (per mg/kg-d) for carcinogens. For criteria derived from ATSDR MRLs (reported in units of parts-per-million) or obtained from occupational exposure limits, the published values were converted as follows.

For ATSDR MRLs:

$$Risk\ Criterion\ \left(\frac{\mu g}{m^3}\right) = \frac{MRL\ (ppm)\ x\ Molecular\ Weight\ \left(\frac{g}{mol}\right)\ x\ 1000\left(\frac{l}{m^3}\right)}{24.45\left(\frac{l}{mol}\right)\ (molar\ volume, ideal\ gas\ at\ STP)^{15}}$$

To convert an OSHA PEL (or NIOSH REL or ACGIH TWA) (40-hour work week) to a biogas project screening value:

$$Risk\ Criterion\ \left(\frac{\mu g}{m^3}\right) = \frac{REL\left(\frac{mg}{m^3}\right)\ x\ 40\left(\frac{hr}{wk}\right)\ x\ 1000\left(\frac{\mu g}{mg}\right)}{168\left(\frac{hr}{wk}\right)\ x\ 30\ (UF_H)}$$

For cases where STELs were used to develop an acute screening value, the UFH of 30 was applied without the additional adjustment for exposure duration.

Table IV-2 contains several criteria derived via route-to-route extrapolation of oral reference doses (RfDs). To obtain the inhalation values, the oral criteria were multiplied by a body weight-to-breathing rate factor of 3.5 kg/m^3. The criteria presented in Table IV-3 for chemical groups are in units of parts-per-million (ppm). Estimating risk based on ppm values assumes that the toxicity of any particular member of a group is proportional to the number of molecules absorbed, as opposed to the weight absorbed. Any criteria reported in µg/m^3 in the original sources were converted to ppm (see ATSDR MRL conversion above).

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[15] SATP = Standard Ambient Temperature and Pressure.

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC ($\mu g/m^3$)	Source Acute	Chronic NC ($\mu g/m^3$)	Source Chronic	SFi (kg-d/mg)	Source SFi
Acetaldehyde	75-07-0	4.7E+02	OEHHA REL	1.4E+02	OEHHA REL	1.0E-02	OEHHA SFi
Acetone	67-64-1	6.2E+04	ATSDR MRL	3.4E+04	ATSDR MRL		
Acetonitrile	75-05-8	3.5E+03	OSHA PEL	6.0E+01	USEPA RfC		
Acrolein	107-02-8	2.5E+00	OEHHA REL	3.5E-01	OEHHA REL		
Acrylonitrile	107-13-1	7.2E+02	OSHA PEL	5.0E+00	OEHHA REL	1.0E+00	OEHHA SFi
Allyl Chloride	107-05-1	2.0E+02	OSHA PEL	1.0E+00	USEPA RfC	2.1E-02	OEHHA SFi
Ammonia	7664-41-7	3.2E+03	OEHHA REL	2.0E+02	OEHHA REL		
Aniline	62-53-3			1.0E+00	USEPA RfC	5.7E-03	OEHHA SFi
Arsenic (inorganic and arsine)	7440-38-2	2.0E-01	OEHHA REL	1.5E-02	OEHHA REL	1.2E+01	OEHHA SFi
Benzene	71-43-2	1.3E+03	OEHHA REL	6.0E+01	OEHHA REL	1.0E-01	OEHHA SFi
Benzyl Chloride	100-44-7	2.4E+02	OEHHA REL			1.7E-01	OEHHA SFi
Bis(2-chloroethyl)ether	111-44-4					2.5E+00	OEHHA SFi
Bis(2-ethylhexyl)phthalate	117-81-7			1.0E+01	OEHHA Draft REL	8.4E-03	OEHHA SFi
Bromomethane	74-83-9	3.9E+03	OEHHA REL	5.0E+00	OEHHA REL		
Butadiene, 1,3-	106-99-0	6.6E+02	Draft OEHHA REL	7.0E+00	OEHHA Draft REL	6.0E-01	OEHHA SFi
Butane, n-	106-97-8			1.5E+04	NIOSH REL		

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[16] This table contains health values for constituents that were identified in the studies reviewed. Since representative biogas concentration data was not available for every table entry, risk calculations were performed on only a subset of 95 of the listed constituents. Also note that screening criteria were omitted for the following groups: Polychlorinated Dibenzodioxins/Dibenzofurans, Polychlorinated Biphenyls, and the carcinogenic Polyaromatic Hydrocarbons; these constituents were not measured above detection limits in the studies reviewed.

[17] Abbreviations are defined at the end of the table.

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC ($\mu g/m^3$)	Source Acute	Chronic NC ($\mu g/m^3$)	Source Chronic	SFi (kg-d/mg)	Source SFi
Butanol, n-	71-36-3	5.0E+03	OSHA PEL	6.0E+01	USEPA Draft RfC		
Butanone, 2-	78-93-3	1.3E+04	OEHHA REL	5.0E+03	USEPA RfC		
Butoxyethanol, 2-	111-76-2			1.9E+02	NIOSH REL		
Carbon Disulfide	75-15-0	6.2E+03	OEHHA REL	8.0E+02	OEHHA REL		
Carbon monoxide	630-08-0	2.3E+04	OEHHA REL				
Carbon Tetrachloride	56-23-5	1.9E+03	OEHHA REL	4.0E+01	OEHHA REL	1.5E-01	OEHHA SFi
Carbonyl Sulfide	463-58-1	6.5E+03	OEHHA Draft REL	2.2E+02	OEHHA Draft REL		
Chlorobenzene	108-90-7			1.0E+03	OEHHA REL		
Chloroform	67-66-3	1.5E+02	OEHHA REL	3.0E+02	OEHHA REL	1.9E-02	OEHHA SFi
Chloromethane	74-87-3	1.0E+03	ATSDR MRL	9.0E+01	USEPA RfC		
Chloroprene	126-99-8			2.0E+01	USEPA RfC	1.1E+00	USEPA IUR
Chlorotoluene, 2-	95-49-8	1.3E+04	NIOSH REL	2.0E+03	NIOSH REL		
Copper and compds.	7440-50-8	1.0E+02	OEHHA REL	2.0E-02	OEHHA Draft REL		
Cresols (methylphenol isomers)	1319-77-3			6.0E+02	OEHHA REL		
Crotonaldehyde	123-73-9			4.8E+01	OSHA PEL		
Cumene (Isopropylbenzene)	98-82-8			4.0E+02	USEPA RfC	8.4E-02	OEHHA Draft SFi
Cyclohexane	110-82-7			6.0E+03	USEPA RfC		
Cyclopentane	287-92-3			1.4E+04	NIOSH REL		
DDT, 4,4'-	50-29-3					3.4E-01	USEPA IUR
Dibromochloromethane	124-48-1					9.4E-02	OEHHA SFi
Dibromoethane, 1,2-	106-93-4	3.3E+01	NIOSH REL	8.0E-01	OEHHA REL	2.5E-01	OEHHA SFi

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC (µg/m^3)	Source Acute	Chronic NC (µg/m^3)	Source Chronic	SFi (kg-d/mg)	Source SFi
Dichlorobenzene, 1,2-	95-50-1	1.0E+04	OSHA PEL				
Dichlorobenzene, 1,4-	106-46-7	1.2E+04	ATSDR MRL	8.0E+02	OEHHA REL	4.0E-02	OEHHA SFi
Dichlorodifluoromethane	75-71-8			1.0E+03	OEHHA Draft REL		
Dichloroethane, 1,1-	75-34-3					5.7E-03	OEHHA SFi
Dichloroethane, 1,2-	107-06-2			4.0E+02	OEHHA REL	7.2E-02	OEHHA SFi
Dichloroethene, 1,1-	75-35-4			7.0E+01	OEHHA REL		
Dichloropropane, 1,2-	78-87-5			4.0E+00	USEPA RfC	3.6E-02	OEHHA SFi
Dichloropropene, trans-1,3-	10061-02-6			2.0E+01	USEPA RfC	1.4E-02	USEPA IUR
Di-n-butyl phthalate	84-74-2			5.3E-01	OEHHA MADLi		
Dioxane, 1,4-	123-91-1	3.0E+03	OEHHA REL	3.0E+03	OEHHA REL	2.7E-02	OEHHA SFi
Endosulfan I	959-98-8			3.3E-01	CDPR RfC		
Endrin	72-20-8			7.9E-01	OSHA PEL		
Epichlorohydrin	106-89-8	1.3E+03	OEHHA REL	3.0E+00	OEHHA REL	8.0E-02	OEHHA SFi
Ethyl Chloride	75-00-3	4.0E+04	ATSDR MRL	3.0E+04	OEHHA REL		
Ethyl Mercaptan	75-08-1	4.3E+01	NIOSH REL	1.0E+01	ACGIH TLV		
Ethylbenzene	100-41-4	2.2E+04	ATSDR MRL	2.0E+03	OEHHA REL	8.7E-03	OEHHA SFi
Ethylene Oxide	75-21-8	3.0E+02	NIOSH REL	1.0E+00	OEHHA MADLi	3.1E-01	OEHHA SFi
Formaldehyde	50-00-0	5.5E+01	OEHHA REL	9.0E+00	OEHHA REL	2.1E-02	OEHHA SFi
Formic acid	64-18-6			7.1E+01	OSHA PEL		
Furanmethanol, 2-	98-00-0	2.0E+03	ACGIH STEL	3.2E+02	ACGIH TWA		

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC (µg/m^3)	Source Acute	Chronic NC (µg/m^3)	Source Chronic	SFi (kg-d/mg)	Source SFi
Furfural	98-01-1			1.6E+02	OSHA PEL		
Heptachlor	76-44-8					4.1E+00	Cal PHG data
Heptachlor epoxide	1024-57-3					5.5E+00	Cal PHG data
Heptane, n-	8031-33-2	6.0E+04	NIOSH REL	2.8E+03	NIOSH REL		
Hexachlorobenzene	118-74-1					1.8E+00	OEHHA SFi
Hexachlorocyclopentadiene	77-47-4			2.0E-01	USEPA RfC		
Hexane, n-	110-54-3	6.0E+04	NIOSH REL	7.0E+03	OEHHA REL		
Hexanone	591-78-6			3.2E+01	NIOSH REL		
Hydrogen cyanide	74-90-8			9.0E+00	OEHHA REL		
Hydrogen Sulfide	7783-06-4	4.2E+01	OEHHA REL	1.0E+01	OEHHA REL		
Isopropanol	67-63-0	3.2E+03	OEHHA REL	2.0E+03	OEHHA Draft REL		
Lead	7439-92-1			2.5E-02	OEHHA MADLi	4.2E-02	OEHHA SFi
Mercury (alkyl compds)	593-74-8	1.3E+00	OSHA PEL	8.0E-02	OSHA PEL		
Mercury (inorganic)	7439-97-6	6.0E-01	OEHHA REL	3.0E-02	OEHHA REL		
Methacrylic Acid	79-41-4			5.6E+02	OSHA REL		
Methyl Isobutyl Ketone	108-10-1			3.0E+03	USEPA RfC		
Methyl Mercaptan	74-93-1	3.3E+01	NIOSH REL	7.9E+00	ACGIH TLV		
Methyl Methacrylate	80-62-6			1.0E+02	OEHHA Draft REL		
Methylal	109-87-5			2.5E+04	OSHA PEL		
Methylcyclohexane	108-87-2			1.3E+04	ACGIH TWA		
Methylene Chloride	75-09-2	1.4E+04	OEHHA REL	4.0E+02	OEHHA REL	3.5E-03	OEHHA SFi

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC (µg/m³)	Source Acute	Chronic NC (µg/m³)	Source Chronic	SFi (kg-d/mg)	Source SFi
Methylphenol, 3-	108-39-4			6.0E+02	OEHHA REL		
Methylphenol, 4-	106-44-5			6.0E+02	OEHHA REL		
Methyl-t-butylether (MTBE)	1634-04-4			8.0E+03	OEHHA REL	1.8E-03	OEHHA SFi
Naphthalene	91-20-3			9.0E+00	OEHHA REL	1.2E-01	OEHHA SFi
Nitrobenzene	98-95-3			9.0E+00	USEPA RfC	1.4E-01	USEPA IUR
Nitrosodiethanolamine, n-	1116-54-7					2.8E+00	OEHHA SFi
Nitrosodiethylamine, n-	55-18-5					3.6E+01	OEHHA SFi
Nitrosodimethylamine, n-	62-75-9					1.6E+01	OEHHA SFi
Nitrosodi-n-butylamine, n-	924-16-3					1.1E+01	OEHHA SFi
Nitrosodi-n-propylamine, n-	621-64-7					7.0E+00	OEHHA SFi
Nitrosomorpholine, n-	59-89-2					6.7E+00	OEHHA SFi
Nitroso-n-methylethylamine, n-	10595-95-6					2.2E+01	OEHHA SFi
Nitrosonornicotine, n-	16543-55-8					1.4E+00	OEHHA SFi
Nitrosopiperidine, n-	100-75-4					9.4E+00	OEHHA SFi
Nitrosopyrrolidine, n-	930-55-2					2.1E+00	OEHHA SFi
Octamethylcyclotetrasiloxane	556-67-2	4.0E+03	OEHHA REL	7.0E+02	OEHHA REL		
Pentachlorophenol	87-86-5			1.0E+02	OEHHA Draft REL	1.8E-02	OEHHA SFi
Pentane, n-	8031-35-4	6.0E+04	NIOSH REL	2.8E+03	NIOSH REL		
Perchloroethane	67-72-1			3.0E+01	USEPA RfC	3.9E-02	OEHHA SFi
Phenol	108-95-2	5.8E+03	OEHHA REL	2.0E+02	OEHHA REL		
Phosphine	7803-51-2			8.0E-01	OEHHA REL		
Polybrominated Biphenyls	13654-09-6					3.0E+01	OEHHA SFi
Propane	74-98-6			1.4E+04	OSHA PEL		
Propene	115-07-1			3.0E+03	OEHHA REL		

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC (µg/m^3)	Source Acute	Chronic NC (µg/m^3)	Source Chronic	SFi (kg-d/mg)	Source SFi
Propionaldehyde	123-38-6			8.0E+00	USEPA RfC		
Propylene Oxide	75-56-9	3.1E+03	OEHHA REL	3.0E+01	OEHHA REL	1.3E-02	OEHHA SFi
Pyridine	110-86-1			1.2E+02	OSHA PEL		
Styrene	100-42-5	2.1E+04	OEHHA REL	9.0E+02	OEHHA REL		
Sulfur Dioxide	7446-09-5	6.6E+02	OEHHA REL	7.8E+01	Federal NAAQS		
Tetrachloroethane, 1,1,2,2-	79-34-5			5.5E+01	NIOSH REL	2.0E-01	OEHHA SFi
Tetrachloroethylene	127-18-4	2.0E+04	OEHHA REL	3.5E+01	OEHHA REL	2.1E-02	OEHHA SFi
Tetrachlorophenol, 2,3,4,6-	58-90-2			9.0E+01	OEHHA Draft REL		
Tetrahydrofuran	109-99-9			2.0E+03	USEPA RfC		
Thiophenol	108-98-5	1.7E+01	NIOSH REL				
Toluene	108-88-3	3.7E+04	OEHHA REL	3.0E+02	OEHHA REL		
Tribromomethane	75-25-2			4.0E+01	NIOSH REL		
Trichloroethane, 1,1,1-	71-55-6	6.8E+04	OEHHA REL	1.0E+03	OEHHA REL		
Trichloroethane, 1,1,2-	79-00-5					5.7E-02	OEHHA SFi
Trichloroethylene	79-01-6	3.6E+04	OSHA PEL	6.0E+02	OEHHA REL	7.0E-03	OEHHA SFi
Trichlorofluoromethane	75-69-4	1.9E+05	ACGIH STEL	2.0E+04	OEHHA Draft REL		
Trichlorophenol, 2,4,6-	88-06-2					7.0E-02	OEHHA SFi
Trimethylbenzene, 1,2,3-	95-63-6			2.0E+01	USEPA Draft RfC		
Trimethylbenzene, 1,2,4-	95-63-6			2.0E+01	USEPA Draft RfC		

Table IV-1: Health Risk Criteria for Biogas Constituents with Established Values[16,17]

Constituent	CAS	Acute NC (µg/m^3)	Source Acute	Chronic NC (µg/m^3)	Source Chronic	SFi (kg-d/mg)	Source SFi
Trimethylbenzene, 1,3,5-	108-67-8			2.0E+01	USEPA Draft RfC		
Vinyl Acetate	108-05-4			2.0E+02	OEHHA REL		
Vinyl Chloride	75-01-4	1.8E+05	OEHHA REL	1.0E+02	USEPA RfC	2.7E-01	OEHHA SFi
Xylenes (any isomer or mixture)	1330-20-7	2.2E+04	OEHHA REL	7.0E+02	OEHHA REL		
Zinc	7440-66-6	5.0E+02	OSHA PEL (ZnO)	9.0E-01	OEHHA Draft REL		

Abbreviations:
OEHHA REL or SFi = OEHHA Reference Exposure Level (for Acute or Chronic Non-Cancer "NC" Effects) or Inhalation Slope Factor (for carcinogens)
USEPA RfC or IUR = USEPA Reference Concentration or Inhalation Unit Risk
OSHA PEL or NIOSH REL = Federal OSHA Permissible Exposure Limit or NIOSH Recommended Exposure Level (adjusted for exposure duration with added UF of 30)
ACGIH TLV = ACGIH Threshold Limit Value (adjusted for exposure duration with added UF of 30)
OEHHA MADLi = OEHHA Maximum Allowable Dose Level (Inhalation)
CDPR RfC = California Department of Pesticide Regulation Reference Concentration
CalPHG = California Public Health Goal for Drinking Water

Table IV-2: Non-Cancer Health Risk Criteria for Biogas Constituents based on Route-to-Route Extrapolation or Chemical Surrogates[1]

Constituent	CAS	Acute (µg/m³)	Source Acute (Surrogate Chemical)	Chronic (µg/m³)	Source Chronic (Surrogate Chemical)
Antimony	7440-36-0	--	--	2.0E-01	Draft OEHHA REL (SbO3)
Acenaphthene	83-32-9	--	--	2.1E+02	USEPA Oral RfD converted to REL
Anthracene	120-12-7	--	--	1.1E+03	USEPA Oral RfD converted to REL
Fluoranthene	206-44-0	--	--	1.4E+02	USEPA Oral RfD converted to REL
Fluorene	86-73-7	--	--	1.4E+02	USEPA Oral RfD converted to REL
Pyrene	129-00-0	--	--	1.1E+02	USEPA Oral RfD converted to REL
Methylnaphthalene, 1-	90-12-0	--	--	1.3E+01	OEHHA REL (Naphthalene)
Methylnaphthalene, 2-	91-57-6	--	--	1.3E+01	OEHHA REL (Naphthalene)
Methacrolein	78-85-3	2.5E+00	OEHHA REL (Acrolein)	3.5E-01	OEHHA REL (Acrolein)
Abbreviations: OEHHA REL = OEHHA Reference Exposure Level USEPA RfD = USEPA Oral Reference Dose					

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[1] This table contains health values for constituents that were identified in the various studies reviewed. However, representative biogas concentration data was not available for every table entry such that risk calculations were performed on a subset of the listed constituents.

Table IV-3: Non-Cancer Biogas Screening Criteria for Various Chemical Groups

Group	Group Name	Description of Group Membership	Group Surrogate Chemical	Acute (ppm)	Source Acute	Chronic (ppm)	Source Chronic
1	Alkanes (6 Carbons or less)[1]	Group 1 alkanes listed in Appendix B tables	n-Pentane	20	NIOSH REL 610 ppm	0.95	NIOSH REL 120 ppm
2	Alkanes (7 Carbons or more)[1]	Group 2, Appendix B	n-Heptane	14.7	NIOSH REL 440 ppm	0.67	NIOSH REL 85 ppm
3	Cycloalkanes	Group 3, Appendix B	Cyclohexane	--	--	1.7	USEPA RfC 6 mg/m^3
4	"n-Hexane-Like" Chemicals	Group 4, Appendix B, plus n-hexane	n-Hexane	17	NIOSH REL 510 ppm	2	OEHHA REL 7 mg/m^3
5	Alkenes and Dienes	Group 5 Appendix B, plus propene	Propene	--	--	1.7	OEHHA REL 3 mg/m^3
8	Alcohols[1]	Group 8, Appendix B	n-Butanol	16.7	OSHA PEL 50 ppm	0.02	USEPA RfC (draft) 0.06 mg/m^3
9	Ethers	Group 9, Appendix B, plus tetrahydrofuran	Tetrahydrofuran	--	--	1.59	OSHA PEL 200 ppm
10	Aldehydes	Group 10, Appendix B	Propionaldehyde	--	--	0.003	USEPA RfC 0.008 mg/m^3
11	Ketones[1]	Group 11, Appendix B	Methyl Ethyl Ketone	--	--	0.34	OEHHA REL (draft) 1 mg/m^3
12	Carboxylic Acids	Group 12, Appendix B	Acetic Acid (Acute) Formic Acid (Chronic)	0.5	NIOSH REL 15 ppm	0.04	OSHA PEL 5 ppm

[1] These groups do not include chemicals that share a toxicological similarity to either n-hexane or its metabolites.

Table IV-3: Non-Cancer Biogas Screening Criteria for Various Chemical Groups

Group	Group Name	Description of Group Membership	Group Surrogate Chemical	Acute (ppm)	Source Acute	Chronic (ppm)	Source Chronic
13	Esters	Group 13, Appendix B, plus ethyl acetate	1,3-Dimethylbutyl Acetate	--	--	0.4	NIOSH REL 50 ppm
19	Chlorofluorocarbons (CFCs)	Group 19, Appendix B	Trichlorofluoro-methane (Acute) Dichlorodifluoro-methane (Chronic)	33	ACGIH STEL 1000 ppm	0.24	OEHHA REL (draft) 1 mg/m^3
20	Alkyl Thiols (Mercaptans)	Group 20, Appendix B	Alkyl Thiols	0.017	NIOSH REL 0.5 ppm	0.004	ACGIH TWA 0.5 ppm
22	Siloxanes	Group 22, Appendix B	D4 Siloxane	0.3	OEHHA REL 4 mg/m^3	0.058	OEHHA REL 0.7 mg/m^3

Table IV-4: Biogas Constituents and Groups Lacking Inhalation Criteria

CAS	Constituent or Group
208-96-8	Acenaphthylene
	Alkyl sulfides (Group 21)
	Alkynes (Group 14)
	Benzenes (Alkyl; Groups 15 and 16)
	Benzenes (Chlorinated; Group 18)
	Benzenes (Styrenes; Group 17)
191-24-2	Benzo(g,h,i)perylene
95-16-9	Benzothiazole
100-51-6	Benzyl alcohol
259-79-0	Biphenylene
33617-38-8	Bis(trimethylsiloxy)benzaldehyde, 2,4-
75-27-4	Bromodichloromethane
74-96-4	Bromoethane
111-34-2	Butane, 1-(ethenyloxy)-
1615-75-4	Chloro-1-fluoroethane, 1-
95-57-8	Chlorophenol, 2-
540-54-5	Chloropropane, 1-
72-54-8	DDD, 4,4'-
5385-75-1	Dibenzo(a,e)fluoranthene
74-95-3	Dibromomethane
	Dichlorobutene
156-60-5	Dichloroethene, trans-1,2-
120-83-2	Dichlorophenol, 2,4-
27554-26-3	Diisooctylphthalate
	Dimethoxymethyl propanoate
	Dimethyl furan
1066-42-8	Dimethyldisilanol
575-43-9	Dimethylnaphthalene, 1,5-
593-80-6	Dimethyltelluride
646-06-0	Dioxolane, 1,3-
7421-93-4	Endrin aldehyde
5101-44-0	Ethynylphenol, 2-
10401-11-3	Ethynylphenol, 3-
110-00-9	Furan
72-43-5	Methoxychlor
	Methyl furan
78-94-4	Methyl vinyl ketone

Table IV-4: Biogas Constituents and Groups Lacking Inhalation Criteria

CAS	Constituent or Group
	Methyl-1,3-butadiene, 2-
625-74-1	Methyl-1-nitropropane, 2-
	Methylated Arsenic compounds
	Pentadiene, 1,3-
85-01-8	Phenanthrene
	Propanal, 3-(ethylthio)-
	Propylthiophene
1551-27-5	Propylthiophene, 2-
75-65-0	t-Butyl alcohol
	Tetrachloroethane
630-20-6	Tetrachloroethane, 1,1,1,2-
97-99-4	Tetrahydro-2-furanmethanol
110-02-1	Thiophene
95-95-4	Trichlorophenol, 2,4,5-
	Trifluorobenzene
594-10-5	Trimethylantimony
593-91-9	Trimethylbismuth
1066-40-6	Trimethylsilanol
	Trimethyltin compounds

B. Biogas Constituents of Concern

OEHHA staff completed a risk screening evaluation for individual biogas constituents having toxicity screening criteria and for the toxicity groups defined in Table IV-3. We used the exposure adjustment factors derived by ARB staff for the residential and worker scenario air models (see Chapter III section D) along with the highest measured constituent concentration values (primarily from the GTI dataset) to estimate potential health risks. High values from the GTI dataset were used for calculating potential exposure to the individual biogas constituents (See Appendix B Table B-4). For evaluating the groups, both GTI data and concentrations from the AP-42 Update, Table 2-8, were used.[1] Hazard quotients were calculated by taking the ratio of the effective exposure concentration to the appropriate non-cancer screening value for each constituent having non-cancer criteria.

Potential cancer risks were estimated for the residential and worker scenarios using OEHHA Air Toxics "Hotspots" risk assessment guidelines (OEHHA, 2012). For residential risks, the guidelines recommend age-specific values for breathing rate and time spent at home, as well as age-specific sensitivity factors. The values used for the stovetop (non-combustion) exposure scenario are provided in Table IV-5:

Table IV-5: Exposure Parameters for Cancer Risk Calculations				
Age Category (yr)	IR_i = Inhalation rate (m^3/kg-d)	ED_i = Exposure duration (yr)	SF_i = Sensitivity factor (unitless)	FAH_i = Fraction of time at home (unitless)
3rd Trimester	0.361	0.3	10	0.85
0 < 2	1.09	2	10	0.85
2 < 16	0.745	14	3	0.72
16 < 30	0.335	14	1	0.73

The formula to estimate the weighted-average exposure for each biogas constituent for the four age categories throughout a 30.3 year exposure period is:

$$Exposure\ Rate \left(\frac{mg}{kg \cdot day}\right) = C_r \ x \ DF_r \ x \left(\frac{1}{AT}\right) \sum_{i=1}^{4} IR_i \ x \ ED_i \ x \ SF_i \ x \ FAH_i$$

Where IR_i, ED_i, SF_i, and FAH_i are defined as above, and where:

C_r = Constituent concentration in biogas (raw and cleaned) in a residence (highest measured values, mg/m^3)

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[1] In two instances other data sources were used to estimate exposure concentrations, as specified in Table IV-9, below.

DF$_r$ = Modeled long-term exposure adjustment factor for a residence (unitless)

AT = Averaging time to pro-rate less-than-lifetime exposures in cancer risk calculations (70 yr)

To calculate a "high-end" value for exposure in the 1-year residential gas-leak scenario, only the exposure parameters for the "0 < 2" year age group were used in the formula.

The equation for the worker exposure scenario is:

$$Exposure\ Rate\ \left(\frac{mg}{kg \cdot day}\right) = \frac{C_w\ x\ DF_w\ x\ IR_w\ x\ EF_w\ x\ ED_w}{AT}$$

Where:

C$_w$ = Constituent concentration in biogas in a workplace (highest measured values, mg/m^3)

DF$_w$ = Modeled long-term exposure adjustment factor for a workplace (unitless)

IR$_w$ = Worker 8-hour breathing rate (0.23 m^3/kg-8 hr); 95th percentile for moderate exertion)

EF$_w$ = Exposure frequency (5/7 d/d)

ED$_w$ = Duration of employment (25 yr; 95th percentile value)

AT = Averaging time to pro-rate less-than-lifetime exposures in cancer risk calculations (70 yr)

A factor to account for the number of weeks per year worked (49/52) was not added to the exposure calculation since many production workers regularly work overtime hours (e.g., recent Department of Labor statistics indicate that the average overtime hours for production workers is approximately 4 hours per week.) The exposure rates were then multiplied by the Inhalation Slope Factors to produce estimated lifetime cancer risk estimates.

The preliminary biogas constituents of concern were then defined according to the following rationale. For chemicals with quantified risks, constituents whose risk values were greater than the following risk-thresholds were placed on the list:

- Residential Exposure Scenario: 0.01 for HQs and 1E-6 (1 chance per million) for cancer risks
- Worker Exposure Scenario: 0.3 for HQs and 3E-5 (30 chances per million) for cancer risks

The risk thresholds for the worker scenario were set at 30 times the values for the general population, which is consistent with the method used above to derive general

public health criteria from OSHA or NIOSH risk criteria (where an additional safety factor of 30 was applied to the occupational value to protect sensitive members of the general population). The potential cancer risks and the acute and chronic hazard quotients for the biogas constituents and groups are provided in Tables IV-6 through IV-9. The constituents that had cancer risks or hazard quotients greater than the screening values were placed on the list of preliminary constituents of concern. (The preliminary constituents of concern are highlighted in the tables.)

Table IV-6: Cancer Risk Estimates for Biogas/Biomethane Constituent Concentrations with the Highest Risk (top 10 risks shown; chemicals exceeding screening risks highlighted)

Raw Biogas				
Constituent	**SFi[1] (kg-d/mg)**	**Conc. (mg/m^3)**	**Risk Residential**	**Risk Worker**
Arsenic	1.2E+01	3.39E-01	1.79E-05	1.07E-04
Benzene	1.0E-01	9.58E+00	4.21E-06	2.51E-05
Vinyl Chloride	2.7E-01	2.38E+00	2.82E-06	1.68E-05
p-Dichlorobenzene	4.0E-02	1.52E+01	2.66E-06	1.59E-05
n-Nitroso-di-n-propylamine	7.0E+00	6.23E-02	1.91E-06	1.14E-05
Ethylbenzene	8.7E-03	3.47E+01	1.33E-06	7.92E-06
Naphthalene	1.2E-01	1.14E+00	5.99E-07	3.58E-06
1,2-Dichloroethane	7.2E-02	1.82E+00	5.76E-07	3.44E-06
1,1,2-Trichloroethane	5.7E-02	2.07E+00	5.19E-07	3.10E-06
Tetrachloroethylene	2.1E-02	5.56E+00	5.13E-07	3.06E-06
Biomethane				
Constituent	**SFi (kg-d/mg)**	**Conc. (mg/m^3)**	**Risk Residential**	**Risk Worker**
Benzene	1.0E-01	3.19E+00	1.40E-06	8.37E-06
Vinyl Chloride	2.7E-01	8.44E-01	1.00E-06	5.97E-06
n-Nitroso-di-n-propylamine	7.0E+00	1.92E-02	5.89E-07	3.52E-06
Lead	4.20E-02	1.55E-01	2.86E-08	1.71E-07
Naphthalene	1.20E-01	3.67E-02	1.93E-08	1.15E-07
1,2-Dichloropropane	3.60E-02	9.10E-02	1.44E-08	8.59E-08
Acetaldehyde	1.00E-02	2.65E-01	1.16E-08	6.95E-08
Carbon Tetrachloride	1.50E-01	1.26E-02	8.33E-09	4.97E-08
Formaldehyde	2.10E-02	6.99E-02	6.45E-09	3.85E-08
Bis(2-ethylhexyl)phthalate	8.40E-03	9.74E-02	3.59E-09	2.14E-08

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[1] SFi = Inhalation Slope Factor used to calculate potential cancer risk.

Table IV-7: Chronic Hazard Quotients for Biogas/Biomethane Constituent Concentrations with Highest Risk (top 10 HQs shown, chemicals exceeding screening risks highlighted)

Raw Biogas				
Constituent	**Chronic Screening Value (µg/m³)**	**Conc. (mg/m³)**	**Residential HQ**	**Worker HQ**
Hydrogen Sulfide	1.0E+01	9.16E+03	3.04E+01	4.08E+02
Arsenic	1.5E-02	3.39E-01	7.50E-01	1.01E+01
Antimony	2.0E-01	4.17E-01	6.92E-02	9.30E-01
Methyl Mercaptan	7.9E+00	1.20E+01	5.04E-02	6.77E-01
Methacrolein	3.5E-01	3.12E-01	2.96E-02	3.98E-01
Toluene	3.0E+02	9.80E+01	1.08E-02	1.46E-01
Sulfur Dioxide	7.8E+01	2.03E+01	8.62E-03	1.16E-01
Benzene	6.0E+01	9.58E+00	5.30E-03	7.12E-02
Tetrachloroethylene	3.5E+01	5.56E+00	5.27E-03	7.09E-02
Ammonia	2.0E+02	2.79E+01	4.63E-03	6.21E-02

Biomethane				
Constituent	**Chronic Screening Value (µg/m³)**	**Conc. (mg/m³)**	**Residential HQ**	**Worker HQ**
Hydrogen Sulfide	1.0E+01	2.61E+02	8.65E-01	1.16E+01
Copper and compds.	2.0E-02	2.50E-01	4.15E-01	5.58E+00
Lead	2.5E-02	1.55E-01	2.06E-01	2.77E+00
Toluene	3.00E+02	1.17E+02	1.29E-02	1.74E-01
Zinc	9.00E-01	2.53E-01	9.33E-03	1.25E-01
Methyl Mercaptan	7.94E+00	1.61E+00	6.75E-03	9.07E-02
Antimony and Compds.	2.00E-01	3.20E-02	5.31E-03	7.14E-02
Di-n-butylphthalate	5.25E-01	4.90E-02	3.10E-03	4.16E-02
Carbonyl Sulfide	2.20E+02	1.30E+01	1.96E-03	2.63E-02
Benzene	6.0E+01	3.19E+00	1.77E-03	2.37E-02

Table IV-8: Acute Hazard Quotients for Biogas/Biomethane Constituent Concentrations with Highest Risk (top 10 HQs shown, chemicals exceeding screening risks highlighted)

Raw Biogas				
Constituent	**Acute Screening Value (µg/m^3)**	**Conc. (mg/m^3)**	**Residential HQ**	**Worker HQ**
Hydrogen Sulfide	4.2E+01	9.16E+03	2.78E+01	9.73E+01
Arsenic	2.0E-01	3.39E-01	2.16E-01	7.56E-01
Methyl Mercaptan	3.3E+01	1.20E+01	4.61E-02	1.61E-01
Methacrolein	2.5E+00	3.12E-01	1.59E-02	5.57E-02
Sulfur Dioxide	6.6E+02	2.03E+01	3.91E-03	1.37E-02
Ethyl Mercaptan	4.3E+01	7.62E-01	2.24E-03	7.85E-03
Octamethylcyclotetra-siloxane	4.0E+03	6.61E+01	2.11E-03	7.37E-03
Thiophenol	1.7E+01	2.25E-01	1.69E-03	5.91E-03
Ammonia	3.2E+03	2.79E+01	1.11E-03	3.88E-03
Benzene	1.3E+03	9.58E+00	9.40E-04	3.29E-03
Biomethane				
Constituent	**Acute Screening Value (µg/m^3)**	**Conc. (mg/m^3)**	**Residential HQ**	**Worker HQ**
Hydrogen Sulfide	4.2E+01	2.61E+02	7.91E-01	2.77E+00
Methyl Mercaptan	3.3E+01	1.61E+00	6.17E-03	2.16E-02
Methacrolein	2.5E+00	1.18E-02	6.01E-04	2.10E-03
Octamethylcyclotetra-siloxane	4.00E+03	1.61E+01	5.12E-04	1.79E-03
Toluene	3.70E+04	1.17E+02	4.03E-04	1.41E-03
Copper	1.00E+02	2.50E-01	3.19E-04	1.12E-03
Benzene	1.30E+03	3.19E+00	3.13E-04	1.10E-03
Carbonyl Sulfide	6.50E+03	1.30E+01	2.54E-04	8.90E-04
Formaldehyde	5.50E+01	6.99E-02	1.62E-04	5.67E-04
Sulfur Dioxide	6.60E+02	6.55E-01	1.27E-04	4.43E-04

Table IV-9: Hazard Quotients for Chemical Groups[1]

Group	Name	Screening Values (ppm)			Acute HQ		Chronic HQ		Notes
		Acute	Chronic	Biogas High Conc. (ppm)	Resident	Worker	Resident	Worker	
1	Alkanes (6 Carbons or less, minus methane, ethane, & propane)	20	0.95	124.00	0.001	0.003	0.004	0.058	GTI Data[2] (Biomethane values were higher than in biogas in this instance)
2	Alkanes (7 Carbons or more)	14.7	0.67	137.00	0.001	0.004	0.007	0.091	GTI Data (Sum of Heptanes through Dodecanes)
3	Cycloalkanes	-	1.7	15.00	-	-	0.000	0.004	GTI Data[2]
4	"n-Hexane-Like" Alkanes	17	2	47.00	0.000	0.001	0.001	0.010	GTI Data[2]
5 & 7	Alkenes, Dienes, & Terpenes	-	1.7	149.80	-	-	0.003	0.039	USEPA 2008 (sum of alkenes) and UKEA 2002 (Table A1.7) (sum of non-aromatic Terpenes)
8	Alcohols	16.7	0.02	6.30	0.000	0.000	0.010	0.140	GTI and USEPA 2008 (sum of Ethanol,Isopropanol, and Benzyl Alcohol values)
9	Ethers	-	1.59	2.10	-	-	0.000	0.001	USEPA 2008 (sum of Tetrahydrofuran, MTBE, and 1,4-dioxane)
10	Aldehydes	-	0.003	0.60	-	-	0.007	0.089	GTI Data[2] (high values were found in biomethane)

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[1] The exposure adjustment factors developed in Chapter III were applied to the sum of concentrations for each group; in some cases, as noted, the highest totals were found in biomethane.
[2] Concentrations were based on the highest values for each detected member of in the defined group; constituents that were not detected in any sample were assumed to be absent.

Table IV-9: Hazard Quotients for Chemical Groups[1]

Group	Name	Screening Values (ppm)			Acute HQ		Chronic HQ		Notes
		Acute	Chronic	Biogas High Conc. (ppm)	Resident	Worker	Resident	Worker	
11	Ketones	-	0.34	27.70	-	-	0.003	0.036	USEPA 2008 (sum of Acetone, Methyl Ethyl Ketone, and Methyl Isobutyl Ketone)
12	Carboxylic Acids	0.5	0.04	0.53	0.000	0.000	0.000	0.003	PG&E 2008; (sum of Acetic and Lactic acids; values available for biomethane only)
13	Esters	-	0.4	636.50	-	-	0.053	0.710	USEPA 2008; bounding estimate using NMOC value (as C6)
19	Chlorofluorocarbons (CFCs)	33	0.24	4.00	0.000	0.000	0.001	0.007	GTI Data[2] (high values found in biomethane)
20	Alkyl Thiols (Mercaptans)	0.017	0.004	8.46	0.063	0.222	0.070	0.943	GTI Data[2]
22	Siloxanes	0.3	0.058	4.22	0.002	0.006	0.002	0.032	GTI Data[2]

Two of the 14 chemical groups showed screening values greater than the above stated risk thresholds: alkyl thiols and esters. Regarding the esters group, the highest HQ values were 0.05 for a resident and 0.7 for a worker. However, it was not placed on the preliminary constituents of concern list because the concentration values used in the calculation were not from analytical data for ester compounds, but were instead derived using the average Non-Methane Organic Carbon (NMOC) concentration reported in the U.S. EPA AP-42 document for municipal landfills. Using the NMOC concentration as a surrogate for the actual measurement of esters represents a highly conservative upper bound, since the NMOC value represents all carbon-containing chemicals in the biogas samples. Given that the screening HQs for esters were only above the risk cutoffs by a factor of 5 or less, and were not above 1.0, staff judged that alkyl esters normally found in biogas do not represent constituents of concern.

The alkyl thiols group values exceeded the risk thresholds and were placed on the preliminary constituents of concern list. It should be noted that methyl mercaptan and i-propyl mercaptan would have qualified to be preliminary constituents of concern based upon the individual constituent calculations. These thiols are members of the alkyl thiols group and therefore are covered by the group designation.

The final constituents of concern list was obtained from the preliminary constituents of concern list by retaining the constituents that were determined to be present in biogas at levels significantly higher than in natural gas. The limited nature of the datasets, both in sample quantity as well as coverage of the variety of biogas and natural gas streams for California, precluded a determination based on formal statistical methods. Instead, a 3-tier decision process was developed to carry out the biogas-natural gas comparison. A preliminary constituent of concern was judged to be present in levels significantly greater than in natural gas, and thus placed on the final constituent of concern list, if it met any one of the following conditions (in order):

(i)   The constituent was not found in any natural gas sample;
(ii)   Its highest measured concentration in biogas was greater than the highest concentration found in natural gas; or,
(iii)   Its average biogas value was larger than the average natural gas value.

Five of the preliminary constituents of concern were placed on the final list based upon meeting the first criterion of not being found in the natural gas samples: p-dichlorobenzene, n-nitroso-di-n-propylamine, vinyl chloride, antimony, and lead. The second criterion was met by the following constituents, which were also placed on the constituents of concern list: ethylbenzene, toluene, methacrolein, hydrogen sulfide, and copper.[24]
Since the high concentrations of benzene and alkyl thiols in biogas were less than the respective concentrations in natural gas, the average values for these constituents were compared per the third decision criterion. Based upon this comparison, alkyl thiols were added to the list of constituents of concern since average concentrations of thiols in

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[24] Note that in carrying out the significance comparisons, we used AP-42 Update concentrations to support and confirm the GTI dataset.

biogas were higher than in natural gas. However, based on a similar comparison, benzene did not qualify for the final list. In this case the average concentration of benzene in natural gas was more than 5 times greater than the average concentrations found in biogas. These comparisons are shown in Tables IV-10 through IV-12. The final constituents of concern list is given in Table IV-13. (Instances in which natural gas concentrations are higher than in biogas are highlighted.) Appendix C contains toxicity summaries for the final constituents of concern.

Table IV-10: Preliminary Constituents of Concern Detected in Biogas and Natural Gas, and Comparison of High Concentration Values (in ppmv unless otherwise noted; Natural Gas values > Biogas highlighted)

Constituent	Pipeline Quality Natural Gas	Landfills			POTWs		Dairy Farms	
		Biogas	USEPA 2008	Biomethane	Biogas	Biomethane	Biogas	Biomethane
Benzene	38.6	3.0	22	< 1	< 1	< 1	0.01	0.027
Ethylbenzene	1.0	8.0	8.8	< 1	< 1	< 1	0.34	0.003
Toluene	15.8	33	90.1	1.40	31	< 1	0.15	0.11
Methacrolein	0.001	0.11	--	0.004	< 0.0001	< 0.0001	--	--
Alkyl Thiols	9.0	6.8	6.1	< 0.05	1.04	1.15	7.3	< 0.05
Hydrogen Sulfide	0.5	152	334	0.53	300	0.16	6570	< 0.05
Copper (µg/m3)	73	< 30	--	250	< 30	< 30	< 20	< 20

Table IV-11: Benzene Average and High Values in Natural Gas and Landfill Biogas Samples (ppmv)

	Pipeline Quality Natural Gas	Landfills		
		Biogas	USEPA 2008	Biomethane
Mean[1]	13.4	1.7	2.4	< 1
Highest Site Value	38.6	3	22	< 1
Sites Sampled	8	6	41	7

Table IV-12: Alkyl Thiols Average and High Values in Natural Gas and Dairy Biogas Samples (ppmv)

	Pipeline Quality Natural Gas	Dairy	
		Biogas	Biomethane
Mean	2.1	2.7	< 0.05
Highest Site Value	9.0	7.3	< 0.05
Sites Sampled	7	12	3

Table IV-13: Final Constituents of Concern List

Alkyl Thiols (Mercaptans)
Antimony
Arsenic
Copper
p-Dichlorobenzene
Ethylbenzene
Hydrogen Sulfide
Lead
Methacrolein
n-Nitroso-di-n-Propylamine
Toluene
Vinyl Chloride

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[1] Mean of site means for landfills, and mean of 8 different sources of natural gas.

C. Health Protective Levels for the Constituents of Concern

Health-protective concentrations for the constituents of concern may be defined by using the above exposure and risk formulae along with target (i.e., acceptable) risk levels. OEHHA staff based the risk levels on the values that have been typically used by the Air Pollution Control Districts for risk management under the California Air Toxics "Hotspots" program: a lifetime cancer risk of 1E-5 (10 chances per million) for exposure to carcinogens, and a hazard index of 1.0 for non-cancer effects. Since there are several biogas constituents of concern, the potential for additive risks was taken into consideration. Thus, the target risk levels for calculating health protective levels were set at:

- An HQ of 0.1 for non-cancer risks for the general population, and of 3.0 for the unprotected worker scenario
- A lifetime additional risk of 1E-6 (1 chance per million) for cancer risks for the general population, and 3E-5 (30 chances per million) for the unprotected worker scenario

The resulting health-protective concentration levels for the constituents of concern are presented in Table IV-14.

Table IV-14: Health Protective Concentrations for Constituents of Concern in Biomethane[26]

Based on Cancer Risks		
Constituent	**Biomethane Concentration Level (mg/m³)**	
	Residential Leak (1E-6)	**Worker Exposure Scenario (1E-5)**
Arsenic[27]	0.019	0.032
Ethylbenzene	26	44
p-Dichlorobenzene	5.7	10
n-Nitroso-di-n-propylamine	0.033	0.055
Vinyl Chloride	0.84	1.4
Based on Chronic Non-Cancer Risks		
Constituent	**Biomethane Concentration Level (mg/m³)** (in ppm for thiols group)	
	Residential Leak (HQ = 0.1)	**Worker Exposure Scenario (HQ = 3.0)**
Antimony	0.60	1.3
Copper	0.060	0.13
Hydrogen Sulfide	30	67
Lead	0.075	0.17
Methacrolein	1.1	2.4
Alkyl Thiols (Mercaptans)[28]	12 ppm	27 ppm
Toluene	904	2018

References

(OEHHA, 2012) "Air Toxics Hot Spots Program Risk Assessment Guidelines, Technical Support Document, Exposure Assessment and Stochastic Analysis, Final" August 2012.

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[26] Assumes that the source concentrations are decreased by the exposure adjustment factors 3.3E-5 and 4.46E-4, respectively, for modeled residential leak and worker exposures.

[27] Residential and worker concentration limits for arsenic based on non-cancer effects would have been 0.045 and 0.10 mg/m³, respectively.

[28] Total of alkyl mercaptans including methyl mercaptan and i-propyl mercaptan.

V.   RECOMMENDATIONS TO THE CPUC

In this chapter, we recommend health-based standards and associated monitoring, testing, reporting and recordkeeping requirements for biomethane injected into a common carrier natural gas pipeline ("pipeline") in California.

A. Risk Management – Identification of Health-Protective Standards

As specified in AB 1900, ARB staff is to provide recommendations to the CPUC on health based standards for biomethane. The standards should identify constituents of concern found in biogas and identify concentration limits for these constituents of concern necessary to protect public health. ARB staff's recommended health based standards rely on OEHHA's risk analysis presented in Chapter IV and a risk management decision-making approach consistent with ARB's Risk Management Guidelines for New and Modified Sources of Toxic Air Pollutants (Risk Management Guidelines or Guidelines). (ARB, 1993)

The Risk Management Guidelines were approved by the ARB in 1993. The approach outlined in the Guidelines continues to be used today by ARB and the local air pollution control and air quality management districts when making risk management decisions about sources of toxic air contaminants. The Guidelines identify trigger levels and lower and upper action levels for potential cancer risk and total non-cancer hazard indexes to be considered when approving a permit. The Guidelines' risk levels reflect the uncertainty and variability in risk assessments and provide public health protection. These are summarized in Table V-1 below.

Table V-1: Risk Management Guidelines Cancer and Non-Cancer Risk Thresholds

Risk Management Levels		Potential Cancer Risk (Chances in a million)	Non-Cancer Total Hazard Index	Permitting Action
Trigger Level		1	0.2	Approve
Action Range:	Lower Level	10	1	Approve with Best Available Control Technology
	Upper Level	100	10	Deny

ARB staff is proposing a similar approach as used in the Guidelines for the biomethane health standards. Table V-2 lists the recommended risk management levels for the constituents of concern and also briefly summarizes the actions that would be taken at each risk management level. These actions are briefly described below and in more detail in Section B that follows.

Table V-2: ARB Staff Recommended Cancer and Non-Cancer Risk Management Thresholds for Biomethane Constituents of Concern

Risk Management Levels		Potential Cancer Risk (Chances in a million)	Non-Cancer Total Hazard Index	Action
Trigger Level		$\geq 1^a$	$\geq 0.1^a$	Routine Monitoring Required
Action Range:	Lower Level	$\geq 10^b$	$\geq 1^b$	After 3 exceedances in 12-month period, shut off & repair
	Upper Level	$\geq 25^c$	$\geq 5^c$	Immediate shut off and repair

a. For any single compound
b. Sum of all compounds exceeding the trigger level
c. Any single compound or sum of all compounds exceeding the trigger level
d. *The trigger level is applied to an individual constituent of concern whereas the lower and upper levels are based on the sum of the potential cancer risk or hazard quotient for all the constituents of concern present at levels above the trigger level.

As shown in Table V-2, ARB staff modified the non-cancer trigger level for an individual compound from 0.2 in the Guidelines to 0.1. This change was made to be consistent with OEHHA's recommended health values. ARB staff also changed the upper level cancer action range from 100 to 25 and the upper level non-cancer action range from 10 to 5. These changes provide an additional margin of safety and are more closely aligned with local air district requirements.[29]

Briefly, the approach used by ARB staff for risk management was to use the OEHHA health protective levels as the "trigger" for requiring routine monitoring of a constituent of concern. If an individual constituent of concern was determined to be present in the upgraded biomethane at a concentration that would result in either a potential cancer risk of ≥ 1 in a million or a hazard quotient of ≥ 0.1, then that constituent would be subject to quarterly monitoring. Upon each quarterly monitoring event, the operator is to determine the total potential cancer risk and hazard index for the constituents of concern subject to monitoring and verify if the risk levels are below the lower action level (potential cancer risk ≥ 10 in a million or a HI of ≥ 1). If the total risk levels exceed the lower action levels 3 times in a 12-month period, the biomethane flow to the pipeline would be shut off (typically diverted to a flare) and the operator would need to determine how to bring the measured levels in the biomethane to below the lower action level. If at any time the total potential cancer risk or hazard index for the constituents of concern subject to monitoring were to exceed the upper action level (potential cancer risk ≥ 25 in a million or a HQ ≥ 5) the facility would also be subject to shut down.

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[29] South Coast Air Quality Management District's Rule 1402 has a maximum allowable hazard quotient of 5.

In the following sections, additional detail is provided on the monitoring, testing, reporting and recordkeeping requirements recommended by ARB staff.

B. Monitoring and Testing Requirements

ARB staff's recommended monitoring and testing requirements are based on the risk range that the constituents of concern fall under. Quarterly monitoring is recommended for any constituents of concern that exceed the trigger level identified for that compound. Operators are then required to determine the total potential cancer and non-cancer risks for all the constituents of concern that are subject to quarterly monitoring. If the combined risk exceeds the upper action level, or the lower action level three times in a 12-month period, then the flow to the pipeline must be shut off.

The constituents of concern that must be measured depend on the biogas source. In Table V-3, the constituents of concern for the three sources of biogas are noted with a checkmark, along with the trigger levels for each compound. As can be seen, landfill biomethane is to be evaluated for the presence of all 12 constituents of concern, while for POTWs there are six, and for dairies there are five.

For the AB 1900 effort, ARB staff established the recommended health based standards for individual compounds based on the potential residential exposures. This is because the residential exposures, estimated based on the health risk assessment, resulted in the highest risk values (as shown in Chapter IV, Table IV-14), and controlling emissions to protect the residential user will also protect the utility worker[30].

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[30] These biomethane standards will not address worker exposure to raw biogas, which could occur at a biomethane production facility, a facility that converts raw biogas to energy on-site, a landfill gas collection system, or any facility that produces biogas. These workers would, however, be covered by OSHA standards.

Table V-3: Recommended Risk Management Levels for Constituents of Concern

Constituent of Concern	Risk Management Levels (Health Based Standards) mg/m^3 (ppmv)			Source Specific Constituents of Concern		
	Trigger Level	Lower Action Level	Upper Action Level	Land-fills	POTW	Dairy
Carcinogenic Constituents of Concern						
Arsenic	0.019 (0.006)	0.19 (0.06)	0.48 (0.15)	✓		
p-Dichlorobenzene	5.7 (0.95)	57 (9.5)	140 (24)	✓	✓	
Ethylbenzene	26 (6.0)	260 (60)	650 (150)	✓	✓	✓
n-Nitroso-di-n-propylamine	0.033 (0.006)	0.33 (0.06)	0.81 (0.15)	✓		✓
Vinyl Chloride	0.84 (0.33)	8.4 (3.3)	21 (8.3)	✓	✓	
Non-carcinogenic Constituents of Concern						
Antimony	0.60 (0.12)	6.0 (1.2)	30 (6.1)	✓		
Copper	0.060 (0.02)	0.60 (0.23)	3.0 (1.2)	✓		
Hydrogen Sulfide	30 (22)	300 (216)	1,500 (1,080)	✓	✓	✓
Lead	0.075 (0.009)	0.75 (0.09)	3.8 (0.44)	✓		
Methacrolein	1.1 (0.37)	11 (3.7)	53 (18)	✓		
Alkyl thiols (mercaptans)	N/A (12)	N/A (120)	N/A (610)	✓	✓	✓
Toluene	904 (240)	9,000 (2,400)	45,000 (12,000)	✓	✓	✓

ARB staff recommends that initial monitoring be conducted prior to the first injection of biomethane into the pipeline, and then periodic testing be performed The frequency of the periodic testing would be dependent on whether the individual constituents are above the trigger levels, and the total potential cancer and non-cancer risks associated with all the constituents of concern above the trigger levels.

Monitoring for hydrogen sulfide and mercaptans represents a special situation because the utility companies already closely monitor these compounds. For hydrogen sulfide, this is due to health and safety concerns, and its corrosive properties in pipelines. For mercaptans, monitoring is done to ensure that proper odorant levels are maintained. Utility gas quality specifications in tariff rules (e.g., PG&E Rule 21, SoCal Gas Rule 30)

require lower levels for both of these compounds than the "trigger" levels specified above in Table V-3. For example, both PG&E and SoCal Gas tariffs prohibit hydrogen sulfide levels exceeding 4 ppm (compared to 22 ppm listed in Table V-3). Similarly, PG&E and SoCal Gas tariffs prohibit mercaptan levels (as sulfur) above 8 and 5 ppm, respectively, compared to 12 ppm in Table V-3. Furthermore, the utilities measure these compounds more frequently than the recommendations for constituents of concern discussed here. The utilities continuously measure for hydrogen sulfide from sources containing this compound, which covers most sources of pipeline gas. For mercaptans, an odorant "smell" test is performed periodically (monthly for SoCal Gas) to ensure that the gas is properly odorized. In addition, instrument-based testing is sometimes used to ensure that mercaptan levels are not too high. Given that the utility tariff levels are below the trigger levels specified above, we recommend that existing monitoring procedures used to ensure compliance with tariff requirements be used to satisfy the monitoring procedures that we are recommending, as long as the monitoring is conducted at least as frequently.

Pre-Injection Startup Testing

Prior to injecting biomethane into the pipeline, a representative sample of the biomethane should be tested for the constituents of concern specific to that biogas source (as noted in Table V-3) to determine the presence of constituents above detection levels, and where found, the associated concentrations of constituents. The recommended test methods are provided in Table V-4. ARB staff recommends that two tests be conducted over a 2-4 week period once the production facility is operational and prior to when the biomethane is first injected into the pipeline to ensure the stability and performance of the upgrading system.

The utility and the biomethane production facility should agree upon a continuous monitoring method to verify that the upgrading process is operating effectively. If a monitoring method cannot be agreed upon, then we recommend that the tariff requirements for natural gas be used as an indicator that the upgrading system is operating effectively. For biomethane injection facilities in other states, only the natural gas tariff requirements are monitored (with some exceptions for siloxanes and a few other compounds, depending on the project).

Table V-4: Recommended Test Methods for Constituents of Concern

Constituent of Concern	Test Method
Metals	
Lead, Antimony, Arsenic and Copper	EPA Method 29 (AAS and/or ICP), EPA 200.8
Nitroso Compounds	
n-Niroso-di-n-Propylamine	EPA Method 8270 (GC/MS)
Sulfur Compounds	
Hydrogen Sulfide	ASTM D4084, D7165, D7493 (online monitoring), ASTM D5504, D6228 (lab)
Total Mercaptans	ASTM D7165, D7493 (online monitoring), ASTM D5504, D6228
SVOCs, VOCs, and Alkyl Benzenes	
p-Dichlorobenzene, Vinyl Chloride, Methacrolein, Ethylbenzene, and Toluene	TO-15 (GC/MS), TO-11A for Methacrolein (Determination of Formaldehyde Adsorbent Cartridge (HPLC))

During the pre-injection testing, if any constituent of concern in the biomethane is found to be above the lower action level, as listed in Table IV-3, then the biomethane cannot be injected into the natural gas pipeline and the operator should make modifications to the upgrading system to lower the concentrations of the constituent of concern to levels below the lower action level.

If all the constituents of concern in the biomethane are found to be below the detection level, or measured in concentrations below the lower action level in both pre-injection tests, then the biomethane may be injected into the common carrier pipeline, subject to compliance with the periodic testing requirements specified below. It is important to note, that these testing requirements do not supersede any other requirements relating to pipeline integrity, heating value, and other requirements not related to health-based standards.

Repeat of pre-injection startup testing for all the constituents of concern should be conducted with some slight modifications when:

- A change in biogas source at the facility or upgrading equipment design that the CPUC, in consultation with the ARB and OEHHA, determines will potentially increase the level of any constituent of concern over the previously measured baseline levels. Replacing a component with a functionally-equivalent component should not constitute a change in equipment design.

- Shut-off of biomethane to the pipeline due to testing that indicates a total potential cancer or non-cancer risk for the constituents of concern in biomethane

above the upper action level, or 3 exceedances of the lower action level in a 12 month period.

Under a modified startup procedure, it would not be necessary to conduct two tests over a 2-4 week period prior to reintroducing the biomethane into the pipeline. If the first test demonstrates that all the constituents are below the LAL then injection can resume and it is not necessary to retest prior to injection. However, all the constituents of concern would be reevaluated with regard to periodic testing. This would mean compounds that may have been tested biennially (because they were found to be below a trigger level twice in annual testing) or annually (because the compound is part of a group of compounds whose collective risk below the lower action level four consecutive times – see group 2 compounds below) would have to again go through the testing required to demonstrate eligibility for less frequent testing.

<u>Periodic Testing of Constituents of Concern</u>

Representative samples of the biomethane being injected into a natural gas common carrier pipeline should be periodically tested for constituents of concern using the test methods specified in Table V-4 according to the frequencies specified below.

- Constituents of concern not found above test method detection levels in biomethane or below the trigger level (i.e., group 1 compounds) should be monitored at least once for every 12 months of injection into the common carrier pipeline. Individual constituents found to be below trigger levels during two consecutive annual tests can then be tested once every two years.
- Any constituents of concern found at or above the trigger level for that constituent of concern (i.e., group 2 compounds) should be monitored quarterly (at least once every 3 months of injection into the common carrier pipeline) and the total potential cancer risk and non-cancer risk estimated.

  ✓ The total potential cancer risk for group 2 compounds can be estimated by summing the individual potential cancer risk for each carcinogenic constituent of concern found in Table V-3. Specifically, the cancer risk can be calculated using the ratio of the concentration of the constituent in biomethane to the health protective ("trigger") concentration value corresponding to one in a million cancer risk for that specific constituent found in Table VI-3, and then summing the risk for all the group 2 constituents. To calculate the total non-cancer chronic risk, the process is similar. The risk can be calculated using the ratio of the concentration of the constituent in biomethane to the health protective concentration value corresponding to a hazard quotient of 0.1 for that specific noncarcinogenic constituent found inTable V-3, then multiplying the ratio by 0.1, and then summing the noncancer chronic risk for all these group 2 constituents. ARB staff will develop a spreadsheet tool that biomethane producers can use to calculate the combined cancer or noncancer chronic risk.

- ✓ If the quarterly testing over a 12 month period demonstrates that an individual constituent of concern within the group 2 compounds is below the trigger level four consecutive times, then monitoring for that constituent can be reduced to once every 12 months of injection.
- ✓ If the quarterly testing over a 12 month period demonstrates that the total potential cancer risk or non-cancer risks for the group 2 constituents being monitored is at a level below the lower action level, monitoring can be reduced to once for every 12 months of injection for all the constituents of concern.

- If, in a 12 month period, there are three exceedances of the lower action level for the constituents of concern (with the exceedances being lower than the upper action level), the operator will shut off the supply of the biomethane and determine necessary adjustments to bring the potential cancer and non-cancer risks for the constituents of concern to levels below the lower action level.
- If any test result indicates the potential cancer or non-cancer risks for the constituents of concern is above the upper action level, the operator will shut off the supply of the biomethane to the pipeline and determine necessary adjustments/modifications to bring the potential cancer and non-cancer risk levels to below the lower action level.

A flow chart depicting the recommended monitoring plan is provided in Figure V-1. Note that the flow chart and above description is meant to provide a general structure for monitoring procedures. It does not address all potential testing scenarios. For example, a group 1 compound subject to annual or biennial testing, could subsequently revert to quarterly testing if it is monitored and found above the trigger level.

Figure V-1: Flowchart of ARB Staff Recommended Monitoring for Constituents of Concern
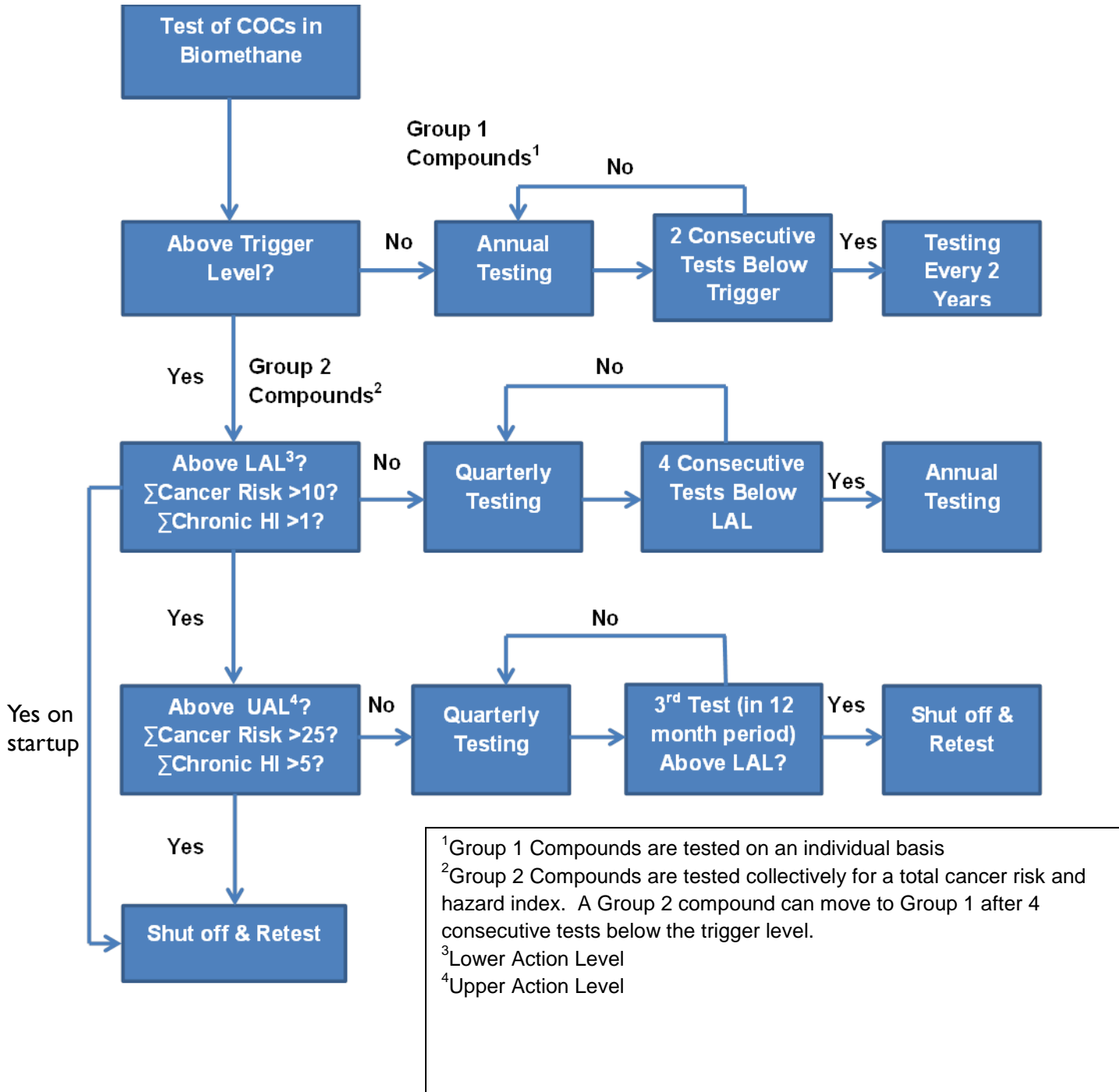
Based on the available data, for most biomethane projects it is unlikely that the constituents of concern will be above the trigger level. In Table V-5, we provide a comparison of the trigger level, lower action level, and the maximum concentration that was noted for each biomethane source in the data analyzed. As can be seen, for most compounds, the maximum values found are well below the trigger levels. In all cases, the maximum levels are below the lower action level which indicates that from a public health perspective, the injection of biomethane does not present additional health risk as compared to natural gas. For hydrogen sulfide, the high level noted in Table V-5 (187 ppm) is an anomaly because the raw biogas at this site was subjected to only partial clean up and was not intended to produce a pipeline quality product gas.

Based on the data in Table V-5, and the testing recommended in this document, we do not believe more frequent testing by the utilities should be necessary to demonstrate compliance with the recommended risk management strategy, except in special situations where the CPUC, in consultation with ARB and OEHHA, agree that more frequent monitoring is appropriate. We also believe that any additional utility testing should count toward the periodic testing requirements recommended here.

Table V-5: Comparison of Trigger Level, Lower Action Level and Observed Maximum Biomethane Concentrations for the Constituents of Concern

Constituent	Trigger Level OEHHA Health Protective Limit (ppm)	Risk Mgmt. Lower Action Level Standard (ppm)	Landfill Maximum (ppm)	Dairy Maximum (ppm)	POTW Maximum (ppm)
Vinyl Chloride	0.33	3.30	0.330	BDL*	BDL
Dichlorobenzenes (as p-Dichlorobenzene)	0.95	9.47	0.002	BDL	BDL
n-Nitroso-di-n-propylamine	0.006	0.06	BDL	0.004	BDL
Ethylbenzene	6	60	0.001	0.003	
Arsenic	0.006	0.06	BDL	BDL	BDL
Hydrogen Sulfide	22	216	0.530	BDL	187**
Antimony	0.12	1.2	0.006	BDL	BDL
Methacrolein	0.37	3.7	0.004	BDL	BDL
Toluene	240	2400	1.4	0.11	31**
Alkyl thiols (Mercaptans)	12	120	BDL	BDL	1.15**
Copper	0.02	0.23	0.096	BDL	BDL
Lead	0.009	0.09	0.018	BDL	BDL

*BDL= Below detection level.

** Each of these values were from biogas that was only subject to partial cleanup and not intended for pipeline injection.

We believe that copper merits some additional evaluation. Copper was not found in any of the raw biogas samples analyzed, and only in a few of the biomethane samples in a 2009 GTI report (GTI, 2009). Furthermore, it was found in one of the field blanks in a 2012 GTI report (GTI, 2012). This raises the possibility that it was introduced in either the upgrading equipment or the sampling apparatus used for testing. We intend to further investigate copper as the CPUC rulemaking progresses to determine whether it is appropriate to require monitoring of this compound, or if the risk management approach needs to be adjusted.

C. Reporting and Recordkeeping Requirements

AB 1900 directs Air Resources Board staff to provide recommendations on reporting and recordkeeping requirements. Discussed below are our general recommendations. Our expectation is that some of the details would be further developed through the CPUC regulatory process to ensure that the recordkeeping and reporting associated with ensuring public health aligns with the requirements to ensure pipeline integrity. Our recommendations are summarized below:

- Biomethane producers ("producers") shall notify the CPUC (and the CPUC shall notify the ARB and OEHHA) within 30 days of the date when they first inject into the natural gas common carrier pipeline, the producer company name, contact person, location of facility and injection point.
- The testing entity (utility or producer) shall provide the CPUC (and the CPUC shall provide the ARB and OEHHA) with the "Startup Testing" results (concentrations of constituents of concern and associated test methods and concentrations of any additional constituents beyond those recommended in this document, if applicable) within 30 days of receiving the test data. The testing entity will also note whether monitoring and recordkeeping of hydrogen sulfide and mercaptans conducted subject to utility tariff requirements will be used to meet the monitoring and recordkeeping recommended in this document for constituents of concern.
- The testing entity (utility or producer) shall maintain records of all test results (concentrations of constituents of concern and associated test methods) for at least 3 years from the date when the tests were conducted. These records would not be required for hydrogen sulfide and mercaptans when these compounds are monitored continuously, or more frequently than recommended for constituents of concern in this document, and are subject to utility tariff monitoring and reporting requirements.
- The producers and utility shall provide an annual report to the CPUC (and the CPUC shall provide the report to ARB and OEHHA) containing the following information:
  - ✓ All test data (concentrations of constituents of concern and identification of associated test methods) received during the report period
  - ✓ Annual biomethane production rate
  - ✓ Monitoring parameters used to ensure that the upgrading system is operating effectively

- ✓ Dates of any shutoff events, the reason for the shutoff, the actions taken to resume injection into the pipeline, and the start of re-injection into the pipeline (if applicable).
- If the utility is the testing entity, the utility shall provide the following test data to the producer:
  - ✓ Test results of constituents of concern within two weeks of receiving the data
  - ✓ Test results of constituents of concern within 24 hours of receiving the data when it results in shutoff of biomethane to the pipeline.
- If the producer is the testing entity, the producer shall provide the above information to the utility.

References

(ARB, 1993) Risk Management Guidelines for New and Modified Sources of Toxic Air Pollutants, California Air Resources Board, July 1993.
http://www.arb.ca.gov/diesel/documents/rmg793.pdf

(GTI, 2009) "Pipeline Quality Biogas: Guidance Document for Dairy Waste, Wastewater Treatment Sludge and Landfill Conversion, Final Reports: Tasks 1, 2, 3, and 4," Gas Technology Institute, December 2009.

(GTI, 2012) "Guidance Document for the Introduction of Landfill-Derived Renewable Gas into Natural Gas Pipelines," Gas Technology Institute, 2009.

APPENDIX A

AB 1900

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Assembly Bill No. 1900

CHAPTER 602

An act to amend Section 25420 of, and to repeal and add Section 25421 of, the Health and Safety Code, to add Section 25326 to the Public Resources Code, and to add Sections 399.24 and 784 to the Public Utilities Code, relating to energy.

[Approved by Governor September 27, 2012. Filed Secretary of State September 27, 2012.]

BILL TEXT
THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1.
Section 25420 of the Health and Safety Code is amended to read:

25420.
For purposes of this chapter, the following definitions apply:

(a) "Biogas" means gas that is produced from the anaerobic decomposition of organic material.

(b) "Biomethane" means biogas that meets the standards adopted pursuant to subdivisions (c) and (d) of Section 25421 for injection into a common carrier pipeline.

(c) "Board" means the State Air Resources Board.

(d) "CalRecycle" means the Department of Resources Recycling and Recovery.

(e) "Commission" means the Public Utilities Commission.

(f) "Common carrier pipeline" means a gas conveyance pipeline, located in California, that is owned or operated by a utility or gas corporation, excluding a dedicated pipeline.

(g) "Dedicated pipeline" means a conveyance of biogas or biomethane that is not part of a common carrier pipeline system, and which conveys biogas from a biogas producer to a conditioning facility or an electrical generation facility.

(h) "Department" means the Department of Toxic Substances Control.

(i) "Gas corporation" has the same meaning as defined in Section 222 of the Public Utilities Code and is subject to rate regulation by the commission.

(j) "Hazardous waste landfill" means a landfill that is a hazardous waste facility, as defined in Section 25117.1.

(k) "Office" means the Office of Environmental Health Hazard Assessment.

(l) "Person" means an individual, trust, firm, joint stock company, partnership, association, business concern, limited liability company, or corporation. "Person" also includes any city, county, district, and the state or any department or agency thereof, or the federal government or any department or agency thereof to the extent permitted by law.

SEC. 2.
Section 25421 of the Health and Safety Code is repealed.

SEC. 3.
Section 25421 is added to the Health and Safety Code, to read:

25421.
(a) On or before May 15, 2013, all of the following shall be completed:

(1) The office, in consultation with the board, the department, CalRecycle, and the California Environmental Protection Agency, shall compile a list of constituents of concern that could pose risks to human health and that are found in biogas at concentrations that significantly exceed the concentrations of those constituents in natural gas. The office, in consultation with the board, the department, CalRecycle, and the California Environmental Protection Agency, shall update this list at least every five years.

(2) The office shall determine health protective levels for the list of constituents of concern identified pursuant to paragraph (1). In determining those health protective levels, the office shall consider potential health impacts and risks, including, but not limited to, health impacts and risks to utility workers and gas end users. The office shall update these levels at least every five years.

(3) The board shall identify realistic exposure scenarios and, in consultation with the office, shall identify the health risks associated with the exposure scenarios for the constituents of concern identified by the office pursuant to paragraph (1). The board shall update the exposure scenarios, and, in consultation with the office, the health risks associated with the exposure scenarios, at least every five years.

(4) Upon completion of the responsibilities required pursuant to paragraphs (1) through (3), the board, in consultation with the office, the department, CalRecycle, and the California Environmental Protection Agency shall determine the appropriate concentrations of constituents of concern. In determining those concentrations, the board shall use the health protective levels identified pursuant to paragraph (2) and the exposure scenarios identified pursuant to paragraph (3). The concentrations shall be updated at least every five years by the board in consultation with the office, the department, CalRecycle, and the California Environmental Protection Agency.

(5) The board, in consultation with the office, the department, CalRecycle, and the California Environmental Protection Agency, shall identify reasonable and prudent monitoring, testing, reporting, and recordkeeping requirements, separately for each source of biogas, that are sufficient to ensure compliance with the health protective standards adopted pursuant to subdivision (d). The board, in consultation with the office, the department, CalRecycle and the California Environmental Protection Agency shall update the monitoring, testing, reporting, and recordkeeping requirements at least every five years.

(b) Actions taken pursuant to subdivision (a) shall not constitute regulations and shall be exempt from the administrative regulations and rulemaking provisions of the Administrative Procedure Act (Chapter 3.5 (commencing with Section 11340) of Division 2 of Title 2 of the Government Code).

(c) On or before December 31, 2013, for biomethane that is to be injected into a common carrier pipeline, the commission shall, by rule or order, adopt standards that specify, for constituents that may be found in that biomethane, concentrations that are reasonably necessary to ensure both of the following:

(1) The protection of human health. In making this specification, the commission shall give due deference to the determinations of the board pursuant to paragraph (4) of subdivision (a).

(2) Pipeline and pipeline facility integrity and safety.

(d) To ensure pipeline and pipeline facility integrity and safety, on or before December 31, 2013, the commission, giving due deference to the board's determinations, shall, by rule or order, adopt the monitoring, testing, reporting, and recordkeeping requirements identified pursuant to paragraph (5) of subdivision (a).

(e) Every five years, or earlier if new information becomes available, the commission shall review and update the standards for the protection of human health and pipeline integrity and safety adopted pursuant to subdivision (c), as well as the monitoring, testing, reporting, and recordkeeping requirements adopted pursuant to subdivision (d).

(f) (1) A person shall not inject biogas into a common carrier pipeline unless the biogas satisfies both the standards set by the commission pursuant to subdivision (c), as well as the monitoring, testing, reporting, and recordkeeping requirements of subdivision (d).

(2) The commission shall require gas corporation tariffs to condition access to common carrier pipelines on the applicable customer meeting the standards and requirements adopted by the commission pursuant to subdivisions (c) and (d).

(g) (1) A person shall not knowingly sell, supply, or transport, or knowingly cause to be sold, supplied, or transported, biogas collected from a hazardous waste landfill to a gas corporation through a common carrier pipeline.

(2) A gas corporation shall not knowingly purchase gas collected from a hazardous waste landfill through a common carrier pipeline.

SEC. 4.
Section 25326 is added to the Public Resources Code, to read:

25326.
(a) The commission shall hold public hearings to identify impediments that limit procurement of biomethane in California, including, but not limited to, impediments to interconnection. The commission shall offer solutions to those impediments as part of the integrated energy policy report prepared pursuant to Section 25302.

(b) For the purposes of this section, "biomethane" means biogas that meets the standards adopted pursuant to subdivisions (c) and (d) of Section 25421 of the Health and Safety Code for injection into a common carrier pipeline.

SEC. 5.
Section 399.24 is added to the Public Utilities Code, to read:

399.24.
(a) To meet the energy and transportation needs of the state, the commission shall adopt policies and programs that promote the in-state production and distribution of biomethane. The policies and programs shall facilitate the development of a variety of sources of in-state biomethane.

(b) For the purposes of this section, "biomethane" means biogas that meets the standards adopted pursuant to subdivisions (c) and (d) of Section 25421 of the Health and Safety Code for injection into a common carrier pipeline.

SEC. 6.
Section 784 is added to the Public Utilities Code, to read:

784.
For each gas corporation, the commission shall adopt pipeline access rules that ensure that each gas corporation provides nondiscriminatory open access to its gas pipeline system to any party for the purposes of physically interconnecting with the gas pipeline system and effectuating the delivery of gas.

SEC. 7.
This act shall become operative only if this act and Assembly Bill 2196 of the 2011–12 Regular Session are both enacted and become effective on or before January 1, 2013.

SEC. 8.
No reimbursement is required by this act pursuant to Section 6 of Article XIIIB of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIIIB of the California Constitution.

APPENDIX B

Lists of Constituents

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Appendix B
Lists of Constituents and Chemical Groups Found in Biogas
and Natural Gas Sources

Appendix B provides a compilation of the list of constituents identified by ARB and OEHHA staff as present or likely to be present in biogas derived from landfills, dairies, and POTWs. The constituents are provided in four tables, B-1 through B-4, and are based upon information reported in the environmental science literature, as well as government and industry reports. Additional data for biogas from municipal landfills, wastewater treatment, and natural gas was obtained from biogas-related businesses operating in the United States.

The list of identified constituents was divided into tables based upon the sources from which the information was obtained. Table B-1 contains chemicals and chemical groups that have been identified in recent analyses of biogas samples in the United States by the Gas Technology Institute, and using additional California-specific data for landfills and POTWs. (GTI 2009 a, b, c, d; and GTI 2012, LACSD 2012; SCAQMD 2012; JWPCP 2011) As noted in Chapter II of this report, these were chosen as the primary quantitative data sources for the risk evaluation. Several of these studies also analyzed trace constituents in pipeline-quality natural gas and any unique chemicals found in the natural gas samples were included in the table. The "Table B-1" constituents were categorized into chemical groups for ease of review, as well as to assist in the risk evaluation. As is discussed in Chapter IV of this report, several of these groups are treated as sets of toxicologically similar chemicals and a single risk screening value is developed for them). The last section of Table B-1 contains a "group of groups," (Group 27). This is a list of various chemical categories that were reported in the reference studies but which were, for the most part, not used in the risk evaluation.

Table B-2 is compiled from municipal landfill gas data reported by the U.S. EPA (U.S. EPA 2008) and from a municipal landfill study by the United Kingdom Environment Agency (UKEA) (UKEA 2002). These were used as supplementary information sources in the risk evaluation. The biogas data reviewed in the U.S. EPA report was obtained mainly during the mid-1990s and early 2000s. The UKEA concentration data was from 2001 and 2002, although its list of trace constituents was based on a wider set of data including pre-1990s information from U.K. municipal landfills. Both the U.S. EPA and UKEA reports identified many of the same chemicals that have been found at municipal landfill sites in the "Table B-1" reference studies. However, they also listed a variety of chemicals that likely derive from microbial action upon materials such as papers, wood, foods, and other biological wastes. Table B-2 only includes the additional landfill gas constituents not already listed in Table B-1. These were also organized into chemical groups.

Table B-3 includes several additional biogas constituents that have been reported in the environmental science literature (Rasi 2009; Grumping, et al. 1999; Hensel, et al. 2000; Hirner, et al. 1994; Glindemann, et al. 2005). Finally, Table B-3 lists several chemicals that are likely to be produced upon combustion of biogas and will be evaluated in future

updates to these recommendations. The information from the academic studies was used primarily in a qualitative way, for example, to identify additional constituents that were not looked for in other studies, or else to confirm the identification of chemicals reported in the primary data sources.

Concentrations of constituents in biogas, biomethane and natural gas from the GTI datasets are provided in Table B-4. This is an Excel workbook containing individual worksheets for each set of gas data used in the health risk assessment of the individual constituents. Each worksheet contains data for individual constituent maximum concentrations from the specified data source and is separated by gas type (e.g. natural gas, raw dairy, clean dairy, etc.). Also included in the workbook are three additional sheets summarizing the maximum concentrations for each constituent in natural gas, raw biogas and cleaned (upgraded) biomethane.

(References noted in Appendix B are provided in Chapter II of the report)

Table B-1

Constituents and Chemical Groups Identified in Recent Samples of Biogas from Municipal Landfills, Wastewater Treatment Plants and Dairy Farms in the U.S. and California[31]

Group Number	Constituent	CAS
1	**Alkanes (C6 and lower)**	
	Ethane	74-84-0
	i-Butane	75-28-5
	i-Pentane	78-78-4
	Methane	74-82-8
	n-Butane	106-97-8
	n-Pentane	109-66-0
	Propane	74-98-6
2	**Alkanes (C7 and greater)**	
	2,2,4-Trimethylpentane	540-84-1
	n-Heptane	8031-33-2
3	**Alkanes (Cyclic)**	
	1-Ethyl-2-methylcyclohexane	3728-54-9
	Cyclohexane	110-82-7
	Cyclopentane	287-92-3
	Methylcyclohexane	108-87-2
	Methylcyclopentane	96-37-7
4	**Alkanes (Hexane-Like)**	
	3-Ethylhexane	619-99-8
	n-Hexane	110-54-3
5	**Alkenes and Dienes**	
	1,3-Butadiene	106-99-0
	Propene	115-07-1
8	**Alcohols**	
	Benzyl Alcohol	100-51-6
	Butanol	71-36-3
	Ethanol	64-17-5
9	**Ethers**	
	Tetrahydrofuran	109-99-9
10	**Aldehydes**	

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[31] Data sources: GTI 2009a, b, c, and d, GTI 2012, LACSD 2012; SCAQMD 2012; JWPCP 2011.

Group Number	Constituent	CAS
	Acetaldehyde	75-07-0
	Benzaldehyde	100-52-7
	Butanal	123-72-8
	Hexanaldehyde	66-25-1
	Pentanaldehyde (Valeraldehyde)	110-62-3
	Propionaldehyde	123-38-6
	p-Tolualdehyde	104-87-0
11	**Ketones**	
	2-Butanone	78-93-3
	Acetone	67-64-1
	Methyl Isobutyl Ketone (MIBK)	108-10-1
15	**Benzenes (monoalkyl)**	
	Ethylbenzene	100-41-4
	Isopropylbenzene (cumene)	98-82-8
	n-Butylbenzene	104-51-8
	n-Propylbenzene	103-65-1
	sec-Butylbenzene	135-98-8
	t-Butylbenzene	98-06-6
	Toluene	108-88-3
16	**Benzenes (polyalkyl)**	
	1,2,4-Trimethylbenzene	95-63-6
	1,3,5-Trimethylbenzene	108-67-8
	4-Ethyltoluene	622-96-8
	m/p-Xylenes	179601-23-1
	m-Xylene	108-38-3
	o-Xylene	95-47-6
	p-Isopropyltoluene (Cymene)	99-87-6
	p-Xylene	106-42-3
	Xylene (mixed isomers)	1330-20-7
17	**Benzenes (styrenes)**	
	Styrene	100-42-5
18	**Benzenes (chlorinated)**	
	1,2,3-Trichlorobenzene	87-61-6
	1,2,4-Trichlorobenzene	120-82-1
	1,2-Dichlorobenzene	95-50-1
	1,3-Dichlorobenzene	541-73-1
	1,4-Dichlorobenzene	106-46-7
	Chlorobenzene	108-90-7

Table B-1 (continued)

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Table B-1 (continued)		
Group Number	**Constituent**	**CAS**
	Chlorofluorocarbons (CFCs)	
	1,2-Dichlorotetrafluoroethane (CFC-114)	76-14-2
	Dichlorodifluoromethane	75-71-8
	Trichlorofluoromethane (Freon 11)	75-69-4
20	**Alkyl Thiols**	
	Ethyl Mercaptan	75-08-1
	i-Propyl Mercaptan	75-33-2
	Methyl Mercaptan	74-93-1
	n-Propyl Mercaptan	107-03-9
	t-Butyl Mercaptan	75-66-1
21	**Alkyl Sulfides**	
	Carbon Disulfide	75-15-0
	Carbonyl Sulfide	463-58-1
	Diethyl Disulfide	110-81-6
	Dimethyl Disulfide	624-92-0
	Dimethyl Sulfide	75-18-3
	Dimethyl Trisulfide	3658-80-8
	Methyl Ethyl Sulfide	625-80-9
	Tetrahydrothiophene	110-01-0
22	**Organosilicon Compounds**	
	Decamethylcyclopentasiloxane (D5)	541-02-6
	Decamethyltetrasiloxane (L4)	141-62-8
	Hexamethylcyclotrisiloxane (D3)	541-05-9
	Hexamethyldisiloxane (L2)	107-46-0
	Octamethylcyclotetrasiloxane (D4)	556-67-2
	Octamethyltrisiloxane (L3)	107-51-7
23	**Volatile Organics (VOCs)**	
	1,1,1-Trichloroethane	71-55-6
	1,1,2,2-Tetrachloroethane	79-34-5
	1,1,2-Trichloroethane	79-00-5
	1,1-Dichloroethane	75-34-3
	1,1-Dichloroethene	75-35-4
	1,2-Dibromoethane	106-93-4
	1,2-Dichloroethane	107-06-2
	1,2-Dichloroethylene	540-59-0
	1,2-Dichloropropane	78-87-5
	1,4-Dioxane	123-91-1
	1-Bromo-2-methylpropane	78-77-3

Table B-1 (continued)		
Group Number	Constituent	CAS
	2-Chlorotoluene	95-49-8
	2-Methyl-1-nitropropane	625-74-1
	4-Chlorotoluene	106-43-4
	Acetonitrile	75-05-8
	Acrolein	107-02-8
	Acrylonitrile	107-13-1
	Allyl Chloride	107-05-1
	Benzene	71-43-2
	Benzyl Chloride	100-44-7
	bis(2-Chloroethyl)ether	111-44-4
	bis(2-Chloroisopropyl)ether	108-60-1
	Bromodichloromethane	75-27-4
	Bromomethane	74-83-9
	Carbon Tetrachloride	56-23-5
	Chloroform	67-66-3
	Chloromethane	74-87-3
	Chloroprene	126-99-8
	cis-1,2-Dichloroethylene	156-59-2
	Crotonaldehyde	123-73-9
	Dibromochloromethane	124-48-1
	Epichlorohydrin	106-89-8
	Ethyl Acetate	141-78-6
	Ethyl Chloride	75-00-3
	Ethylene Oxide	75-21-8
	Formaldehyde	50-00-0
	Methacrolein	78-85-3
	Methylene Chloride	75-09-2
	Methyl-t-Butyl Ether (MTBE)	1634-04-4
	Perchloroethane	98299-61-7
	Phosgene	75-44-5
	Propylene Oxide	75-56-9
	Tetrachloroethylene	127-18-4
	trans-1,2-Dichloroethene	156-60-5
	trans-1,3-Dichloropropene	10061-02-6
	Tribromomethane (Bromoform)	75-25-2
	Trichloroethylene	79-01-6
	Vinyl Acetate	108-05-4
	Vinyl Chloride	75-01-4

Group Number	Constituent	CAS
	Table B-1 (continued)	
	Semivolative Organics (SVOCs)	
	1-Methylnaphthalene	90-12-0
	2,4-Dimethylphenol	105-67-9
	2-Chlorophenol	95-57-8
	2-Methylnaphthalene	91-57-6
	4,4'-DDD	72-54-8
	4,4'-DDT	50-29-3
	4-Chloroaniline	106-47-8
	4-Nitrophenol	100-02-7
	Acenaphthene	83-32-9
	Aniline	62-53-3
	bis(2-Ethylhexyl)adipate	103-23-1
	bis(2-Ethylhexyl)phthalate	117-81-7
	Bromo-2-fluorobenzene	1072-85-1
	Cresols (mixed isomers)	1319-77-3
	Dibenzofuran	132-64-9
	Diethylphthalate	84-66-2
	Di-n-butylphthalate	84-74-2
	Endosulfan I	959-98-8
	Endosulfan II	33213-65-9
	Endosulfan sulfate	1031-07-8
	Endrin	72-20-8
	Endrin aldehyde	7421-93-4
	Fluorene	86-73-7
	Heptachlor	76-44-8
	Heptachlor epoxide	1024-57-3
	Hexachlorocyclopentadiene	77-47-4
	m/p-cresols (3,4-methylphenols)	15831-10-4
	Methoxychlor	72-43-5
	Naphthalene	91-20-3
	Nitrobenzene	98-95-3
	N-Nitroso-di-n-propylamine	621-64-7
	Phenanthrene	85-01-8
	Phenol	108-95-2
	Pyridine	110-86-1
	Thiophene	110-02-1
	Thiophenol	108-98-5

Table B-1 (continued)		
Group Number	**Constituent**	**CAS**
25	**Metallic Compounds**	
	Antimony	7440-36-0
	Arsenic	7440-38-2
	Chromium (assumed Cr III)	7440-47-3
	Copper	7440-50-8
	Lead	7439-92-1
	Manganese	7439-96-5
	Mercury	7439-97-6
	Zinc	7440-66-6
26	**Inorganic Compounds**	
	Ammonia	7664-41-7
	Carbon Dioxide	124-38-9
	Hydrogen	1333-74-0
	Hydrogen Sulfide	7783-06-4
	Nitrogen	7727-37-9
	Oxygen	7782-44-7
	Sulfur Dioxide	7446-09-5
27	**Multi-Chemical Groupings**	
	Aldehydes and Ketones	--
	Biologicals	--
	C1-Thiophenes	--
	C2-Thiophenes	--
	C3 Benzenes	--
	C5-C7 Cycloalkanes	--
	Chlorinated Phenols	--
	Decanes	--
	Dialkyl Nitrosamines	--
	Dichlorobenzenes	--
	Dodecanes	--
	Halocarbons	--
	Halogenated Compounds	--
	Heptanes	--
	Hexanes	--
	Hexanes plus	--
	Individual Unidentified Sulfur Compounds (all as monosulfides)	--
	Mercaptans	--
	Nonanes	--
	Octanes	--

Table B-1 (continued)		
Group Number	**Constituent**	**CAS**
	Organosilicon Compounds	--
	Oxygen/Argon	--
	Polychlorinated Biphenyls	--
	Polychlorinated Dibenzofurans	--
	Polychlorinated Dibenzo-p-Dioxins	--
	Polynuclear Aromatic Hydrocarbons (PAHs)	--
	Siloxanes	--
	SVOCs (Semivolatile Organics)	--
	Tetradecanes	--
	Total from Cyclopentane to Eicosanes +	--
	Total Sulfur (ppm)	--
	Total TO-14 Halocarbons	--
	Tridecanes	--
	Undecanes	--
	VOCs (Volatile Organics)	--
	Volatile Metals	--

Table B-2 Additional Constituents Identified in Municipal Landfill Biogas from the U.S., Canada, and the U.K.[32] (list includes only unique chemicals not reported in other biogas reference studies)			
Group 1 Alkanes (C6 and lower)	2,2-dimethylbutane 2,2-dimethylpropane	2,3-dimethylbutane 2-methylbutane	2-methylpentane 3-methylpentane
Group 2 Alkanes (C7 and greater)	2,2,3-trimethylbutane 2,3,3-trimethylpentane 2,3,4-trimethylhexane 2,3,4-trimethylpentane 2,2,5-trimethylhexane 2,4,6-trimethylheptane 2,2-dimethylhexane 2,2-dimethylpentane 2,3-dimethylheptane 2,3-dimethylpentane 2,4-dimethylpentane 2,4-dimethylheptane 2,4-dimethylhexane 2,5-dimethylheptane 2,5-dimethylhexane 2,6-dimethylheptane 2,6-dimethyloctane 2,6-dimethynonane	3,3-dimethylpentane 3,5-dimethyloctane 3,6-dimethyloctane 2-methyldecane 2-methylheptane 2-methylhexane 2-methylnonane 2-methyloctane 3-ethyl-4-methylheptane 3-ethylpentane 3-methyldecane 3-methylheptane 3-methylnonane 3-methyloctane 4-methyldecane 4-methylheptane 4-methylnonane 4-methyloctane	5-methyldecane eicosane heneicosane heptadecane hexadecane n-decane n-dodecane n-nonane n-octane nonadecane n-tetradecane n-tridecane n-undecane octadecane pentadecane tetradecane trimethylhexane
Group 3 Alkanes (Cyclic)	1,1,3-trimethylcyclohexane 1,2,4-trimethylcyclohexane 1,2,4-trimethylcyclopentane 1,3,5-trimethylcyclohexane 1,1-dimethylcyclopropane 1,2-dimethylcyclohexane (cis) 1,2-dimethylcyclopropane 1,3-dimethylcyclohexane (cis) 1,3-dimethylcyclohexane (trans) 1,3-dimethylcyclopentane 1,3-dimethylcyclopentane (trans) 1,4-dimethylcyclohexane (cis) 1,4-dimethylcyclohexane (trans)	(1-methylethyl)cyclohexane 1-ethyl-2-methylcyclohexane 1-ethyl-2-methylcyclopentane 1-ethyl-3-methylcyclohexane 1-ethyl-3-methylcyclopentane 1-ethyl-4-methylcyclohexane 1-methyl-2-propylcyclopentane 2-methylpropylcyclohexane butylcyclohexane cyclobutane cycloheptane decahydronaphthalene dimethylcyclohexane	dimethylcyclopentane ethylcyclohexane ethylcyclopentane ethylcyclopropane ethylmethylcyclohexane methylcycloheptane methylcyclobutane methylcyclopropane methylethylcyclohexane propylcyclohexane tetramethylcyclohexane trimethylcyclopentane

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[32] References: USEPA 2008, Table 2-8, UKEA 2002.

Table B-2 (continued)			
Group 4 Alkanes (Hexane-Like)	3-ethylhexane 3-methylhexane		
Group 5 Alkenes and Dienes	1,10-undecadiene 1,11-dodecadiene 1,4-pentadiene 1,6-heptadiene 1,8-nonadiene 1,9-decadiene 1-butene 1-decene 1-heptene 1-hexene 1-methylcyclohexene 1-methylcyclopentene 1-nonene 1-octene 1-pentene 1-undecene 2,5-dimethylpentene 2-butene (cis) 2-butene (trans)	2-ethyl-1-butene 2-heptene (cis) 2-heptene (trans) 2-hexene (cis) 2-hexene (trans) 2-methyl-1-butene 2-methyl-1-pentene 2-methyl-1-propene 2-methyl-2-butene 2-octene (cis) 2-octene (trans) 2-pentene (cis) 2-pentene (trans) 3-heptene (cis) 3-methyl-1-butene 3-methyl-1-pentene 3-methyl-2-pentene (cis) 3-methyl-2-pentene (trans)	4-methyl-1-hexene 4-methyl-1-pentene 4-methyl-2-pentene (cis) 4-methyl-2-pentene (trans) butene cyclohexene cyclopentene dodecene ethene hexadiene methylenecyclohexane n-decene nonene n-undecene octadiene pentene propadiene (allene) propene
Group 6 1,3-Dienes	1,3-butadiene 1,3-pentadiene	2-methyl-1,3-butadiene	
Group 7 Terpenes	3-carene 4-carene camphene carene	decahydro-4,8,8-trimethyl-9-methylene-(1a,3aß,4a,8aß)-1,4-methanoazulene limonene phellandrene	ß-pinene thujene α-pinene γ-terpinene
Group 8 Alcohols	1-propanol 2-(2-hydroxypropoxy)-1-propanol 2-butanol 2-ethyl-1-butanol 2-methyl-1-propanol	2-ethyl-1-hexanol 3-methyl-2-butanol 3-methyl-2-pentanol 3-pentanol amyl alcohol	3-methyl-1-butanol n-hexanol methanol methyl isobutyl carbinol
Group 9 Ethers	dimethyl ether dipropyl ether	methyl ethyl ether	tetrahydrofuran

Table B-2 (continued)		
Group 10 Aldehydes	benzaldehyde butanal	decanal nonanal	octanal
Group 11 Ketones	1-phenyl-1-propanone 2-ethyl-cycloheptanone 2-pentanone 3-methyl-2-butanone	acetophenone cyclohexanone cyclopentanone dimethyl-3-pentanone	methyl ethyl ketone methyl isobutyl ketone methyl isopropyl ketone
Group 12 Carboxylic Acids	acetic acid benzoic acid	2,2-dimethylpropanoic acid butyric acid	propionic acid
Group 13 Esters	amyl acetate (mixed isomers) butyl acetate butyl butyrate butyl formate dimethylethyl methanoate ethyl 2-methyl butyroate ethyl butyrate ethyl caproate ethyl dimethyl propanoate ethyl isovalerate ethyl pentanoate	ethyl propionate hexyl methanoates isobutyl formate methyl 2-methylbutanoate methyl acetate methyl butyrate methyl caproate methylethyl butanoate methylethyl propanoate methyl isobutyrate	methyl isovalerate methyl pentanoate methyl propanoate methylpropyl ethanoate n-butyl propionate n-propyl acetate n-propyl butyrate pentyl methanoate propylmethyl propanoate propyl propionate
Group 14 Alkynes	acetylene butynes	propyne	
Group 16 Benzenes (Polyalkyl)	1,2,3-trimethylbenzene 1,2-diethylbenzene 1,3-diethylbenzene 1,4-diethylbenzene 1-ethyl-2,3-dimethylbenzene	1-methyl-2-propylbenzene 1-methyl-3-propylbenzene 1-methyl-4-propylbenzene 2-ethyl-1,3-dimethylbenzene 2-ethyltoluene	3-ethyltoluene isobutylbenzene ß-cymene tetramethylbenzene
Group 17 Benzenes (Styrenes)	1-ethenyl-3-ethylbenzene dimethyl styrene	ethyl vinyl benzene methyl-4- isopropenylbenzene	vinyl toluene
Group 18 Benzenes (Chlorinated)	1,2,3,4-tetrachlorobenzene 1,2,3-trichlorobenzene	1,2,4-trichlorobenzene	pentachlorobenzene
Group 19 CFCs	1,1,1,2-tetrafluorochloroethane 1,1,1-trichlorotrifluoroethane 1,1,1-trifluorochloroethane 1,1,2,2-tetrafluoroethane 1,1,2-trichlorotrifluoroethane	1,1-difluoro-1-chloroethane 1,2-dichloro-1-fluoroethane 1,2-dichlorotetrafluoroethane 1-chloro-1,1-difluoroethane	chlorofluoromethane chlorotrifluoroethene chlorotrifluoromethane dichlorofluoromethane

	1,1,2-trifluoro-1,2-dichloroethane 1,1,2-trifluoro-1-chloroethane 1,1-chlorofluoroethane 1,1-dichlorotetrafluoroethane	2,2-difluoropropane bromochlorodifluoromethane bromochlorofluoromethane carbon tetrafluoride chlorodifluoromethane	dichlorodifluoromethane tetrafluorochloroethane trichlorofluoromethane
Group 20 Alkyl Thiols	1-butanethiol 1-pentanethiol 2-butanethiol	2-methyl-1-propanethiol 2-propene-1-thiol amyl mercaptan	heptanethiol n-hexanethiol
Group 21 Alkyl Sulfides	1-(ethylthio)butane dibutyl sulfide dibutyl trisulfide diethyl sulfide dimethyl tetrasulfide dipropyl sulfide dipropyl trisulfide ethyl butyl trisulfide ethyl isobutyl disulfide	ethyl isopropyl disulfide ethyl n-propyl disulfide ethyl propyl trisulfide methyl butyl disulfide methyl butyl trisulfide methyl ethyl disulfide methyl ethyl sulfide methyl ethyl trisulfide	methyl isopropyl sulfide methyl isopropyl disulfide methyl propyl disulfide methyl propyl trisulfide n-butyl disulfide pentyl trisulfide propyl butyl disulfide propyl butyl trisulfide
Group 22 Organosilicon Compounds	dodecamethylcyclohexasiloxane		
Table IV-1 Constituents (See Section IV of the main document; these constituents have established criteria)	2-butoxyethanol 2-furanmethanol 2-hexanone camphor carbon monoxide formic acid	furfural hexachlorobenzene hexachlorobutadiene hydrogen chloride hydrogen cyanide	methacrylic acid methylal methyl methacrylate sulphuric acid tribromomethane
Table IV-4 Constituents (See Section IV of the main document; these constituents do not have criteria and will require additional research.)	1-(ethenyloxy)-butane 1,1,1,2-tetrachloroethane 1,3-dioxolane 1,3-dichloropropene (cis) 1,4-dichlorobutane 1,6-dimethylnaphthalene 2,5-dimethylthiophene 2-ethylthiophene 2-ethynylphenol 2-propyl thiophene 3-(ethylthio)propanal 3-ethynylphenol	3-methylthiophene benzothiazole biphenylene bromodichloromethane bromoethane dibromochloromethane dibromomethane dichlorobutene di-isooctylphthalate dimethoxymethyl propanoate dimethyl furan	furan hexylbenzene indane (2,3-dihydroindene) methyl furan methyl vinyl ketone pentylbenzene propylthiophene t-butyl alcohol tetrachloroethane tetrahydro-2-furanmethanol trifluorobenzene

Table B-3 Constituents Identified in Biogas from Selected Academic Studies and Possible Combustion Products[33] (includes unique chemicals not reported in other biogas reference studies)	
Group	Constituent
Group 19: Chlorofluorocarbons (CFCs)	1-Chloro-1-fluoroethane
Group 22: Organosilicon Compounds	Trimethylsilanol Dimethyldisilanol 2,4-bis(trimethylsiloxy)benzaldehyde
Group 23: Volatile Organics (VOCs)	1-Chloropropane
Group 24: Semivolatile Organics (SVOCs)	Methylthiophenes Ethylthiophenes
Group 25: Metallic Compounds	Dimethyl Tellurium Trimethyl Bismuth Trimethyl Antimony Trimethyl Tin Compounds Arsine and Methyl Arsines
Group 26: Inorganic Compounds	Phosphine
Group 28: Possible Combustion Products	Hydrogen Bromide Hydrogen Chloride Hydrogen Fluoride Metal Oxides Phosphates/Phosphoric Acid Silica (crystalline) Sulfur Dioxide/Sulfates

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[33] References: AFSSET 2008, Grumping, et al. 1999, Glindemann, et al. 2005, Hensel, et al. 2000, Hirner, et al. 1994, Rasi 2009.

Table B-4
Constituent Concentration Data for Biogas, Biomethane, and Natural Gas from the GTI Datasets
Table B-4 provides each set of gas data used in the health risk assessment of the individual constituents. A Microsoft Excel file is available upon request.

Type of Gas	Tab Name	Source of Data
Natural gas data	Nat Gas GTI A Values	(GTI A) Guidance Document for the Introduction of Landfill-Derived Renewable Gas into Natural Gas Pipelines, Gas Technology Institute, May 2, 2012.
Natural gas data	Nat Gas GTI B Values	(GTI B*) FINAL REPORT DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736, Pipeline Quality Biogas: Guidance Document for Dairy Waste, Wastewater Treatment Sludge and Landfill Conversion, FINAL REPORTS: TASKS 1, 2, 3 and 4, December 31, 2009. According to GTI, Tables 23-30 were mislabeled in the GTI report. The units in Tables 23-30 should be reported as ppb, corresponding to the data in the appendix. The data included in this excel workbook have been corrected to reflect the correct concentration units.
Natural gas data	Air Liquide NG Values	Medal, a division of Air Liquide Advanced Technologies U.S. LLC. HALOGENS AND CARCINOGENS IN PIPELINE NATURAL GAS. 17 March 2012. Email communication on 1/22/2013 from Charlie Anderson.
Raw landfill	Landfill Raw GTI B Values	(GTI B*) FINAL REPORT DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736
Clean Landfill	Landfill Clean GTI B Values	(GTI B*) FINAL REPORT DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736
Raw landfill	LA Landfill Raw Values	Los Angeles County Sanitation Districts. Email communication sent November 14, 2012 with nine Excel file attachments providing landfill gas data for Puente Hills, Scholl Canyon, and Calabasas Landfills covering 2009, 2010, and 2011. (LACSD)
Clean Landfill	Landfill Clean GTI A Values	(GTI A) Guidance Document for the Introduction of Landfill-Derived Renewable Gas into Natural Gas Pipelines," Gas Technology Institute, May 2, 2012.
Raw POTW	WWTP GTI B Raw Values	(GTI B*) FINAL REPORT DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736
Clean POTW	WWTP GTI B Clean Values	(GTI B*) FINAL REPORT DOT PROJECT NUMBER 250/GTI PROJECT NUMBER 20736
Raw POTW	WWTP Raw SCAQMD Values	Retrofit Digester Gas Engine with Fuel Gas Clean-up and Exhaust Emission Control Technology. South Coast Air Quality Management District Contract #10114. Pilot Testing of Emission Control System Plant 1 Engine 1. Orange County Sanitation District Project No. J-79. FINAL REPORT, July 2011
Raw POTW	WWTP Raw JWPCP Values	Joint Water Pollution Control Plant operated by LA County Sanitation District 8/10/2001. Email from South Coast AQMD on 8/22/12 with data attached.
Raw Dairy	Dairy Raw GTI tsk 2 Values	(GTI Task 2) Pipeline Quality Biomethane: North American Guidance Document for Introduction of Diary Waste Derived Biomethane into Existing Natural Gas Networks, Gas Technology Institute, Task 2 Final Report, Laboratory Testing and Analysis, GTI Project Number 20614. Sept. 30, 2009
Clean Dairy	Dairy Clean GTI tsk 2 Values	(GTI Task 2) Pipeline Quality Biomethane
Natural Gas	Nat gas highest conc list	contains the highest measured concentration for each constiuents found in all samples of natural gas
raw biogas	raw biogas highest conc list	contains the highest measured concentration for each constituent found in all samples of raw biogas (POTW, Landfill and Dairy)
treated biomethane	clean biometh highest conc list	contains the highest measured concentration for each constituent found in all samples of treated biomethane (POTW, Landfill and Dairy)
Notes:		
#N/A-information is not available		
concentration information for groups of compounds is not typically included in this data set (e.g. c3 benzenes, c6+ hydrocarbons)		
*According to GTI, Tables 23-30 were mislabeled in the GTI report. The units in Tables 23-30 should be reported as ppb, corresponding to the data in the appendix. The data included in this excel workbook have been corrected to reflect the correct concentration units.		

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	16,600.000
Oxygen/Argon	#N/A	7782-44-7		1,300.000
Nitrogen	#N/A	7727-37-9	28.01	12,000.000
Methane	#N/A	74-82-8	16.04	967,100.000
Ethane	#N/A	74-84-0	30.069	22,100.000
Propane	Alkanes	74-98-6	44.0956	2,700.000
i-Butane	Alkanes	75-28-5	58.12	410.000
n-Butane	Alkanes	106-97-8	58.12	490.000
i-Pentane	Alkanes	78-78-4	72.17	140.000
n-Pentane	Alkanes	8031-35-4	72.17	110.000
C5-C7 Cycloalkanes	#N/A			
Cyclopentane	Alkanes	287-92-3	70.1329	17.000
Methylcyclopentane	#N/A	96-37-7	84.16	14.000
Cyclohexane (benzene)	Alkanes	110-82-7	84.1595	15.000
Methylcyclohexane	Alkanes	108-87-2	98.1861	18.000
Hexanes	Alkanes	110-54-3	86.175	119.000
Heptanes	#N/A	142-82-5	100.2019	57.000
2,2,4-Trimethylpentane	#N/A	540-84-1	114.2285	2.000
Octanes	#N/A	111-65-9	114.2285	32.000
Nonanes	#N/A	111-84-2	128.2551	14.000
Decanes	#N/A	124-18-5	142.2817	4.000
Undecanes	#N/A	1120-21-4	156.3083	1.000
Dodecanes	#N/A	112-40-3	170.3348	1.000
Tridecanes	#N/A	629-50-5	184.3614	1.000
Tetradecanes	#N/A	629-59-4	198.388	1.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.082	0.480
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	0.590
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.090
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	0.190
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.162	0.260
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	2.360
Dimethyl Sulfide	#N/A	75-18-3	62.13	1.180
1,3-Butadiene	VOC	106-99-0	54.09	11.300
Acrylonitrile	VOC	107-13-1	53.0627	4.000
Benzene	VOC	71-43-2	78.11	21.900
Toluene	Alkyl Benzenes	108-88-3	92.14	15.500
m,p-Xylene-used mixed isomer cas	Alkyl Benzenes	1330-20-7	106.165	4.800
o-Xylene used mixed isomer cas	Alkyl Benzenes	1330-20-7	106.165	1.500
2-methylnaphthalene	PAHs	91-57-6	142.21	2.400

Constituent	Assigned Group	CAS	MW	Conc (PPM)
1-methylnaphthalene	PAHs	90-12-0	142.1971	1.400
Di-n-butyl phthalate	SVOC	84-74-2	278.3435	0.700
Bis(2-ethylhexyl)phthalate	SVOC	117-81-7	390.5561	0.700
Acetaldehyde	VOC	75-07-0	44.05	0.095
Acetone	VOC	67-64-1	58.08	0.103
Propionaldehyde	VOC	123-38-6	58.0791	0.003
Crotonaldehyde	VOC	123-73-9	70.09	0.008
Methacrolein (Isobutenal)	Missing	78-85-3	70.0898	0.010
Butanol	VOC	71-36-3	74.1216	0.038
copper	Metals	7440-50-8	63.546	0.029
zinc	Metals	7440-66-6	65.39	0.010
mercury	Metals	7439-97-6	200.59	0.000
sum mixed isomer Xylene	Alkyl Benzenes	1330-20-7	106.165	6.300

Table B-4: Nat Gas GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	7,600.000
Nitrogen	#N/A	7727-37-9	28.01	3,700.000
Methane	#N/A	74-82-8	16.04	974,420.000
Ethane	#N/A	74-84-0	30.07	24,880.000
Propane	Alkanes	74-98-6	44.10	4,020.000
Propene	VOC	115-07-1	42.08	60.000
i-Butane	Alkanes	75-28-5	58.12	560.000
n-Butane	Alkanes	106-97-8	58.12	780.000
i-Pentane	Alkanes	78-78-4	72.17	240.000
n Pentane	Alkanes	8031-35-4	72.15	180.000
Cyclopentane	Alkanes	287-92-3	70.13	24.000
Methylcyclopentane	#N/A	96-37-7	84.16	17.000
Cyclohexane	Alkanes	110-82-7	84.16	18.000
Methylcyclohexane	Alkanes	108-87-2	98.19	25.000
Benzene	VOC	71-43-2	78.11	7.000
Toluene	Alkyl Benzenes	108-88-3	92.14	6.000
Ethyl benzene	Alkyl Benzenes	100-41-4	106.17	1.000
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	2.000
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	1.000
Hexane	Alkanes	110-54-3	86.18	185.000
Heptane	#N/A	142-82-5	100.20	86.000
2,2,4 Trimethylpentane	#N/A	540-84-1	114.23	4.000
Octanes	#N/A	111-65-9	114.23	40.000
Nonanes	#N/A	111-84-2	128.26	11.000
Decanes	#N/A	124-18-5	142.28	2.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	0.500
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	7.940
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	5.380
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	0.490
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	1.530
Dimethyl Sulfide	#N/A	75-18-3	62.13	0.200
Methyl Ethyl Sulfide	#N/A	625-80-9	118.24	1.230
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.240
Thiophene	Sulfur Compds	110-02-1	84.14	0.120

Table B-4: Nat Gas GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Benzene	VOC	71-43-2	78.11	0.014
Carbon Tetrachloride	VOC	56-23-5	153.82	0.001
Toluene	Alkyl Benzenes	108-88-3	92.14	0.110
Dibromochloromethane	VOC	124-48-1	208.28	0.002
Ethyl Benzene	Alkyl Benzenes	100-41-4	106.17	0.062
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.194
Styrene	VOC	100-42-5	104.15	0.000
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.182
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.019
n Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.036
1,3,5 Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.158
1,2,4 Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.474
sec Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.013
p Isopropyltoluene	#N/A	99-87-6	134.22	0.018
Benzyl Alcohol	SVOC	100-51-6	108.14	0.001
n Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.018
Nitrobenzene	SVOC	98-95-3	123.11	0.009
Naphthalene	PAHs	91-20-3	128.17	0.008
2 Methylnaphthalene	PAHs	91-57-6	142.20	0.001
1 Methylnaphthalene	PAHs	90-12-0	142.20	0.003
Di n butylphthalate	#N/A	84-74-2	278.34	0.001
Copper	Metals	7440-50-8	63.55	0.026
Zinc	Metals	7440-66-6	65.38	0.039
Formaldehyde	VOC	50-00-0	30.03	0.006
Acetaldehyde	VOC	75-07-0	44.05	0.028
Acetone	VOC	67-64-1	58.08	0.033
Acrolein	VOC	107-02-8	56.06	0.000
Propionaldehyde	VOC	123-38-6	58.08	0.001
Methacrolein	Missing	78-85-3	70.09	0.001
Crotonaldehyde	#N/A	123-73-9	70.09	0.000
2 Butanone	VOC	78-93-3	72.11	0.007
Butanal	#N/A	123-72-8	72.11	0.001
Benzaldehyde	#N/A	100-52-7	106.12	0.002
Pentanal	#N/A	110-62-3	86.13	0.000
sum mixed isomer xylene tier 1	Alkyl Benzenes	1330-20-7	106.17	3.000

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Chloromethane	VOC	74-87-3	50.49	36.65364
Bromomethane	VOC	74-83-9	94.94	0.37288
Trichloromonofluoromethane	#N/A	75-39-4	137.37	0.11825
1,1-Dichloroethene	VOC	75-35-4	96.94	0.07695
Ethanol	#N/A	64-17-5	46.06844	0.40946
t-1,2-Dichloreothene	VOC	156-60-5	96.94	0.12916
Hexane	Alkanes	110-54-3	86.18	40.68571
Vinyl Acetate	VOC	108-05-4	86.09	2.22562
Cyclohexane	Alkanes	110-82-7	84.16	15.64204
Chloroform	VOC	67-66-3	119.38	3.98269
Ehthyl Acetate	#N/A	141-78-6	88.105	7.52265
Tetrahydrofuran	VOC	109-99-9	72.11	4.94484
Carbon Tetrachloride	VOC	56-23-5	153.82	0.05626
Heptane	#N/A	142-82-5	100.21	40.70924
Benzene	VOC	71-43-2	78.11	38.8142
Trichloroethylene	VOC	79-01-6	131.4	0.17408
Bromodichloromethane	VOC	75-27-4	163.8	0.13241
1,4-dioxane	VOC	123-91-1	88.11	0.04988
Tolune	Alkyl Benzenes	108-88-3	92.14	15.83375
4-Methyl-2-pentanone(MIBK)	VOC	108-10-1	100.16	1.07763
Ethylbenzene	Alkyl Benzenes	100-41-4	106.17	0.89242
m/p-Xylene	Alkyl Benzenes	1330-20-7	106.16	4.38279
o-Xylene	Alkyl Benzenes	1330-20-7	106.16	1.11434
Styrene	VOC	100-42-5	104.15	0.03811
Tribromomethane	VOC	75-25-2	252.73	0.04064
1,3,5-trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.35689
1,2,4-trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.34061
Propane, 1-bromo-2-methyl-	VOC	78-77-3	137.02	4.89775
Hexane, 3-ethyl-	#N/A	619-99-8	114.2285	52.4215
Propane, 2-methyl-1-nitro-	VOC	625-74-1	103.121	4.6128
Propane, 2-methyl-1-nitro-	VOC	625-74-1	103.121	10.44018
Cyclohexane, 1-ethyl-2-methyl-	#N/A	3728-54-9	126.24	6.80592
Propane, 2-methyl-1-nitro-	VOC	625-74-1	103.121	4.75827
Propane, 2-methyl-1-nitro-	VOC	625-74-1	103.121	7.661
BFB (IS)	VOC	1072-85-1	175	0.01
sum mixed isomer xylenes	Alkyl Benzenes	1330-20-7	106.16	5.49713

Appendix B
Table B-4: Landfill Raw GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Hydrogen	#N/A	1333-74-0	2.02	3,000.000
Carbon Dioxide	#N/A	124-38-9	44.01	400,800.000
Nitrogen	#N/A	7727-37-9	28.01	36,900.000
Methane	#N/A	74-82-8	16.04	648,520.000
Propane	Alkanes	74-98-6	44.10	30.000
Propene	VOC	115-07-1	42.08	20.000
i-Butane	Alkanes	75-28-5	58.12	20.000
i-Pentane	Alkanes	78-78-4	72.17	30.000
Cyclopentane	Alkanes	287-92-3	70.13	4.000
Methylcyclopentane	#N/A	96-37-7	84.16	2.000
Cyclohexane	Alkanes	110-82-7	84.16	6.000
Methylcyclohexane	Alkanes	108-87-2	98.19	3.000
Benzene	VOC	71-43-2	78.11	3.000
Toluene	Alkyl Benzenes	108-88-3	92.14	23.000
Ethyl benzene	Alkyl Benzenes	100-41-4	106.17	5.000
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	9.000
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	2.000
C3 Benzenes	#N/A			8.000
Hexane	Alkanes	110-54-3	86.18	47.000
Heptane	#N/A	142-82-5	100.20	31.000
2,2,4 Trimethylpentane	#N/A	540-84-1	114.23	2.000
Octanes	#N/A	111-65-9	114.23	20.000
Nonanes	#N/A	111-84-2	128.26	17.000
Decanes	#N/A	124-18-5	142.28	43.000
Undecanes	#N/A	1120-21-4	156.31	23.000
Dodecanes	#N/A	112-40-3	170.33	3.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	152.000
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	0.210
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.840
Carbon Disulfide	Sulfur Compds	75-15-0	76.14	0.220
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	4.100
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	2.210
n Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.130

Table B-4: Landfill Raw GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	0.310
Dimethyl Sulfide	#N/A	75-18-3	62.13	19.600
Methyl Ethyl Sulfide	#N/A	625-80-9	118.24	0.050
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.380
Dimethyl Trisulfide	#N/A	3658-80-8	126.25	0.020
Thiophene	Sulfur Compds	110-02-1	84.14	0.210
C1 Thiophenes	#N/A			0.100
C2 Thiophenes	#N/A			0.060
Dichlorodifluoromethane	VOC	75-71-8	120.91	2.050
1,2 Dichlorotetrafluoroethane (CFC 114)	#N/A	76-14-2	170.92	0.330
Trichlorofluoromethane	VOC	75-69-4	137.37	0.510
Chloromethane	VOC	74-87-3	50.49	0.140
Dichloromethane(Methylene Chloride)	VOC	75-09-2	84.93	2.480
Chloroethane	VOC	75-00-3	64.51	0.880
1,1 Dichloroethane	VOC	75-34-3	98.96	0.200
1,2 Dichloroethane	VOC	107-06-2	98.96	0.220
Vinyl Chloride	VOC	75-01-4	62.50	0.640
cis 1,2 Dichloroethene	VOC	156-59-2	96.94	0.530
Trichloroethane	VOC	79-00-5	133.40	0.380
Tetrachloroethene	VOC	127-18-4	165.83	0.280
1,2 Dichloroethane	VOC	107-06-2	98.96	0.000
Benzene	VOC	71-43-2	78.11	0.002
Carbon Tetrachloride	VOC	56-23-5	153.82	0.001
Trichloroethene	VOC	79-01-6	131.39	0.000
Toluene	Alkyl Benzenes	108-88-3	92.14	0.101
trans 1,3 Dichloropropene	VOC	10061-02-6	110.97	0.001
Tetrachloroethene	VOC	127-18-4	165.83	0.004
Chlorobenzene	SVOC	108-90-7	112.56	0.002
Ethyl Benzene	Alkyl Benzenes	100-41-4	106.17	0.096
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.100
Styrene	VOC	100-42-5	104.15	0.014
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.084
1,1,2,2 Tetrachloroethane	VOC	79-34-5	167.85	0.001

Table B-4: Landfill Raw GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.022
2 Chlorotoluene	SVOC	95-49-8	126.58	0.006
n Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.025
4 Chlorotoluene	SVOC	106-43-4	126.58	0.004
1,3,5 Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.124
tert Butylbenzene	Alkyl Benzenes	98-06-6	134.22	0.013
1,2,4 Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.323
sec Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.016
Phenol	SVOC	108-95-2	94.11	0.002
bis(2 Chloroethyl)ether	VOC	111-44-4	143.01	0.001
1,3 Dichlorobenzene	#N/A	541-73-1	147.00	0.000
1,4 Dichlorobenzene	SVOC	106-46-7	147.00	0.147
p Isopropyltoluene	#N/A	99-87-6	134.22	0.760
Benzyl Alcohol	SVOC	100-51-6	108.14	0.243
1,2 Dichlorobenzene	SVOC	95-50-1	147.00	0.003
3,4 Methylphenol (o,p cresol) used p-cresol	SVOC	106-44-5	108.13	0.001
n Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.015
N nitroso di n propylamine	Nitroso Compds	621-64-7	130.19	0.012
2,4 Dimethylphenol	#N/A	105-67-9	122.16	0.001
1,2,4 Trichlorobenzene	#N/A	120-82-1	181.45	0.005
Naphthalene	PAHs	91-20-3	128.17	0.217
4 Chloroaniline	SVOC	106-47-8	127.60	0.003
1,2,3 Trichlorobenzene	#N/A	87-61-6	181.45	0.001
2 Methylnaphthalene	PAHs	91-57-6	142.20	0.033
1 Methylnaphthalene	PAHs	90-12-0	142.20	0.016
Acenaphthene	#N/A	83-32-9	154.21	0.005
4 Nitrophenol	SVOC	100-02-7	139.11	0.002
Dibenzofuran	SVOC	132-64-9	106.20	0.002
Diethylphthalate	SVOC	84-66-2	222.24	0.001
Fluorene	#N/A	86-73-7	166.22	0.002
Phenanthrene	PAHs	85-01-8	178.23	0.001
Di n butylphthalate	#N/A	84-74-2	278.34	0.002
Mercury	Metals	7439-97-6	200.59	0.000

Table B-4: Landfill Raw GTI B Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Arsenic	Metals	7440-38-2	74.92	0.111
Antimony	Metals	7440-36-0	121.76	0.084
Zinc	Metals	7440-66-6	65.38	0.042
Hexamethyldisilane	#N/A	1450-14-2	146.38	0.950
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	1.375
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.77	0.380
4,4'-DDT	Pesticides	50-29-3	354.48	0.000
Formaldehyde	VOC	50-00-0	30.03	0.003
Acetaldehyde	VOC	75-07-0	44.05	0.060
Acetone	VOC	67-64-1	58.08	0.368
Propionaldehyde	VOC	123-38-6	58.08	0.016
Methacrolein	Missing	78-85-3	70.09	0.109
Crotonaldehyde	#N/A	123-73-9	70.09	0.018
2 Butanone	VOC	78-93-3	72.11	0.345
Butanal	#N/A	123-72-8	72.11	0.037
Benzaldehyde	#N/A	100-52-7	106.12	0.011
Pentanal	#N/A	110-62-3	86.13	0.017
p Tolualdehyde	#N/A	104-87-0	120.15	0.057
Hexanal	#N/A	66-25-1	100.16	0.006
sum mixed isomer xylenes tier 1	Alkyl Benzenes	1330-20-7	106.17	11.000

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Hydrogen	#N/A	1333-74-0	2.02	10,000.000
Carbon Dioxide	#N/A	124-38-9	44.01	14,200.000
Nitrogen	#N/A	7727-37-9	28.01	94,900.000
Methane	#N/A	74-82-8	16.04	979,180.000
Propane	Alkanes	74-98-6	44.10	40.000
Propene	VOC	115-07-1	42.08	20.000
Hexane plus	#N/A		0.00	14.000
Cyclopentane	Alkanes	287-92-3	70.13	2.000
Methylcyclopentane	#N/A	96-37-7	84.16	1.000
Cyclohexane	Alkanes	110-82-7	84.16	1.000
Methylcyclohexane	Alkanes	108-87-2	98.19	1.000
Benzene	VOC	71-43-2	78.11	1.000
Hexane	Alkanes	110-54-3	86.18	8.000
Heptane	Alkanes	8031-33-2	100.20	1.000
Decanes	#N/A	124-18-5	142.28	1.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	0.530
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	0.080
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.880
Dimethyl Sulfide	#N/A	75-18-3	62.13	1.880
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.170
Dichlorodifluoromethane	VOC	75-71-8	120.91	3.600
1,2 Dichlorotetrafluoroethane (CFC 114)	#N/A	76-14-2	170.92	0.170
Trichlorofluoromethane	VOC	75-69-4	137.37	0.240
Chloroethane	VOC	75-00-3	64.51	0.660
Vinyl Chloride	VOC	75-01-4	62.50	0.330
Benzene	VOC	71-43-2	78.11	0.014
Carbon Tetrachloride	VOC	56-23-5	153.82	0.001
1,2 Dichloropropane	VOC	78-87-5	112.99	0.020
Trichloroethene	VOC	79-01-6	131.39	0.001
Toluene	Alkyl Benzenes	108-88-3	92.14	0.017
Dibromochloromethane	VOC	124-48-1	208.28	0.001
Tetrachloroethene	VOC	127-18-4	165.83	0.000
Ethyl Benzene	Alkyl Benzenes	100-41-4	106.17	0.001
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.001
Xylenes(any isomer or mixture)	Alkyl Benzenes	1330-20-7	106.17	0.001
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.000
n Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.000
1,3,5 Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.001
1,2,4 Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.004
sec Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.000

Constituent	Assigned Group	CAS	MW	Conc (PPM)
1,4 Dichlorobenzene	SVOC	106-46-7	147.00	0.002
p Isopropyltoluene	#N/A	99-87-6	134.22	0.021
n Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.000
Naphthalene	PAHs	91-20-3	128.17	0.007
2 Methylnaphthalene	PAHs	91-57-6	142.20	0.001
1 Methylnaphthalene	PAHs	90-12-0	142.20	0.000
Diethylphthalate	SVOC	84-66-2	222.24	0.001
Di n butylphthalate	#N/A	84-74-2	278.34	0.002
Copper	Metals	7440-50-8	63.55	0.096
Zinc	Metals	7440-66-6	65.38	0.042
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	1.325
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.77	0.200
Formaldehyde	VOC	50-00-0	30.03	0.002
Acetaldehyde	VOC	75-07-0	44.05	0.017
Acetone	VOC	67-64-1	58.08	0.314
Acrolein	VOC	107-02-8	56.06	0.001
Propionaldehyde	VOC	123-38-6	58.08	0.009
Methacrolein	Missing	78-85-3	70.09	0.004
Crotonaldehyde	#N/A	123-73-9	70.09	0.001
2 Butanone	VOC	78-93-3	72.11	0.198
Butanal	#N/A	123-72-8	72.11	0.009
Benzaldehyde	#N/A	100-52-7	106.12	0.002
sum mixed isomer xylene	Alkyl Benzenes	1330-20-7	106.17	0.003

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Benzene	VOC	71-43-2	78.10	2.900
Chloroform	VOC	67-66-3	119.40	0.021
m-Dichlorobenzene	#N/A	541-73-1	147.00	0.062
o-Dichlorobenzene	SVOC	95-50-1	147.00	0.270
p-Dichlorobenzene	SVOC	106-46-7	147.00	0.610
(1,2-dichloroethane) Ethylene Dichloride	VOC	107-06-2	99.00	0.450
Methylene Chloride	VOC	75-09-2	84.90	1.700
(tetrachloroethylene) Perchloroethylene	VOC	127-18-4	165.80	0.820
Trichloroethylene	VOC	79-01-6	131.40	0.280
Vinyl Chloride	VOC	75-01-4	62.50	0.930
Methyl-Tert-Butyl-Ether	VOC	1634-04-4	88.20	0.230
Freon 11 (CCL3F)	VOC	75-69-4	137.40	0.760
Ethyl Benzene	Alkyl Benzenes	100-41-4	106.17	8.000
Chlorobenzene	SVOC	108-90-7	112.60	2.300
(1,1,1 trichloroethane) Methyl Chloroform	VOC	71-55-6	133.40	0.038
Toluene	Alkyl Benzenes	108-88-3	92.10	16.000
1,1-Dichloroethene- (Vinylidene Chloride)	VOC	75-35-4	96.90	0.450
m-Xylene	Alkyl Benzenes	1330-20-7	106.20	7.000
o-Xylene	Alkyl Benzenes	1330-20-7	106.20	4.400
p-Xylene	Alkyl Benzenes	1330-20-7	106.20	7.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.00	170.000
Acetonitrile	VOC	75-05-8	41.00	0.250
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.10	1.100
1,3- Butadiene	VOC	106-99-0	54.10	0.056
mixed isomers xylene	Alkyl Benzenes	1330-20-7	106.20	18.400

Constituent	Assigned Group	CAS	MW	Conc (PPM)
2-butanone	VOC	78-93-3	72.10	0.096
Acetaldehyde	VOC	75-07-0	44.10	0.147
Acetone	VOC	67-64-1	58.10	0.522
Antimony	Metals	7440-36-0	121.80	0.006
Chloroethane	VOC	75-00-3	64.50	0.310
Chromium	#N/A	7440-47-3	52.00	0.082
Copper	Metals	7440-50-8	63.50	0.045
Crotonaldehyde	VOC	123-73-9	70.10	0.054
Dichlorodifluoromethane	VOC	75-71-8	120.90	2.300
Formaldehyde	VOC	50-00-0	30.00	0.057
Hexanaldehyde	#N/A	66-25-1	100.10	0.250
Lead	Metals	7439-92-1	207.20	0.018
Manganese	Metals	7439-96-5	54.90	0.029
Mercury	Metals	7439-97-6	200.60	0.000
Octamethylcyclotetrasiloxane	Siloxanes	556-67-2	296.20	0.000
p-Tolualdehyde	#N/A	104-87-0	120.20	0.011
Toluene	Alkyl Benzenes	108-88-3	92.10	1.400
Valeraldehyde	#N/A	110-62-3	86.10	0.107
Xylene (mixed isomers)	Alkyl Benzenes	1330-20-7	106.20	1.000
Zinc	Metals	7440-66-6	65.40	0.095
Carbon Dioxide	#N/A	124-38-9	44.01	22,100
Oxygen/Argon	#N/A	N/A	0.00	4,500
Nitrogen	#N/A	7727-37-9	28.01	60,300
Hydrogen	#N/A	1333-74-0	2.02	8,700
Methane	#N/A	74-82-8	16.04	994,100
Ethane	#N/A	74-84-0	30.07	30.000
Hexane Plus	#N/A	N/A	0.00	13.000
c5-c7 cycloalkanes	#N/A	N/A	0.00	2.000
cyclopentane	Alkanes	287-92-3	70.13	1.000
methylcyclopentane	#N/A	96-37-7	84.16	1.000
cyclohexane	Alkanes	110-82-7	84.16	1.000
methylcyclohexane	Alkanes	108-87-2	98.21	1.000
heavier aromatics	#N/A	N/A		1.000
c3 benzenes	#N/A	N/A		1.000
c6+ hyrdrocarbons	#N/A	N/A		10.000
hexanes	#N/A	N/A		4.000
heptanes	#N/A	N/A		2.000
octances	#N/A	N/A		1.000
nonanes	#N/A	N/A		2.000
decanes	#N/A	N/A		4.000
undecanes	#N/A	N/A		2.000
sulfur dioxide	Sulfur Compds	7446-09-5	64.07	0.250
carbonyl sulfide	Sulfur Compds	463-58-1	60.08	0.080
dimethyl sulfide	#N/A	75-18-3	62.13	5.450
di-n-butyl phthalate	SVOC	84-74-2	278.34	0.004
bis(2-ethylhexyl)phthalate	SVOC	117-81-7	390.56	0.003
Propionaldehyde	VOC	123-38-6	58.08	0.010
butyraldehyde(butanal)	#N/A	123-72-8	72.11	0.069

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	368,800
Methane	#N/A	74-82-8	16.04	654,270
Hexane plus	#N/A			45.000
Toluene	Alkyl Benzenes	108-88-3	92.14	26.000
C3 Benzenes	#N/A			2.000
Nonanes	#N/A	111-84-2	128.26	1.000
Decanes	#N/A	124-18-5	142.28	11.000
Undecanes	#N/A	1120-21-4	156.31	10.000
Dodecanes	#N/A	112-40-3	170.33	3.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	300.0
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.310
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	0.350
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	0.070
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.320
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	0.100
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.030
Thiophenol	Sulfur Compds	108-98-5	110.18	0.050
Benzene	VOC	71-43-2	78.11	0.001
Carbon Tetrachloride	VOC	56-23-5	153.82	0.000
Toluene	Alkyl Benzenes	108-88-3	92.14	0.004
1,1,2,2-Tetrachloroethane	VOC	79-34-5	167.85	0.0005
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.001
n-Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.002
1,3,5-Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.005
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.014
sec-Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.001
1,4-Dichlorobenzene	SVOC	106-46-7	147.00	0.217
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.549
n-Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.002
Naphthalene	PAHs	91-20-3	128.17	0.003
2-Methylnaphthalene	PAHs	91-57-6	142.20	0.003
1-Methylnaphthalene	PAHs	90-12-0	142.20	0.002
4-Nitrophenol	SVOC	100-02-7	139.11	0.003
Di-n-butylphthalate	#N/A	84-74-2	278.34	0.001
Bis(2-ethylhexyl) adipate	SVOC	103-23-1	370.57	0.000
bis(2-Ethylhexyl) phthalate	SVOC	117-81-7	390.56	0.003
Mercury	Metals	7439-97-6	200.59	0.000
Zinc	Metals	7440-66-6	65.38	0.031
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	5.450
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.77	0.780
Formaldehyde	VOC	50-00-0	30.03	0.001

Table B-4: WWTP GTI B Raw Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Acetaldehyde	VOC	75-07-0	44.05	0.005
Acetone	VOC	67-64-1	58.08	0.001
2-Butanone	VOC	78-93-3	72.11	0.0003
Benzaldehyde	#N/A	100-52-7	106.12	0.004
p-Tolualdehyde	#N/A	104-87-0	120.15	0.000
Hexanal	#N/A	66-25-1	100.16	0.003

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	394000.000
Methane	#N/A	74-82-8	16.04	995120.000
Toluene	Alkyl Benzenes	108-88-3	92.14	31.000
C3 Benzenes	#N/A			3.000
Nonanes	#N/A	111-84-2	128.26	1.000
Decanes	#N/A	124-18-5	142.28	9.000
Undecanes	#N/A	1120-21-4	156.31	6.000
Dodecanes	#N/A	112-40-3	170.33	2.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	187.000
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	0.820
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.330
Dimethyl Sulfide	#N/A	75-18-3	62.13	0.160
Benzene	VOC	71-43-2	78.11	0.001
Carbon Tetrachloride	VOC	56-23-5	153.82	0.0003
1,1,2,2-Tetrachloroethane	VOC	79-34-5	167.85	0.0005
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.0004
Di-n-butylphthalate	#N/A	84-74-2	278.34	0.001
bis(2-Ethylhexyl) phthalate	SVOC	117-81-7	390.56	0.006
Zinc	Metals	7440-66-6	65.38	0.086
Acetaldehyde	VOC	75-07-0	44.05	0.0003
Acetone	VOC	67-64-1	58.08	0.001

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	31.900
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.030
Methyl Mercaptan	Sulfur Compds	74-93-1	48.10	0.080
Ethyl Mercaptan	Sulfur Compds	75-08-1	62.13	0.300
Dimethyl Sulfide	#N/A	75-18-3	62.13	0.020
Carbon Disulfide	Sulfur Compds	75-15-0	76.14	0.009
n-Propyl Thiol	Sulfur Compds	107-03-9	76.16	0.800
iso-Propyl Thiol	Sulfur Compds	75-33-2	76.16	0.400
Isopropyl Mercaptan	Sulfur Compds	75-33-2	76.17	0.300
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.300
Hexamethylcyclotrisiloxane (D3)	#N/A	541-05-9	222.46	0.017
Octamethyltrisiloxane (L3)	#N/A	107-51-7	236.53	0.019
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	1.600
Decamethyltetrasiloxane (L4)	#N/A	141-62-8	310.69	0.170
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.85	14.000
Acetone	VOC	67-64-1	58.08	0.088
Benzene	VOC	71-43-2	78.11	0.016
Chlorobenzene	SVOC	108-90-7	112.55	0.006
Cyclohexane	Alkanes	110-82-7	84.16	0.022
1,4-Dichlorobenzene	SVOC	106-46-7	147.00	0.028
cis-1,2-Dichloroethene	VOC	107-06-2	98.96	0.103
trans-1,2-Dichloroethene	VOC	156-60-5	96.94	0.005
Ethyl Acetate	#N/A	141-78-6	88.10	0.022
Ethylbenzene	Alkyl Benzenes	100-41-4	106.16	0.141
4-Ethyltoluene	#N/A	622-96-8	120.21	0.069
Freon 11	VOC	75-69-4	137.37	0.006
n-Heptane	Alkanes	8031-33-2	100.20	0.122
Hexane	Alkanes	110-54-3	86.17	0.210
Methylene Chloride	VOC	75-09-2	84.93	0.014
Methyl Isobutyl Ketone (MIBK)	VOC	108-10-1	100.16	0.005
Propene	VOC	115-07-1	42.08	3.730
Styrene	VOC	100-42-5	104.15	0.025
Tetrachloroethene (PCE)	VOC	127-18-4	165.83	0.011
Tetrachloroethylene	VOC	127-18-4	165.83	0.026
Toluene	Alkyl Benzenes	108-88-3	92.14	7.300
1,2,4-Trichlorobenzene	#N/A	120-82-1	181.45	0.009
Trichloroethene (TCE)	VOC	79-01-6	165.83	0.028

Table B-4: WWTP Raw SCAQMD Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Trichloroethylene	VOC	79-01-6	165.83	0.023
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.240
1,3,5-Trimethylbenzene	#N/A	108-67-8	120.19	0.088
2,2,4-Trimethylpentane	#N/A	540-84-1	114.22	0.066
m & p-Xylene	Alkyl Benzenes	1330-20-7	106.17	0.180
o-Xylene	Alkyl Benzenes	1330-20-7	106.17	0.064
mixed isomer xylene (total)	Alkyl Benzenes	1330-20-7	106.17	0.244

Table B-4: WWTP Raw JWPCP Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	16.500
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.050
Methyl Mercaptan	Sulfur Compds	74-93-1	48.10	0.090
Ethyl Mercaptan	Sulfur Compds	75-08-1	62.13	0.070
Dimethyl Sulfide	#N/A	75-18-3	62.13	0.050
Carbon Disulfide	Sulfur Compds	75-15-0	76.14	0.030
Dimethyl Disulfide	#N/A	624-92-0	94.19	0.040
Isopropyl Mercaptan	Sulfur Compds	75-33-2	76.17	0.160
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.080
Vinyl Chloride	VOC	75-01-4	62.50	0.208
Ethyl Chloride	VOC	75-00-3	64.51	0.016
1,2-Dichloromethane	VOC	75-09-2	84.93	0.080
1,1,1-Trichloroethane	VOC	71-55-6	133.40	0.012
Benzene	VOC	71-43-2	78.11	1.060
Carbon Tetrachloride	VOC	56-23-5	153.82	0.016
Trichloroethene	VOC	79-01-6	131.40	0.028
Toluene	Alkyl Benzenes	108-88-3	92.14	4.760
1,2-Dibromoethane	VOC	106-93-4	187.86	0.012
Perchloroethane	VOC	98299-61-7	236.74	0.008
Chlorobenzene	SVOC	108-90-7	112.55	1.140
m,p-Xylene	Alkyl Benzenes	1330-20-7	106.17	12.400
Styrene	VOC	100-42-5	104.15	0.192
o-Xylene	Alkyl Benzenes	1330-20-7	106.17	3.990
Dichlorobenzes	SVOC	106-46-7	147.00	2.520
Butadlene	VOC	106-99-0	54.09	0.001
1,4-Dioxane	VOC	123-91-1	88.11	0.030
mixed isomer xylenes	Alkyl Benzenes	1330-20-7	106.17	16.390

Table B-4: Dairy raw GTI Tsk2 Values

Constituent	Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	403900.000
Oxygen/Argon	#N/A			29400.000
Nitrogen	#N/A	7727-37-9	28.01	126700.000
Methane	#N/A	74-82-8	16.04	685800.000
Hexane	Alkanes	110-54-3	86.18	4.000
Ammonia	Other	7664-41-7	17.03	40.000
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	6570.000
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	4.090
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	6570.000
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	7.730
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	4.090
Carbon Disulfide	Sulfur Compds	75-15-0	76.14	0.170
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	6.120
Ethyl Mercaptan	Sulfur Compds	75-08-1	62.13	0.300
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	1.350
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.090
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	0.600
Dimethyl Sulfide	#N/A	75-18-3	62.13	0.320
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.320
Diethyl Disulfide	#N/A	110-81-6	225.31	0.150
Thiophene	Sulfur Compds	110-02-1	84.14	0.260
Benzene	VOC	71-43-2	78.11	0.014
Carbon Tetrachloride	VOC	56-23-5	153.82	0.002
Pyridine	SVOC	110-86-1	79.10	0.001
Toluene	Alkyl Benzenes	108-88-3	92.14	0.147
1,1,2-Trichloroethane	VOC	79-00-5	133.40	0.053
Tetrachloroethene	VOC	127-18-4	165.83	0.001
Ethylbenzene	Alkyl Benzenes	100-41-4	106.17	0.034
m/p-Xylenes (used mixed isomers)	Alkyl Benzenes	1330-20-7	106.20	0.045
Styrene	VOC	100-42-5	104.15	0.000
o-Xylene (used mix isomers)	Alkyl Benzenes	1330-20-7	106.20	0.034
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.007
n-Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.011
1,3,5-Trimethylbenzene	#N/A	108-67-8	120.19	0.014
tert-Butylbenzene	Alkyl Benzenes	98-06-6	134.22	0.005

Table B-4: Dairy raw GTI Tsk2 Values

Constituent	Group	CAS	MW	Conc (PPM)
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.042
sec-Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.013
Phenol	SVOC	108-95-2	94.11	0.028
Aniline	SVOC	62-53-3	93.13	0.026
2-Chlorophenol	Chlorophenols	95-57-8	128.56	0.001
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.008
Benzyl Alcohol	SVOC	100-51-6	108.14	0.014
Heptachlor	Pesticides	76-44-8	373.32	0.000013
Heptachlor epoxide	Pesticides	1024-57-3	389.32	0.000013
Endosulfan I	Pesticides	959-98-8	406.92	0.000002
Endrin	Pesticides	72-20-8	380.91	0.000001
4,4'-DDD	Pesticides	72-54-8	320.04	0.000001
Endrin aldehyde	Pesticides	7421-93-4	380.91	0.000006
4,4'-DDT	Pesticides	50-29-3	354.48	0.000016
Methoxychlor	Pesticides	72-43-5	345.65	0.000047
sum mixed isomer xylenes	Alkyl Benzenes	1330-20-7	106.20	0.079

Table B-4: Dairy Clean GTI Tsk2 Values

Constituent	Assigned Group	CAS	MW	Conc (PPM)
Carbon Dioxide	#N/A	124-38-9	44.01	9,500
Oxygen/Argon	#N/A			19,900
Nitrogen	#N/A	7727-37-9	28.01	78,100
Methane	#N/A	74-82-8	16.04	996,300
Ethane	#N/A	74-84-0	30.07	1,100
propane	Alkanes	74-98-6	44.10	280
i-Butane	Alkanes	75-28-5	58.12	50.000
n-Butane	Alkanes	106-97-8	58.12	50.000
i-pentane	Alkanes	78-78-4	72.17	20.000
Hexane Plus (used Hexane only)	#N/A			0.210
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	0.530
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.08	5.280
Benzene	VOC	71-43-2	78.11	0.027
Carbon Tetrachloride	VOC	56-23-5	153.82	0.002
Toluene	Alkyl Benzenes	108-88-3	92.14	0.108
Ethylbenzene	Alkyl Benzenes	100-41-4	106.17	0.003
(m/p-Xylenes (-p cas 106-42-3)	Alkyl Benzenes	1330-20-7	106.17	0.011
o-Xylene	Alkyl Benzenes	1330-20-7	106.17	0.003
1,3,5-Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.001
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.001
Benzyl Alcohol	SVOC	100-51-6	108.14	0.002
N-nitroso-di-n-propylamine	Nitroso Compds	621-64-7	130.22	0.004
Naphthalene	PAHs	91-20-3	128.17	0.002
Di-n-butylphthalate	SVOC	84-74-2	278.34	0.002
bis(2-Ethylhexyl)phthalate	SVOC	117-81-7	390.56	0.001
sum mixed isomer xylene (total)	Alkyl Benzenes	1330-20-7	106.17	0.014

Constituent	Assigned Group	CAS	MW	Conc (PPM)	data source
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	0.590	nat gas GTI A values
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	0.500	nat gas GTI B values
Ethyl benzene	Alkyl Benzenes	100-41-4	106.17	1.000	nat gas GTI B values
Styrene	VOC	100-42-5	104.15	0.038	nat gas Air Liq data
Benzyl Alcohol	SVOC	100-51-6	108.14	0.001	nat gas GTI B values
Benzaldehyde	#N/A	100-52-7	106.12	0.002	nat gas GTI B values
n-Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.036	nat gas GTI B values
n-Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.018	nat gas GTI B values
n-Butane	Alkanes	106-97-8	58.12	780.000	nat gas GTI B values
1,3-Butadiene	VOC	106-99-0	54.09	11.300	nat gas GTI A values
Acrolein	VOC	107-02-8	56.06	0.000	nat gas GTI B values
Acrylonitrile	VOC	107-13-1	53.06	4.000	nat gas GTI A values
BFB (IS)	VOC	1072-85-1	175.00	0.010	nat gas Air Liq data
Vinyl Acetate	VOC	108-05-4	86.09	2.226	nat gas Air Liq data
4-Methyl-2-pentanone(MIBK)	VOC	108-10-1	100.16	1.078	nat gas Air Liq data
1,3,5-trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.357	nat gas Air Liq data
Methylcyclohexane	Alkanes	108-87-2	98.19	25.000	nat gas GTI B values
Tolune	Alkyl Benzenes	108-88-3	92.14	15.834	nat gas Air Liq data
Tetrahydrofuran	VOC	109-99-9	72.11	4.945	nat gas Air Liq data
Thiophene	Sulfur Compds	110-02-1	84.14	0.120	nat gas GTI B values
Hexane	Alkanes	110-54-3	86.18	185.000	nat gas GTI B values
Pentanal	#N/A	110-62-3	86.13	0.000	nat gas GTI B values
Cyclohexane	Alkanes	110-82-7	84.16	18.000	nat gas GTI B values
Octanes	#N/A	111-65-9	114.23	40.000	nat gas GTI B values
Nonanes	#N/A	111-84-2	128.26	14.000	nat gas GTI A values
Undecanes	#N/A	1120-21-4	156.31	1.000	nat gas GTI A values
Dodecanes	#N/A	112-40-3	170.33	1.000	nat gas GTI A values
Propene	VOC	115-07-1	42.08	60.000	nat gas GTI B values
Bis(2-ethylhexyl)phthalate	SVOC	117-81-7	390.56	0.700	nat gas GTI A values
Propionaldehyde	VOC	123-38-6	58.08	0.003	nat gas GTI A values
Butanal	#N/A	123-72-8	72.11	0.001	nat gas GTI B values
Crotonaldehyde	VOC	123-73-9	70.09	0.008	nat gas GTI A values
1,4-dioxane	VOC	123-91-1	88.11	0.050	nat gas Air Liq data

Table B-4: Nat gas highest conc list

Constituent	Assigned Group	CAS	MW	Conc (PPM)	data source
Decanes	#N/A	124-18-5	142.28	4.000	nat gas GTI A values
Carbon Dioxide	#N/A	124-38-9	44.01	16600.000	nat gas GTI A values
Dibromochloromethane	VOC	124-48-1	208.28	0.002	nat gas GTI B values
sum mixed isomer Xylene	Alkyl Benzenes	1330-20-7	106.17	6.300	nat gas GTI A values
sec-Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.013	nat gas GTI B values
Ehthyl Acetate	#N/A	141-78-6	88.11	7.523	nat gas Air Liq data
Heptane	#N/A	142-82-5	100.20	86.000	nat gas GTI B values
t-1,2-Dichloreothene	VOC	156-60-5	96.94	0.129	nat gas Air Liq data
Di-n-butylphthalate	#N/A	84-74-2	278.34	0.001	nat gas GTI B values
Cyclopentane	Alkanes	287-92-3	70.13	24.000	nat gas GTI B values
Cyclohexane, 1-ethyl-2-methyl-	#N/A	3728-54-9	126.24	6.806	nat gas Air Liq data
Crotonaldehyde	#N/A	123-73-9	70.09	0.000	nat gas GTI B values
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	7.940	nat gas GTI B values
Formaldehyde	VOC	50-00-0	30.03	0.006	nat gas GTI B values
2,2,4-Trimethylpentane	#N/A	540-84-1	114.23	4.000	nat gas GTI B values
Carbon Tetrachloride	VOC	56-23-5	153.82	0.056	nat gas Air Liq data
Hexane, 3-ethyl-	#N/A	619-99-8	114.23	52.422	nat gas Air Liq data
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.240	nat gas GTI B values
Propane, 2-methyl-1-nitro-	VOC	625-74-1	103.12	10.440	nat gas Air Liq data
Methyl Ethyl Sulfide	#N/A	625-80-9	118.24	1.230	nat gas GTI B values
Tridecanes	#N/A	629-50-5	184.36	1.000	nat gas GTI A values
Tetradecanes	#N/A	629-59-4	198.39	1.000	nat gas GTI A values
Ethanol	#N/A	64-17-5	46.07	0.409	nat gas Air Liq data
Acetone	VOC	67-64-1	58.08	0.103	nat gas GTI A values
Chloroform	VOC	67-66-3	119.38	3.983	nat gas Air Liq data
Butanol	VOC	71-36-3	74.12	0.038	nat gas GTI A values
Benzene	VOC	71-43-2	78.11	38.814	nat gas Air Liq data
mercury	Metals	7439-97-6	200.59	0.000	nat gas GTI A values
copper	Metals	7440-50-8	63.55	0.029	nat gas GTI A values
Zinc	Metals	7440-66-6	65.38	0.039	nat gas GTI B values
Methane	#N/A	74-82-8	16.04	974420.000	nat gas GTI B values
Bromomethane	VOC	74-83-9	94.94	0.373	nat gas Air Liq data
Ethane	#N/A	74-84-0	30.07	24880.000	nat gas GTI B values

Table B-4: Nat gas highest conc list

Constituent	Assigned Group	CAS	MW	Conc (PPM)	data source
Chloromethane	VOC	74-87-3	50.49	36.654	nat gas Air Liq data
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	5.380	nat gas GTI B values
Propane	Alkanes	74-98-6	44.10	4020.000	nat gas GTI B values
Acetaldehyde	VOC	75-07-0	44.05	0.095	nat gas GTI A values
Dimethyl Sulfide	#N/A	75-18-3	62.13	1.180	nat gas GTI A values
Tribromomethane	VOC	75-25-2	252.73	0.041	nat gas Air Liq data
Bromodichloromethane	VOC	75-27-4	163.80	0.132	nat gas Air Liq data
i-Butane	Alkanes	75-28-5	58.12	560.000	nat gas GTI B values
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	0.490	nat gas GTI B values
1,1-Dichloroethene	VOC	75-35-4	96.94	0.077	nat gas Air Liq data
Trichloromonofluoromethane	#N/A	75-39-4	137.37	0.118	nat gas Air Liq data
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	2.360	nat gas GTI A values
Nitrogen	#N/A	7727-37-9	28.01	12000.000	nat gas GTI A values
Oxygen/Argon	#N/A	7782-44-7	0.00	1300.000	nat gas GTI A values
Propane, 1-bromo-2-methyl-	VOC	78-77-3	137.02	4.898	nat gas Air Liq data
i-Pentane	Alkanes	78-78-4	72.17	240.000	nat gas GTI B values
Methacrolein (Isobutenal)	Missing	78-85-3	70.09	0.010	nat gas GTI A values
2-Butanone	VOC	78-93-3	72.11	0.007	nat gas GTI B values
Trichloroethylene	VOC	79-01-6	131.40	0.174	nat gas Air Liq data
n-Pentane	Alkanes	8031-35-4	72.15	180.000	nat gas GTI B values
Di-n-butyl phthalate	SVOC	84-74-2	278.34	0.700	nat gas GTI A values
1-methylnaphthalene	PAHs	90-12-0	142.20	1.400	nat gas GTI A values
Naphthalene	PAHs	91-20-3	128.17	0.008	nat gas GTI B values
2-methylnaphthalene	PAHs	91-57-6	142.21	2.400	nat gas GTI A values
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.474	nat gas GTI B values
Methylcyclopentane	#N/A	96-37-7	84.16	17.000	nat gas GTI B values
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.019	nat gas GTI B values
Nitrobenzene	SVOC	98-95-3	123.11	0.009	nat gas GTI B values
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.018	nat gas GTI B values
C5-C7 Cycloalkanes	#N/A				nat gas GTI A values

Constituent	Assigned Group	CAS	MW	Conc (PPM)	Data Source
Sulfur Dioxide	Sulfur Compds	7446-09-5	64.06	7.730	Dairy raw GTI Task 2
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	6570.000	Dairy raw GTI Task 2
4-Nitrophenol	SVOC	100-02-7	139.11	0.003	WWT raw GTI B
Ethyl Benzene	Alkyl Benzenes	100-41-4	106.17	8.000	LA Landfill raw
Styrene	VOC	100-42-5	104.15	0.192	WWTP raw JWPCP
Benzyl Alcohol	SVOC	100-51-6	108.14	0.243	landfill raw GTI B values
Benzaldehyde	#N/A	100-52-7	106.12	0.011	landfill raw GTI B values
trans-1,3-Dichloropropene	VOC	10061-02-6	110.97	0.001	landfill raw GTI B values
Heptachlor epoxide	Pesticides	1024-57-3	389.32	0.000	Dairy raw GTI Task 2
Bis(2-ethylhexyl) adipate	SVOC	103-23-1	370.57	0.000	WWT raw GTI B
n-Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.025	landfill raw GTI B values
n-Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.015	landfill raw GTI B values
p-Tolualdehyde	#N/A	104-87-0	120.15	0.057	landfill raw GTI B values
2,4-Dimethylphenol	#N/A	105-67-9	122.16	0.001	landfill raw GTI B values
4-Chlorotoluene	SVOC	106-43-4	126.58	0.004	landfill raw GTI B values
3,4-Methylphenol (o,p-cresol)	SVOC	106-44-5	108.13	0.001	landfill raw GTI B values
Dichlorobenzes	SVOC	106-46-7	147.00	2.520	WWTP raw JWPCP
4-Chloroaniline	SVOC	106-47-8	127.60	0.003	landfill raw GTI B values
1,2-Dibromoethane	VOC	106-93-4	187.86	0.012	WWTP raw JWPCP
1,3- Butadiene	VOC	106-99-0	54.10	0.056	LA Landfill raw
n-Propyl Thiol	Sulfur Compds	107-03-9	76.16	0.800	WWT Raw SCAQMD
(1,2-dichloroethane) Ethylene Dichloride	VOC	107-06-2	99.00	0.450	LA Landfill raw
Octamethyltrisiloxane (L3)	#N/A	107-51-7	236.53	0.019	WWT Raw SCAQMD
Methyl Isobutyl Ketone (MIBK)	VOC	108-10-1	100.16	0.005	WWT Raw SCAQMD
1,3,5-Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.124	landfill raw GTI B values
Methylcyclohexane	Alkanes	108-87-2	98.19	3.000	landfill raw GTI B values
Toluene	Alkyl Benzenes	108-88-3	92.14	26.000	WWT raw GTI B
Chlorobenzene	SVOC	108-90-7	112.60	2.300	LA Landfill raw
Phenol	SVOC	108-95-2	94.11	0.028	Dairy raw GTI Task 2
Thiophenol	Sulfur Compds	108-98-5	110.18	0.050	WWT raw GTI B
Thiophene	Sulfur Compds	110-02-1	84.14	0.260	Dairy raw GTI Task 2
Hexane	Alkanes	110-54-3	86.18	47.000	landfill raw GTI B values
Pentanal	#N/A	110-62-3	86.13	0.017	landfill raw GTI B values
Diethyl Disulfide	#N/A	110-81-6	225.31	0.150	Dairy raw GTI Task 2
Cyclohexane	Alkanes	110-82-7	84.16	6.000	landfill raw GTI B values
Pyridine	SVOC	110-86-1	79.10	0.001	Dairy raw GTI Task 2
bis(2-Chloroethyl)ether	VOC	111-44-4	143.01	0.001	landfill raw GTI B values
Octanes	#N/A	111-65-9	114.23	20.000	landfill raw GTI B values
Nonanes	#N/A	111-84-2	128.26	17.000	landfill raw GTI B values
Dodecanes	#N/A	112-40-3	170.33	3.000	landfill raw GTI B values
Undecanes	#N/A	1120-21-4	156.31	23.000	landfill raw GTI B values
Propene	VOC	115-07-1	42.08	20.000	landfill raw GTI B values
bis(2-Ethylhexyl) phthalate	SVOC	117-81-7	390.56	0.003	WWT raw GTI B
1,2,4-Trichlorobenzene	#N/A	120-82-1	181.45	0.009	WWT Raw SCAQMD
Propionaldehyde	VOC	123-38-6	58.08	0.016	landfill raw GTI B values
Butanal	#N/A	123-72-8	72.11	0.037	landfill raw GTI B values
1,4-Dioxane	VOC	123-91-1	88.11	0.030	WWTP raw JWPCP
Decanes	#N/A	124-18-5	142.28	43.000	landfill raw GTI B values
Carbon Dioxide	#N/A	124-38-9	44.01	403900.000	Dairy raw GTI Task 2

Constituent	Assigned Group	CAS	MW	Conc (PPM)	Data Source
(tetrachloroethylene) Perchloroethylene	VOC	127-18-4	165.80	0.820	LA Landfill raw
Dibenzofuran	SVOC	132-64-9	106.20	0.002	landfill raw GTI B values
mixed isomers xylene	Alkyl Benzenes	1330-20-7	106.20	18.400	LA Landfill raw
Hydrogen	#N/A	1333-74-0	2.02	3000.000	landfill raw GTI B values
sec-Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.016	landfill raw GTI B values
Decamethyltetrasiloxane (L4)	#N/A	141-62-8	310.69	0.170	WWT Raw SCAQMD
Ethyl Acetate	#N/A	141-78-6	88.10	0.022	WWT Raw SCAQMD
Heptane	#N/A	142-82-5	100.20	31.000	landfill raw GTI B values
Hexamethyldisilane	#N/A	1450-14-2	146.38	0.950	landfill raw GTI B values
cis-1,2-Dichloroethene	VOC	156-59-2	96.94	0.530	landfill raw GTI B values
trans-1,2-Dichloroethene	VOC	156-60-5	96.94	0.005	WWT Raw SCAQMD
Methyl-Tert-Butyl-Ether	VOC	1634-04-4	88.20	0.230	LA Landfill raw
Di-n-butylphthalate	#N/A	84-74-2	278.34	0.002	landfill raw GTI B values
Cyclopentane	Alkanes	287-92-3	70.13	4.000	landfill raw GTI B values
Dimethyl Trisulfide	#N/A	3658-80-8	126.25	0.020	landfill raw GTI B values
Crotonaldehyde	#N/A	123-73-9	70.09	0.018	landfill raw GTI B values
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.07	4.090	Dairy raw GTI Task 2
Formaldehyde	VOC	50-00-0	30.03	0.003	landfill raw GTI B values
4,4'-DDT	Pesticides	50-29-3	354.48	0.000	Dairy raw GTI Task 2
2,2,4-Trimethylpentane	#N/A	540-84-1	114.23	2.000	landfill raw GTI B values
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.85	14.000	WWT Raw SCAQMD
Hexamethylcyclotrisiloxane (D3)	#N/A	541-05-9	222.46	0.017	WWT Raw SCAQMD
m-Dichlorobenzene	#N/A	541-73-1	147.00	0.062	LA Landfill raw
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	5.450	WWT raw GTI B
Carbon Tetrachloride	VOC	56-23-5	153.82	0.016	WWTP raw JWPCP
Aniline	SVOC	62-53-3	93.13	0.026	Dairy raw GTI Task 2
N-nitroso-di-n-propylamine	Nitroso Compds	621-64-7	130.19	0.012	landfill raw GTI B values
4-Ethyltoluene	#N/A	622-96-8	120.21	0.069	WWT Raw SCAQMD
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.380	landfill raw GTI B values
Methyl Ethyl Sulfide	#N/A	625-80-9	118.24	0.050	landfill raw GTI B values
Hexanal	#N/A	66-25-1	100.16	0.006	landfill raw GTI B values
Acetone	VOC	67-64-1	58.08	0.368	landfill raw GTI B values
Chloroform	VOC	67-66-3	119.40	0.021	LA Landfill raw
Perchloroethane	VOC	98299-61-7	236.74	0.008	WWTP raw JWPCP
Benzene	VOC	71-43-2	78.11	3.000	landfill raw GTI B values
(1,1,1 trichloroethane) Methyl Chloroform	VOC	71-55-6	133.40	0.038	LA Landfill raw
Endrin	Pesticides	72-20-8	380.91	0.000001	Dairy raw GTI Task 2
Methoxychlor	Pesticides	72-43-5	345.65	0.000047	Dairy raw GTI Task 2
4,4'-DDD	Pesticides	72-54-8	320.04	0.000001	Dairy raw GTI Task 2
Methane	#N/A	74-82-8	16.04	685800.000	Dairy raw GTI Task 2
Chloromethane	VOC	74-87-3	50.49	0.140	landfill raw GTI B values
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	6.120	Dairy raw GTI Task 2
Propane	Alkanes	74-98-6	44.10	30.000	landfill raw GTI B values
Endrin aldehyde	Pesticides	7421-93-4	380.91	0.00001	Dairy raw GTI Task 2
Mercury	Metals	7439-97-6	200.59	0.00021	landfill raw GTI B values
Antimony	Metals	7440-36-0	121.76	0.084	landfill raw GTI B values
Arsenic	Metals	7440-38-2	74.92	0.111	landfill raw GTI B values
Zinc	Metals	7440-66-6	65.38	0.042	landfill raw GTI B values
Chloroethane	VOC	75-00-3	64.51	0.880	landfill raw GTI B values

Constituent	Assigned Group	CAS	MW	Conc (PPM)	Data Source
Vinyl Chloride	VOC	75-01-4	62.50	0.930	LA Landfill raw
Acetonitrile	VOC	75-05-8	41.00	0.250	LA Landfill raw
Acetaldehyde	VOC	75-07-0	44.05	0.060	landfill raw GTI B values
Ethyl Mercaptan	Sulfur Compds	75-08-1	62.13	0.300	WWT Raw SCAQMD
Dichloromethane (Methylene Chloride)	VOC	75-09-2	84.93	2.480	landfill raw GTI B values
Carbon Disulfide	Sulfur Compds	75-15-0	76.14	0.220	landfill raw GTI B values
Dimethyl Sulfide	#N/A	75-18-3	62.13	19.600	landfill raw GTI B values
i-Butane	Alkanes	75-28-5	58.12	20.000	landfill raw GTI B values
i-Propyl Mercaptan	Sulfur Compds	75-33-2	76.16	2.210	landfill raw GTI B values
1,1-Dichloroethane	VOC	75-34-3	98.96	0.200	landfill raw GTI B values
1,1-Dichloroethene- (Vinylidene Chloride)	VOC	75-35-4	96.90	0.450	LA Landfill raw
t-Butyl Mercaptan	Sulfur Compds	75-66-1	90.19	0.600	Dairy raw GTI Task 2
Freon 11 (CCL3F)	VOC	75-69-4	137.40	0.760	LA Landfill raw
Dichlorodifluoromethane	VOC	75-71-8	120.91	2.050	landfill raw GTI B values
1,2-Dichlorotetrafluoroethane (CFC-114)	#N/A	76-14-2	170.92	0.330	landfill raw GTI B values
Heptachlor	Pesticides	76-44-8	373.32	0.00001	Dairy raw GTI Task 2
Ammonia	Other	7664-41-7	17.03	40.000	Dairy raw GTI Task 2
Nitrogen	#N/A	7727-37-9	28.01	126700.000	Dairy GTI Task 2
i-Pentane	Alkanes	78-78-4	72.17	30.000	landfill raw GTI B values
Methacrolein	Missing	78-85-3	70.09	0.109	landfill raw GTI B values
2-Butanone	VOC	78-93-3	72.11	0.345	landfill raw GTI B values
Trichloroethane	VOC	79-00-5	133.40	0.380	landfill raw GTI B values
Trichloroethylene	VOC	79-01-6	131.40	0.280	LA Landfill raw
1,1,2,2-Tetrachloroethane	VOC	79-34-5	167.85	0.001	landfill raw GTI B values
n-Heptane	Alkanes	8031-33-2	100.20	0.122	WWT Raw SCAQMD
Acenaphthene	#N/A	83-32-9	154.21	0.005	landfill raw GTI B values
Diethylphthalate	SVOC	84-66-2	222.24	0.001	landfill raw GTI B values
Phenanthrene	PAHs	85-01-8	178.23	0.001	landfill raw GTI B values
Fluorene	#N/A	86-73-7	166.22	0.002	landfill raw GTI B values
1,2,3-Trichlorobenzene	#N/A	87-61-6	181.45	0.001	landfill raw GTI B values
1-Methylnaphthalene	PAHs	90-12-0	142.20	0.016	landfill raw GTI B values
Naphthalene	PAHs	91-20-3	128.17	0.217	landfill raw GTI B values
2-Methylnaphthalene	PAHs	91-57-6	142.20	0.033	landfill raw GTI B values
2-Chlorotoluene	SVOC	95-49-8	126.58	0.006	landfill raw GTI B values
o-Dichlorobenzene	SVOC	95-50-1	147.00	0.270	LA Landfill raw
2-Chlorophenol	Chlorophenols	95-57-8	128.56	0.001	Dairy raw GTI Task 2
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.323	landfill raw GTI B values
Endosulfan I	Pesticides	959-98-8	406.92	0.000002	Dairy raw GTI Task 2
Methylcyclopentane	#N/A	96-37-7	84.16	2.000	landfill raw GTI B values
tert-Butylbenzene	Alkyl Benzenes	98-06-6	134.22	0.013	landfill raw GTI B values
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.022	landfill raw GTI B values
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.760	landfill raw GTI B values
C2-Thiophenes	#N/A			0.060	landfill raw GTI B values
Oxygen/Argon	#N/A			29400.000	Dairy raw GTI Task 2
Hexane plus	#N/A			45.000	WWT raw GTI B
C3 Benzenes	#N/A			8.000	landfill raw GTI B values
C1-Thiophenes	#N/A			0.100	landfill raw GTI B values

Constituent	Assigned Group	CAS	MW	Conc (PPM)	Data Source
sulfur dioxide	Sulfur Compds	7446-09-5	64.07	0.250	Landfill Clean GTI A values
Hydrogen Sulfide	Sulfur Compds	7783-06-4	34.08	187.000	WWT Clean GTI B
Ethylbenzene	Alkyl Benzenes	100-41-4	106.17	0.003	Dairy Clean GTI task 2
Benzyl Alcohol	SVOC	100-51-6	108.14	0.002	Dairy Clean GTI task 2
Benzaldehyde	#N/A	100-52-7	106.12	0.002	Landfill Clean GTI B values
n-Propylbenzene	Alkyl Benzenes	103-65-1	120.19	0.0005	Landfill Clean GTI B values
n-Butylbenzene	Alkyl Benzenes	104-51-8	134.22	0.000	Landfill Clean GTI B values
p-Tolualdehyde	#N/A	104-87-0	120.20	0.011	Landfill Clean GTI A values
1,4-Dichlorobenzene	SVOC	106-46-7	147.00	0.002	Landfill Clean GTI B values
n-Butane	Alkanes	106-97-8	58.12	50.000	Dairy Clean GTI task 2
Acrolein	VOC	107-02-8	56.06	0.001	Landfill Clean GTI B values
n-Propyl Mercaptan	Sulfur Compds	107-03-9	76.16	0.330	WWT Clean GTI B
1,3,5-Trimethylbenzene	Alkyl Benzenes	108-67-8	120.19	0.001	Landfill Clean GTI B values
methylcyclohexane	Alkanes	108-87-2	98.21	1.000	Landfill Clean GTI A values
Toluene	Alkyl Benzenes	108-88-3	92.14	31.000	WWT Clean GTI B
Hexane	Alkanes	110-54-3	86.18	8.000	Landfill Clean GTI B values
Valeraldehyde	#N/A	110-62-3	86.10	0.107	Landfill Clean GTI A values
cyclohexane	Alkanes	110-82-7	84.16	1.000	Landfill Clean GTI A values
Nonanes	#N/A	111-84-2	128.26	1.000	WWT Clean GTI B
Undecanes	#N/A	1120-21-4	156.31	6.000	WWT Clean GTI B
Dodecanes	#N/A	112-40-3	170.33	2.000	WWT Clean GTI B
Propene	VOC	115-07-1	42.08	20.000	Landfill Clean GTI B values
bis(2-Ethylhexyl) phthalate	SVOC	117-81-7	390.56	0.006	WWT Clean GTI B
Propionaldehyde	VOC	123-38-6	58.08	0.010	Landfill Clean GTI A values
butyraldehyde(butanal)	#N/A	123-72-8	72.11	0.069	Landfill Clean GTI A values
Crotonaldehyde	VOC	123-73-9	70.10	0.054	Landfill Clean GTI A values
Decanes	#N/A	124-18-5	142.28	9.000	WWT Clean GTI B
Carbon Dioxide	#N/A	124-38-9	44.01	394000.000	WWT Clean GTI B
Dibromochloromethane	VOC	124-48-1	208.28	0.001	Landfill Clean GTI B values
Tetrachloroethene	VOC	127-18-4	165.83	0.0005	Landfill Clean GTI B values
Xylene (mixed isomers)	Alkyl Benzenes	1330-20-7	106.20	1.000	Landfill Clean GTI A values
Hydrogen	#N/A	1333-74-0	2.02	10000.000	Landfill Clean GTI B values
sec-Butylbenzene	Alkyl Benzenes	135-98-8	134.22	0.000	Landfill Clean GTI B values
Di-n-butylphthalate	#N/A	84-74-2	278.34	0.002	Landfill Clean GTI B values
Cyclopentane	Alkanes	287-92-3	70.13	2.000	Landfill Clean GTI B values
Crotonaldehyde	#N/A	123-73-9	70.09	0.001	Landfill Clean GTI B values
Carbonyl Sulfide	Sulfur Compds	463-58-1	60.08	5.280	Dairy Clean GTI task 2
Formaldehyde	VOC	50-00-0	30.00	0.057	Landfill Clean GTI A values
Decamethylcyclopentasiloxane (D5)	#N/A	541-02-6	370.77	0.200	Landfill Clean GTI B values
Octamethylcyclotetrasiloxane (D4)	Siloxanes	556-67-2	296.62	1.325	Landfill Clean GTI B values
Carbon Tetrachloride	VOC	56-23-5	153.82	0.002	Dairy Clean GTI task 2
N-nitroso-di-n-propylamine	Nitroso Compds	621-64-7	130.22	0.004	Dairy Clean GTI task 2
Dimethyl Disulfide	#N/A	624-92-0	94.20	0.170	Landfill Clean GTI B values
Hexanaldehyde	#N/A	66-25-1	100.10	0.250	Landfill Clean GTI A values
Acetone	VOC	67-64-1	58.10	0.522	Landfill Clean GTI A values
Benzene	VOC	71-43-2	78.11	1.000	Landfill Clean GTI B values
Lead	Metals	7439-92-1	207.20	0.018	Landfill Clean GTI A values
Manganese	Metals	7439-96-5	54.90	0.029	Landfill Clean GTI A values
Mercury	Metals	7439-97-6	200.60	0.000	Landfill Clean GTI A values
Antimony	Metals	7440-36-0	121.80	0.006	Landfill Clean GTI A values

Constituent	Assigned Group	CAS	MW	Conc (PPM)	Data Source
Chromium	#N/A	7440-47-3	52.00	0.082	Landfill Clean GTI A values
Copper	Metals	7440-50-8	63.55	0.096	Landfill Clean GTI B values
Zinc	Metals	7440-66-6	65.40	0.095	Landfill Clean GTI A values
Methane	#N/A	74-82-8	16.04	996300.000	Dairy Clean GTI task 2
Ethane	#N/A	74-84-0	30.07	1100.000	Dairy Clean GTI task 2
Methyl Mercaptan	Sulfur Compds	74-93-1	48.11	0.820	WWT Clean GTI B
propane	Alkanes	74-98-6	44.10	280.000	Dairy Clean GTI task 2
Chloroethane	VOC	75-00-3	64.51	0.660	Landfill Clean GTI B values
Vinyl Chloride	VOC	75-01-4	62.50	0.330	Landfill Clean GTI B values
Acetaldehyde	VOC	75-07-0	44.10	0.147	Landfill Clean GTI A values
dimethyl sulfide	#N/A	75-18-3	62.13	5.450	Landfill Clean GTI A values
i-Butane	Alkanes	75-28-5	58.12	50.000	Dairy Clean GTI task 2
Trichlorofluoromethane	VOC	75-69-4	137.37	0.240	Landfill Clean GTI B values
Dichlorodifluoromethane	VOC	75-71-8	120.91	3.600	Landfill Clean GTI B values
1,2-Dichlorotetrafluoroethane (CFC-114)	#N/A	76-14-2	170.92	0.170	Landfill Clean GTI B values
Nitrogen	#N/A	7727-37-9	28.01	94900.000	Landfill Clean GTI B values
i-pentane	Alkanes	78-78-4	72.17	20.000	Dairy Clean GTI task 2
Methacrolein	Missing	78-85-3	70.09	0.004	Landfill Clean GTI B values
1,2-Dichloropropane	VOC	78-87-5	112.99	0.020	Landfill Clean GTI B values
2-Butanone	VOC	78-93-3	72.11	0.198	Landfill Clean GTI B values
Trichloroethene	VOC	79-01-6	131.39	0.001	Landfill Clean GTI B values
1,1,2,2-Tetrachloroethane	VOC	79-34-5	167.85	0.000	WWT Clean GTI B
Heptane	Alkanes	8031-33-2	100.20	1.000	Landfill Clean GTI B values
Diethylphthalate	SVOC	84-66-2	222.24	0.001	Landfill Clean GTI B values
di-n-butyl phthalate	SVOC	84-74-2	278.34	0.004	Landfill Clean GTI A values
1-Methylnaphthalene	PAHs	90-12-0	142.20	0.0004	Landfill Clean GTI B values
Naphthalene	PAHs	91-20-3	128.17	0.007	Landfill Clean GTI B values
2-Methylnaphthalene	PAHs	91-57-6	142.20	0.001	Landfill Clean GTI B values
1,2,4-Trimethylbenzene	Alkyl Benzenes	95-63-6	120.19	0.004	Landfill Clean GTI B values
methylcyclopentane	#N/A	96-37-7	84.16	1.000	Landfill Clean GTI A values
Isopropylbenzene	Alkyl Benzenes	98-82-8	120.19	0.0004	Landfill Clean GTI B values
p-Isopropyltoluene	#N/A	99-87-6	134.22	0.021	Landfill Clean GTI B values
Oxygen/Argon	#N/A			19900.000	Dairy Clean GTI task 2
Hexane plus	#N/A			14.000	Landfill Clean GTI B values
c6+ hyrdrocarbons	#N/A			10.000	Landfill Clean GTI A values
hexanes	#N/A			4.000	Landfill Clean GTI A values
decanes	#N/A			4.000	Landfill Clean GTI A values
c5-c7 cycloalkanes	#N/A			2.000	Landfill Clean GTI A values
heptanes	#N/A			2.000	Landfill Clean GTI A values
nonanes	#N/A			2.000	Landfill Clean GTI A values
undecanes	#N/A			2.000	Landfill Clean GTI A values
heavier aromatics	#N/A			1.000	Landfill Clean GTI A values
c3 benzenes	#N/A			1.000	Landfill Clean GTI A values
octances	#N/A			1.000	Landfill Clean GTI A values
Hexane Plus (used Hexane only)	#N/A			0.210	Dairy Clean GTI task 2
C3 Benzenes	#N/A			3.000	WWT Clean GTI B

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APPENDIX C

Toxicity Reviews for the Constituents of Concern

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Appendix C provides toxicity summaries for the final constituents of concern. The summaries are, for the most part, excerpts of toxicology reviews that have been published by OEHHA to support the development of Reference Exposure Levels (RELs) and Cancer Slope Factors and other health risk screening values. Also included are several toxicity summaries published by the National Institute for Occupational Safety and Health (NIOSH) for cases in which a NIOSH screening value was used.

Acrolein Reference Exposure Levels

(2-propenal, acrylic aldehyde, acryladehyde, acraldehyde)

CAS 107-02-8
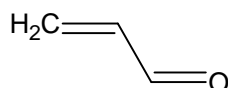
1.   Summary

Acrolein is a powerful irritant. Due to its highly reactive nature, the effects of acrolein are generally limited to the site of contact; skin, eyes and mucous membranes. Inhalation exposure to low levels ($\leq$ 1 ppm) causes irritation of the eyes, nose and throat. Acute exposures to levels above 1 ppm result in mucous hypersecretion and exacerbation of allergic airway response in animal models. Moderately higher exposures may result in severe lacrimation, and irritation of the mucous membranes of the respiratory tract. Death due to respiratory failure has been associated with high level exposures. Long term exposure to acrolein may result in structural and functional changes in the respiratory tract, including lesions in the nasal mucosa, and pulmonary inflammation. The studies reviewed for this document include those published through Spring, 2008.

1.1   Acrolein Acute REL

Reference Exposure Level	**2.5 μg/m³ (1.1 ppb)**
Critical effect(s)	Subjective ocular irritation
Hazard Index target(s)	Eyes

1.2   Acrolein 8-Hour REL

Reference Exposure Level	**0.70 μg/m³ (0.30 ppb)**
Critical effect(s)	Lesions in respiratory epithelium
Hazard Index target(s)	Respiratory

1.3   Acrolein Chronic REL

Reference Exposure Level	**0.35 μg/m³ (0.15 ppb)**
Critical effect(s)	Lesions in respiratory epithelium
Hazard Index target(s)	Respiratory

2. Physical & Chemical Properties

Description	Colorless or yellow liquid with piercing disagreeable odor
Molecular formula	C_3H_4O
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20° C
Boiling point	53° C
Melting point	-87° C
Vapor pressure	220 mm Hg @ 20° C
Flashpoint	-26° C
Explosive limits	2.8% - 31% by volume
Solubility	soluble in ethanol, diethyl ether, and up to 20% w/v in water
Odor threshold	0.5 ppm
Metabolites	glycidaldehyde, acrylic acid
Conversion factor	1 ppm in air = 2.3 mg/m^3 @ 25° C

3. Occurrence and Major Uses

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water-treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1995). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein. Acrolein is a byproduct of fires and is one of several acute toxicants to which firefighters are exposed. It is also formed from atmospheric reactions of 1,3-butadiene. The annual statewide emissions of acrolein from mobile, stationary and natural sources (not including atmospheric transformation) reported in the California Toxics Inventory for 2004 were estimated to be 2,242 tons contributing to a statewide ambient level of 0.53 ppb (CARB, 2005b).

4. Metabolism

The metabolism of acrolein comprises several pathways. It rapidly reacts with sulfhydryl groups, especially protein cysteine residues and glutathione. The glutathione conjugate may be oxidized or reduced to mercapturic acids (N-acetyl –S-2-carboxyethylcysteine and N-acetyl-S-3-hydroxypropylcysteine, respectively), with the reduction pathway predominating, followed by urinary elimination. Alternatively, acrolein may be epoxidized to glycidaldehyde, which is in turn attacked by glutathione and oxidatively processed to the mercapturic acid, N-acetyl-S-2-carboxy-2-hydroxyethylcysteine. In a third pathway, the Michael addition of water to acrolein is followed by oxidation to malonic and finally oxalic acids (Parent et al., 1998). The formation of homopolymers of acrolein is thought to occur but appears to be limited to the gut. Acrolein may also be oxidized to acrylic acid, mainly in the liver. Following inhalation exposure, the predominant metabolites are the 3-hydroxypropyl and 2-carboxyethyl mercapturic acids mentioned above (Linhart et al., 1996).

5. Acute Toxicity of Acrolein

5.1   Acute Toxicity to Adult Humans

Sensory irritation is the primary adverse effect associated with acute, low level exposures to acrolein. The irritative effects of acrolein are noticeable at low levels of exposure (≤ 0.25 ppm) and rapidly become more pronounced with increasing concentration; brief exposure (1.5 min) to 0.3 ppm (0.7 mg/m³) causes irritation of the eyes and nose (Weber-Tschopp et al., 1977). The powerful irritant and lacrimator properties of acrolein led to its use in gas grenades and artillery shells by the French in 1916. At a concentration of 7 mg/m³, acrolein caused severe lacrimation and irritation of the mucous membranes of the respiratory tract (Prentiss, 1937). A case report of respiratory failure and death in individuals exposed to vapors from overheated frying pans containing fat and food items implicated acrolein as the principal toxicant (Gosselin et al., 1979).

Ocular irritation is one of the most sensitive responses to acrolein. In a study by Darley et al. (1960), 36 human volunteers were exposed to 0.06, 1.3-1.6, and 2.0-2.3 ppm for 5 minutes. Acrolein was dissolved in water and delivered to the eyes in a stream of oxygen through face masks. Carbon-filter respirators were worn during exposure so that only the eyes were exposed to the test material. The subjects, who were without a history of chronic upper respiratory or eye problems, rated the degree of eye irritation every 30 seconds during exposure as none (0), medium (1), or severe (2). The individuals' maximum values were used in the analysis that revealed a concentration-dependent incidence of eye irritation (Table 5.1.1). The lowest observed adverse effect level (LOAEL) for eye irritation in human volunteers was estimated by an unspecified method to be 0.06 ppm (0.14 mg/m³) acrolein during the five minute exposures. A NOAEL was not observed in this study.

TABLE 5.1.1 OCULAR IRRITATION WITH ACROLEIN (FROM DARLEY ET AL., 1960)

Acrolein concentration	Irritation score
Filtered air	0.283
0.06 ppm	0.471
1.3-1.6 ppm	1.182
2.0-2.3 ppm	1.476

Ocular and upper respiratory tract irritation were also examined in a chamber study by Weber-Tschopp et al. (1977) involving healthy volunteers. Thirty one men and 22 women were exposed to increasing acrolein levels (0-0.60 ppm) for 40 min, while 21 men and 25 women were exposed to a constant 0.3 ppm for 60 min. Subjective reports of irritation and annoyance, and objective measures of eye-blink and respiratory rates were taken during the exposure periods. During exposure to increasing levels of acrolein, eye irritation, as measured by subjective report and blink frequency, was a more sensitive measure of irritation than nasal irritation. By comparison, for less reactive volatile compounds in studies surveyed by Doty et al. (2004), the thresholds for ocular and intranasal irritation were of the same magnitude. In the Weber-Tschopp study of acrolein, significantly ($p<0.01$) higher eye irritation was first observed at 0.07 ppm, and nasal irritation at 0.26 ppm compared to controls. Significant depression of respiratory

rates was observed at 0.60 ppm (p<0.05). With continuous exposure to 0.3 ppm acrolein, subjective eye and nasal irritation increased rapidly during the first 20 minutes and tended to plateau by 40 min. After 10 min of continuous exposure, a decrease in respiratory rate of 10% was evident in 47% of the subjects, while eye blink rate doubled in 66%. The authors suggest a threshold for adverse effects in the range of 0.09-0.30 ppm.

The effects of irritants such as acrolein may be accentuated in individuals with prior sensitization. Roux et al. (1999) investigated the interaction between passive sensitization of human isolated airways and exposure to pollutants (specifically, ozone and acrolein). Lung tissue from nonatopic, nonasthmatic patients was immunologically sensitized by incubation in sera from atopic asthmatic patients. Roux et al. reported that *in vitro* passive sensitization of the isolated tissues and exposure to acrolein act in a synergistic manner on human bronchial smooth muscle reactivity in response to both specific and nonspecific agonists. In tissues sensitized by incubation in sera from asthmatic patients, preexposure to 0.3 µM acrolein for 10 or 20 minutes significantly increased the maximal contractile response to a specific antigen of the dust mite, *Dermatophagoides pteronyssinus*, by 20.5 ± 6.5 % and 34.9 ± 7.4%, respectively. In addition, in sensitized tissue pre-exposed to 0.3 µM acrolein for 10 minutes, contractile response was increased by 33.5 ± 6.2% and 32.5 ± 5.1% for carbachol and histamine, respectively. Thus acrolein exposure potentially exacerbates asthma.

Mucus hypersecretion is one of the hallmarks of inflammatory airway disorders, including asthma. Borchers et al. (1999b) examined the effect of 0.01-100 nM acrolein on mucus glycoprotein (mucin) gene expression in cultured human airway epithelial cells. After a 4 hour exposure to acrolein in vitro, epithelial cells were found to have elevated mucin mRNA levels. It is not clear whether acrolein acts directly on epithelial cells or indirectly through inflammatory mediators released after acrolein exposure, however, asthma exacerbation is a likely result of acrolein exposure in susceptible individuals.

Persons with pre-existing eye, skin, respiratory, allergic, asthmatic or heart conditions might be at increased risk due to acrolein exposure. As a respiratory irritant, there is evidence that acrolein exacerbates asthma via the induction of bronchial hyper-responsiveness (Leikauf et al., 1989a; Leikauf et al., 1989b; Borchers et al., 1998; Borchers et al., 1999a; Borchers et al., 1999b). Acrolein has been listed as a TAC that may disproportionately impact children due to concerns related to asthma exacerbation.

Cancer patients treated with cyclophosphamide could be at increased risk because acrolein is a metabolite of cyclophosphamide (NTIS, 1981).

The effects of acrolein as an ocular irritant may be enhanced among those who wear contact lenses. Although no data specific to acrolein in this context were located, observations of ocular irritation following exposure to formaldehyde in an anatomy dissecting laboratory may be germane. Tanaka et al. (2003) reported that formaldehyde levels in an anatomy lab peaked at 0.62 ppm shortly after the exposure of cadavers for dissection, with a gradual decrease to 0.11 ppm. Formaldehyde-related irritation of the eyes, nose, throat, airways and skin was reported by 59% of the students. Ocular irritation was significantly (p < 0.001) higher among wearers of contact lenses compared with students without contacts. The ability of contact lenses to trap and concentrate volatile compounds, and to extend the exposure time by limiting the eye's normal

self-cleansing, may make contact lens wearers more susceptible to ocular exposure and irritation by acrolein.

5.2   Acute Toxicity to Infants and Children

The literature specifically examining the effects of acrolein inhalation in infants and children is limited and comprises case studies of accidental exposure, and exposures to multiple substances. The most frequent sources of acrolein in childhood exposures are environmental tobacco smoke (ETS) and acrolein formed from overheated cooking oils. Mahut et al. (1993) describe the case of a 27 month-old boy hospitalized for acute respiratory failure following exposure for about an hour to acrid smoke from vegetable oil burning on an electric hot plate. The child was reportedly cyanotic with labored, crackling breathing, and was experiencing severe respiratory acidosis. Eighteen months following exposure, X-ray and CT scans showed bronchial thickening, massive over-inflation, patchy emphysema and diffuse bronchiectasis. In this case, and in cases of exposure to ETS, infants may be more susceptible to the adverse effects of acrolein in part due to an inability to escape exposure. Children also may be more susceptible to the effects of respiratory irritants due to the immature state of their airways.

As noted in OEHHA (2001): "*OEHHA considers asthma to impact children more than adults. Children have higher prevalence rates of asthma than do adults (Mannino et al., 1998). In addition, asthma episodes can be more severe due to the smaller airways of children, and result in more hospitalizations in children, particularly from the ages of 0 to 4 years, than in adults (Mannino et al., 1998; CDHS, 2000)." "Thus, on a population-wide basis, children are more impacted by asthma than adults, and since acrolein exacerbates asthma, children may be more impacted by acrolein toxicity than adults.*" Data strongly suggesting that acrolein exacerbates asthma derive from studies using human tissue *in vitro* (Roux et al., 1999; Borchers et al., 1999a) and in animals *in vivo* (Leikauf et al., 1989a; 1989b; Borchers et al., 1998; Borchers et al., 1999b).

5.3   Acute Toxicity to Experimental Animals

Experimental exposures of rodents to acrolein at and above levels that are irritating to the eyes and respiratory tract in humans provide evidence for several adverse effects and their possible mechanisms. Acrolein prompts a proliferative response in nasal epithelium as shown by increased DNA synthesis (Roemer et al., 1993) and expression of mucin genes (Borchers et al., 1998). The latter effect in turn is associated with the hyper-secretion of mucus that may contribute to chronic obstructive pulmonary disease and asthma (Borchers et al., 1998). Bronchial hyper-responsiveness, a hallmark of asthma, increases with acrolein exposure (Leikauf et al., 1989a) supporting a connection between acrolein exposure and exacerbation of asthma in humans. The dose-dependent decreases in protective epithelial enzyme activities (Cassee et al., 1996b) and levels of sulfhydryls (Lam et al., 1985; McNulty et al., 1984) are likely to be involved in the observed formation of lesions in the nasal epithelium (Cassee et al., 1996b).

TABLE 5.3.1 ACROLEIN EFFECTS IN EXPERIMENTAL ANIMALS

Study	Model	Exposure	Outcome
Roemer et al. 1993	Proliferation of rat nasal and tracheal epithelium	0, 0.2, 0.6 ppm 6 h/d, 1 or 3 d	Increased DNA synthesis at 0.2 ppm (LOAEL)
Borchers et al. 1998	Mucus hyper-secretion, mucin gene expression in rat trachea and lungs	0.3, 0.75, 1.5, 3.0 ppm 6 h/d, 5 d/w	Hyper-secretion and gene expression at 0.75 ppm. (NOAEL = 0.3 ppm)
Leikauf et al. 1989a	Bronchial hyper-responsiveness and airway resistance in guinea pigs	1.3 ppm, 2 h	Resistance increased from 0.86 to 1.29 ml·cm H_2O/ml. Acetylcholine to double airway resistance dropped from 114 to 44.7 µg/kg/min
Buckley et al. 1984	Nasal histopathology at (RD_{50}) in mice;	1.7 ppm, 6 h/d, 5d	Exfoliation and squamous metaplasia of epithelium
Morris et al. 2003	Decrease in respiratory rate (RD_{50}) in mice	0.3, 1.6, 3.9 ppm, 10 min	Control RD_{50} at 1.50 ppm vs 0.82 ppm in allergic mice
Kane et al. 1979	Decrease in respiratory rate (RD_{50}) in mice	15 min	RD_{50} 1.7 ppm
Cassee et al. 1996b	Histopathology of rat nasal epithelium	0, 0.25, 0.67, 1.4 ppm, 6 h/d, 1-3 d	Dose-dependent lesions and decreased enzyme activities in nasal epithelium
Lam et al. 1985	Sulfhydryl depletion in rat respiratory mucosa	0, 0.1, 0.5, 1.0, 2.5 ppm 3 h	Dose-dependent depletion of non-protein sulfhydryls
McNulty et al. 1984	Sulfhydryl depletion in rat respiratory mucosa and liver	0.1, 0.3, 1, 2.5, 5 ppm 3 h	Dose-dependent depletion of non-protein sulfhydryls in nasal mucosa but not liver

Roemer et al. (1993) exposed Male Sprague Dawley rats by inhalation to 0, 0.2 or 0.6 ppm acrolein for 6 hours per day on one or three successive days. Nasal and tracheal epithelial and free lung cells were analyzed for proliferative responses using 5-bromodeoxyuridine (BrdU) labeling to identify DNA synthesizing cells. A single exposure to acrolein increased the DNA synthesizing cells 3-fold. After three exposures the increase was distinctly lower. All sites analyzed showed approximately the same concentration/response pattern. Since significant changes in cell proliferation were detected at 0.2 ppm (0.46 mg/m^3) acrolein, it is a LOAEL for this experiment.

Enhanced mucus secretion is a normal airway response to inhaled irritants. However, mucus hypersecretion is involved in the development of chronic obstructive pulmonary diseases; as such, it is considered an adverse effect. Borchers et al. (1998) exposed male rats to 3.0 ppm acrolein for 6 hours/day, 5 days/week for up to 12 days and examined the lungs and trachea for mucin cell metaplasia and expression of the mucin genes MUC2 and MUC5ac. The effects of acrolein concentration on mucin mRNA levels were further examined in rats exposed daily to 0.3, 0.75, 1.5, 3.0 ppm. Acrolein exposure resulted in a time-dependent increase in mucous cell differentiation and mucus hypersecretion in rat lungs. These changes were accompanied by increases in lung MUC5ac mRNA to levels 3-fold higher than in controls, and readily immunohistochemically detectable levels of MUC5ac. MUC5ac mRNA was elevated by concentrations as low as 0.75 ppm while MUC2 mRNA was not affected by any of the levels tested. Thus 0.3 ppm (0.69 mg/m^3) is a NOEL for this effect. The trachea of treated animals showed sloughing of the epithelium accompanied by excessive mucus and inflammatory cells in the lumen.

Bronchial hyper-responsiveness is a hallmark of reactive airway diseases such as asthma, and may be induced by inhaled irritants. Leikauf et al. (1989a) exposed guinea pigs to 1.3 ppm acrolein for 2 hours and measured the induction of bronchial hyperresponsiveness by the amount of infused acetylcholine necessary to double specific airway resistance 1, 2, 6, and 24 hours after exposure compared to baseline. The dose of acetylcholine required to double airway resistance decreased from 114.0 ± 6.6 to 44.7 ± 4.2 µg/kg/min ($p < 0.001$) at 2 hours following acrolein exposure and remained low for at least 24 hours. Acrolein exposure was found to increase levels of the bronchoconstrictor leukotriene C_4 (LTC_4) in bronchoalveolar lavage fluids prior to the observation of bronchial hyperresponsiveness. This hyperresponsiveness was prevented by treatment with an inhibitor of LTC_4 synthesis or an LTC_4 receptor antagonist. Acrolein was thus shown to induce bronchial hyperresponsiveness, an effect apparently mediated by LTC_4.

Buckley et al. (1984) investigated whether lesions occur in the respiratory tract of Swiss-Webster mice after exposure to the RD_{50} concentrations of ten sensory irritants including acrolein. After exposure of mice for 6 hr/day for 5 days to 1.7 ppm acrolein, the respiratory tract was examined for histopathologic changes. Acrolein (and all other irritants) produced lesions in the nasal cavity with a distinct anterior-posterior severity gradient. Acrolein specifically caused severe exfoliation and squamous metaplasia of the respiratory epithelium and moderate ulceration of the olfactory epithelium. Acrolein did not induce lesions in the lower respiratory tract.

Morris et al. (2003) compared the respiratory responses to acrolein in healthy mice with those in mice previously sensitized to ovalbumin. Inhalation exposure to ovalbumin prior to acrolein

exposure elicited an allergic response in the sensitized mice that was characteristic of allergic airway disease. Upon subsequent acrolein exposure, the RD_{50}, a measure of the dose required to reduce the respiratory rate by 50%, was 1.50 ppm in naïve mice and 0.82 ppm in the mouse model of allergic airway disease. Thus in sensitized animals, a lower concentration of acrolein is required to elicit the same changes in breathing rate observed in non-allergic animals. In both intact mice and in isolated mouse upper respiratory tracts, acrolein exposure caused a significant ($P < 0.05$) increase in flow resistance, an effect that was immediate and not exposure time dependent. Pretreatment with capsaicin to defunctionalize sensory neurons significantly attenuated the breathing rate and obstructive responses supporting the role of sensory neuron stimulation in the response to acrolein. For comparison, Kane et al. (1979) also used the RD_{50} as a measure of sensory irritation and estimated an RD_{50} of 1.7 ppm in mice during 15 minutes of acrolein exposure.

Cassee et al. (1996b) exposed male Wistar rats to 0, 0.25, 0.67, or 1.4 ppm acrolein for 6 hours per day on one or three successive days. Immediately following the last exposure, the rats were killed. Mucosae from the respiratory or olfactory parts of the nose were collected from 3 rats per group for biochemical analyses. The skulls of the other rats in each group were prepared for histopathology and cell proliferation measurements. Nasal epithelium, examined microscopically, showed dose-dependent evidence of disarrangement, necrosis, thickening, and desquamation of the respiratory/transitional epithelium (Table 5.3.2). Significant basal cell hyperplasia, observed at the lowest dose (0.25 ppm), increased with exposure. The activity of glutathione reductase (GR) was reduced after one-day exposure to acrolein, while the activities of GR, glutathione-S-transferase and aldehyde dehydrogenase were reduced following the three-day exposures. These results and those mentioned below suggest that acrolein interferes with enzyme systems involved in its detoxification.

TABLE 5.3.2 NASAL LESIONS IN RATS WITH ACROLEIN EXPOSURE

(from Cassee et al., 1996b)

Site and type of lesion	Extent	Incidence Low	Medium
Noses examined		5	6
Disarrangement, necrosis, desquamation of respiratory, transitional epithelium	Slight (mainly disarrangement)	4	3
	Moderate	1	3
	Severe and extensive	0	0
Basal cell hyperplasia and/or increased mitotic figures	Slight (focal)	3	2
	Moderate	0	4
	Severe (extensive)	0	0

Pronounced and possibly irreversible biochemical changes occur with acrolein levels that are extremely irritating. Acrolein depletes glutathione (GSH) and other free thiol groups both in vitro and in vivo (McNulty et al., 1984; Lam et al., 1985; Grafstrom et al., 1987; U.S.EPA, 2003; Yang et al., 2004). Inhalation exposure of rats to a concentration of 5 ppm (11.4 mg/m³) for 3 hours caused irreversible depletion of non-protein sulfhydryls in the nasal mucosa (Lam et al., 1985). Under similar exposure conditions, 5 ppm (11.5 mg/m³) for 3 hours, McNulty et al.

(1984) reported a 63% decrease in glutathione in nasal mucosal but not in liver. In addition, ^{14}C-labeled acrolein has been shown to bind irreversibly to sulfhydryl groups on cytochrome P450 in rats (Gurtoo et al., 1981). The binding of acrolein to sulfhydryl groups is localized to the area of contact (e.g., nasal membranes or lung epithelium), and is not a systemic effect (Lam et al., 1985).

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was impaired in a dose-dependent manner following a single exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

The efficiency with which acrolein enters cells of the respiratory tract in large part determines the inspired levels at which toxic effects are observed. Struve et al. (2008) measured the uptake efficiency of 0.6, 1.8 or 3.6 ppm acrolein in isolated upper respiratory tracts of anesthetized, naïve rats under constant velocity, unidirectional flow rates of 100 or 300 ml/min for up to 80 min. Similar studies were also performed on rats with previous exposure to 0.6 or 1.8 ppm acrolein for 6 hours per day, 5 days per week for 14 exposure days prior to nasal uptake studies with 1.8 or 3.6 ppm at 100 ml/min flow rate. Acrolein levels entering and exiting the isolated respiratory tract were measured to determine uptake efficiency. At the end of the exposure period, the animals were killed and the nasal respiratory and olfactory mucosa isolated for measurements of protein, and total and oxidized glutathione. The efficiency of acrolein uptake by the rat nose was dependent on the concentration, flow rate, and duration of acrolein exposure. Uptake efficiency was significantly higher at the lowest exposure than at the higher levels (0.6 > 1.8 ≈ 3.6; p < 0.0001), and at the lower flow rate (100 > 300; p < 0.0061). At both flow rates, the efficiency of uptake significantly declined over the 80 min exposure period (p < 0.001), with a significant interaction between concentration and time (p = 0.01). In naïve rats, glutathione levels dropped in respiratory epithelium but remained largely the same in olfactory epithelium. By comparison, in pre-exposed rats, the acrolein uptake efficiency was higher than in naïve rats. However, the GSH levels at the end of exposure were also higher, perhaps suggesting an adaptive response.

6. Chronic Toxicity of Acrolein

6.1   Chronic Toxicity to Adult Humans

Information regarding the chronic toxicity of acrolein in humans is limited. There is inadequate direct evidence for carcinogenicity of acrolein in humans or experimental animals. However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats (IARC, 1985). Therefore, acrolein has been designated a Group C substance, with possible human carcinogenic potential by the U.S.EPA (1987). In addition, acrolein-DNA adducts have been found in aortic tissue following 6 hour inhalation exposure to 1 and 10 ppm acrolein (Penn et al., 2001).

A source of chronic acrolein exposure for some individuals is tobacco smoking. Much of the pulmonary irritancy associated with tobacco smoke has been attributed to acrolein and research in this area suggests mechanisms for some of acrolein's pulmonary effects. As part of a defense response, pulmonary neutrophils release oxidants, proteases and cytokines such as IL-8, all of

which may promote inflammation and potentiate tissue damage. To limit tissue damage and resolve the inflammation, neutrophils normally undergo constitutive apoptosis. Experiments with isolated human neutrophils exposed to acrolein at levels achievable during active smoking (1-50 µM) found that acrolein inhibited neutrophil apoptosis, increased IL-8 production, and activated mitogen-activated protein kinases (MAPK) (Finkelstein et al., 2001). At acrolein concentrations up to 10 µM, inhibition of apoptosis was accompanied by increased cell viability. At higher acrolein levels, cell viability decreased as necrotic cell death increased. While the mechanisms behind acrolein's concentration-dependent effects on neutrophils are not clear, the effects observed at the lower exposure levels suggest that acrolein may contribute to pulmonary inflammation and exacerbate allergic responses by prolonging the survival of neutrophils, and stimulating the production of inflammation-related cytokines and enzymes. At higher levels, frank cellular toxicity becomes more prominent.

6.2   Chronic Toxicity to Infants and Children

No data addressing the effects of chronic acrolein exposure among infants and children were located. Inasmuch as acrolein is one of the major irritants in environmental tobacco smoke (Takabe et al., 2001) at relatively high concentrations in smokers' homes (1.6-3.6 µg/m^3; 0.70-1.57 ppb (Nazaroff and Singer, 2004)), children living with smokers may be disproportionately exposed to acrolein as they are less able to avoid exposure than are adult nonsmokers. To the extent that respiratory irritants such as acrolein elicit bronchoconstriction and excessive mucus secretion characteristic of asthma, children, with their smaller airways and greater prevalence of asthma, may experience more diminution of pulmonary function and more episodes of asthma with chronic exposure.

6.3   Chronic Toxicity to Experimental Animals

Long-term exposure to acrolein causes structural and functional changes in the respiratory tract. Nasal and pulmonary effects following acrolein exposure for 13 weeks (6 hours/day, 5 days/week) were described by Dorman et al. (2008) in 360 male F344 rats. The whole-body exposures were to air concentrations of 0, 0.02, 0.06, 0.2, 0.6, and 1.8 ppm acrolein, with evaluation of respiratory tract histopathology after 4, 14, 30 and 65 days of exposure, and at 60 days following the end of the 13 week exposure. Body weights of all acrolein exposed rats were depressed but there were reportedly no other significant increases in clinical signs. Formalin-fixed noses were sectioned transversely providing six sections of the nasal cavity at standard levels. Larynx, trachea and lungs were fixed, stained with hematoxylin and eosin, and examined histologically. The study examined both respiratory and olfactory epithelia with the former being the more sensitive as evidenced by inflammation, hyperplasia and squamous metaplasia. Mild hyperplasia of the respiratory epithelia was first observed after 4 days of exposure to ≥ 0.6 ppm. The NOAEL for pathology of nasal respiratory epithelia was 0.2 ppm in the lateral walls of level II, and for olfactory epithelia, 0.6 ppm. At the highest concentration, 1.8 ppm, mild squamous metaplasia was also observed in the larynx and trachea, but no treatment related effects were seen in the lungs. Two months following cessation of exposure, only partial recovery of the olfactory epithelium was observed; primarily in caudal areas where lesions developed more slowly and were less severe.

Schroeter et al. (2008) used data from the above study by Dorman et al. (2008) for the development of a physiological computational fluid dynamics (CFD) model of acrolein nasal dosimetry. The CFD models of Kimbell et al. (1997) and Subramaniam et al. (1998) were modified to estimate kinetic parameters of acrolein flux in rat nasal passages, and allow a cross-species prediction of acrolein flux in humans associated with histopathology. Based on a NOAEL of 0.6 ppm and a LOAEL of 1.8 ppm for olfactory neuronal loss from Dorman et al. (2008), the CFD model predicted a threshold acrolein flux of 72 pg/cm^2-s at region 11, comprising portions of the third ethmoturbinate. Assuming equal tissue doses of acrolein elicit similar responses in the olfactory epithelium of rats and human, an exposure level that may be expected to represent the threshold for olfactory neuronal loss in humans may be estimated. The 99th percentile olfactory flux value that is equal to the threshold of 72 pg/cm^2-s was estimated to be 45 ppb. The authors use this concentration to estimate a human equivalent NOAEL of 8 ppb, and a reference concentration (RfC) of 0.27 ppb.   However, the threshold acrolein flux associated with the lower NOAEL of 0.2 ppm, reported by Dorman et al. (2008) for respiratory epithelium, was not estimated, and an equivalent human threshold and NOAEL is not available. The rationale for this, presented in Dorman et al. (2008), is *"Our CFD modeling efforts have revealed that although the observed NOAEL for the respiratory epithelium is lower than that seen for the olfactory epithelium (i.e., 0.2 vs. 0.6 ppm), in actuality the olfactory epithelial lesion arises at an appreciably lower delivered tissue dose suggesting that the olfactory epithelium is more sensitive to the effects of inhaled acrolein than is the respiratory epithelium (Schroeter et al. (2008)."* The RfC of 0.27 ppb estimated by the authors is thus based on lesion formation at the lowest modeled tissue dose rather than on the more relevant value of the lowest applied acrolein concentration associated with an adverse effect.

Structural and functional changes in the respiratory tract were also examined in male Fischer-344 rats exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)(Kutzman, 1981; Kutzman et al., 1985). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lungs were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed at 6 days post-exposure to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extra-respiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates (increased submucosal lymphoid aggregates), beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions included epithelial necrosis and sloughed cells lying free in the lumen. No lung lesions were observed in the 0.4 ppm group. The LOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

Feron et al. (1978) exposed groups of 20 Syrian golden hamsters, 12 SPF Wistar rats and 4 Dutch rabbits (of both sexes) to acrolein vapor at 0, 0.4, 1.4 and 4.9 ppm (0, 0.92, 3.2, and 11.3 mg/m^3) 6 hours/day, 5 days/week for 13 weeks. The most prominent effects at the highest level included mortality in rats (3 of each sex), and ocular and nasal irritation, growth depression, and

histopathological changes of the respiratory tract in each species. The changes in the airways induced by acrolein consisted of destruction, and hyperplasia and metaplasia of the lining epithelium accompanied by inflammatory alterations. Rats were the most susceptible species examined and showed treatment-related histopathological abnormalities in the nasal cavity down to 0.4 ppm (LOAEL), whereas this level was a NOAEL in hamsters and rabbits. The results for individual rats at 0.4 ppm were not given.

Bouley et al. (1975; 1976) exposed male SPF OFA rats continuously to 0.55 ppm (1.3 mg/m^3) of acrolein for up to 63 days. This level of acrolein led to a greater susceptibility to airborne *Salmonella enteritidis* infection during the first three weeks compared to control rats but it disappeared spontaneously when exposure was continued beyond three weeks. The general toxic effect of diminished weight gain (due to reduced feeding) compared to the control group lasted as long as exposure and disappeared only after acrolein was discontinued. Sneezing, a sign of nasal irritation, was consistently observed in the exposed animals on days 7 through 21 but ceased thereafter. No histopathology of the nasal cavity of or any other tissue was reported.

In one of the few chronic studies reported, Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm (9.2 mg/m^3) acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy, although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure. Thus 4 ppm is a chronic LOAEL for hamsters. As noted above, hamsters appear to be a less sensitive species than rats (Feron et al., 1978).

Exposures of rodents have generally formed the basis for the determination of acrolein's chronic effects. However, an interspecies comparison was conducted by Lyon and associates (Lyon et al., 1970) who investigated the effects of repeated or continuous exposures of acrolein on Sprague-Dawley rats (n = 15/exposure group), guinea pigs (n = 15), beagle dogs (n = 2), and male squirrel monkeys (n = 9). Animals were exposed to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. The results below suggest that dogs and monkeys were more susceptible to acrolein's effects than were the rodents.

Two monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea were observed in monkeys and dogs; 7 of the 9 monkeys repeatedly exposed to 3.7 ppm also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed intermittently to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm continuous exposure groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys,

guinea pigs and dogs. Unfortunately the nasal cavity was not examined in this study. While there were no unexposed control animals for any species, the cross-species comparison shows substantial interspecies variability in susceptibility.

7. Developmental and Reproductive Toxicity

There are no reports of reproductive or developmental toxicity following inhalation exposure to acrolein in humans. Kutzman (1981) studied reproductive fitness in male and female rats following acrolein inhalation for 6 hours/day, 5 days/week for 62 days. Treated males were mated with untreated females, and treated females with untreated males. No treatment-related differences were found in the parameters assessed including pregnancy rate, number of corpora lutea, embryo viability, early and late deaths, and preimplantation losses.   Similarly, the morphology of sperm collected from the epididymides of treated males was examined and reportedly not affected. Bouley et al. (1975; 1976) exposed three male and 21 female SPF-OFA rats continuously to 0.55 ppm (1.26 mg/m^3) acrolein vapor for 25 days. The rats were allowed to mate on day 4 of the exposure. The number of acrolein-exposed pregnant rats and the number and mean body weight of their fetuses were similar to controls.

In rats, acrolein can induce teratogenic and embryotoxic effects when administered directly into the amniotic fluid, or when added to cultured rat embryos (Slott and Hales, 1986). Additionally, acrolein injected into chicken embryos resulted in embryotoxicity and some teratogenic effects at moderate to high doses (0.001-0.1 mg/egg) (Chhibber and Gilani, 1986). However, intravenous injection of acrolein in pregnant rabbits showed no developmental effects in the offspring (Claussen et al., 1980). Based on this latter study, the World Health Organization (1992) concluded that human exposure to acrolein was unlikely to affect the developing embryo.

8. Derivation of Reference Exposure Levels

8.1   Acrolein Acute Reference Exposure Level

Study	Darley et al., 1960
Study population	36 healthy human volunteers
Exposure method	5 min exposure: carbon-filter respirators worn
Exposure continuity	Single exposure
Exposure duration	5 min
Critical effects	subjective ocular irritation
LOAEL	0.06 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	not applied
Human Equivalent Concentration	n/a
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamic (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (greater susceptibility of children to asthma exacerbation)
Cumulative uncertainty factor	60
Reference Exposure Level	2.3 μg/m³ (1.0 ppb)

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document).

The study by Darley et al. (1960) was selected as the best available acute exposure study employing human subjects. In addition, the ocular mucosa and the nasal mucosa are both innervated by cranial nerve V (trigeminal nerve). As noted by Doty et al. (2004), numerous studies employing n-alcohols, ketones, alkylbenzenes, terpenes, butyl acetate and toluene, report thresholds for ocular and intranasal irritation to be of the same magnitude suggesting that for most volatiles, tests of ocular and nasal irritancy are of equivalent sensitivity. Thus the endpoint of ocular irritancy used in this study is expected to also reflect irritancy of the upper respiratory tract. Confidence in this REL calculation is moderate as the LOAEL used is based on an estimated LOAEL of 0.06 ppm rather than a measured level. A default uncertainty factor of 6 is associated with the use of a LOAEL for mild effects in the absence of a NOAEL in acute REL derivations (see Section 4.4.5 of the TSD). Due to its high reactivity, the effects of exposure to acrolein in the air are largely confined to the site of contact, in this case the eyes, with negligible or no systemic effects. This localization of effects to the site of contact is supported by the confinement of acrolein's effects to the upper respiratory tract in the animal studies of acute inhalation exposure. Based on modeling of adults and 3-month old children that takes into account age-related ventilation rates and respiratory tract surface area, the deposition kinetics of reactive gases are generally thought not to be greatly different between adults and children

(Ginsberg et al., 2005). Because of this, a value of 1 is used for the kinetic component of the intraspecies uncertainty factor (UF_{H-k}), rather than a more extended value of $\sqrt{10}$ or 10 which are used where metabolic processes also contribute to inter-individual variability. While ocular irritation is not expected to be substantially different between children and adults, the respiratory irritant effect, with documented potential to exacerbate asthma, is clearly an effect with the potential to differentially impact infants and children. The toxicodynamic component of the intraspecies uncertainty factor UF_{H-d} is therefore assigned an increased value of 10 to account for potential asthma exacerbation. These considerations are applied equally to the acute, 8-hour and chronic REL. Based on this study, an acute REL for acrolein exposure is calculated to be 2.3 $\mu g/m^3$ (1.0 ppb).

As noted in Section 5.1, contact lens wearers may be at greater risk for ocular irritation with acrolein exposure. However, since contact lens users, and infants and children are generally mutually exclusive groups, it is expected that with the ten-fold toxicodynamic UF_{H-d} described above, the acute REL should be adequately protective of these individuals as well.

The acute REL above is supported by a study in humans by Weber-Tschopp et al. (1977). During a 40 minute exposure to increasing concentrations of acrolein, significant ocular irritation was first reported at 0.07 ppm. This represents the LOAEL for this effect and is similar to the LOAEL of 0.06 ppm in Darley et al. (1960). The same uncertainty and adjustment factors, and rationale apply as in Darley, giving an acute REL of 2.7 $\mu g/m^3$ (1.2 ppb).

Study	Weber-Tschopp et al. (1977)
Study population	54 healthy human volunteers
Exposure method	Exposure chamber
Exposure continuity	Increasing concentration (0-0.6 ppm)
Exposure duration	40 min
Critical effects	subjective ocular irritation
LOAEL	0.07 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	not applied
Human Equivalent Concentration	n/a
LOAEL uncertainty factor (UF_L)	6 (no NOAEL)
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
* Toxicokinetic (UF_{A-k})*	1 (default: human study)
* Toxicodynamic (UF_{A-d})*	1 (default: human study)
Intraspecies uncertainty factor	
* Toxicokinetic (UF_{H-k})*	1 (site of contact; no systemic effects)
* Toxicodynamic (UF_{H-d})*	10 (asthma exacerbation in children)
Cumulative uncertainty factor	60
Reference Exposure Level	2.7 $\mu g/m^3$ (1.2 ppb)

Sensory irritancy is the critical response to acute acrolein exposure. For this effect both the Darley and Weber-Tschopp studies found similar effect levels resulting in similar estimates for the acute REL. In consideration of this, we took the geometric mean of the REL values from these studies to derive the acute REL of **2.5 μg/m^3 (1.1 ppb).**

A similar acute REL was calculated as shown below based on lesions in nasal epithelium in rats exposed to acrolein for 6 hours/day for 3 days (Cassee et al., 1996b). There were sufficient data in this study to permit the application of the BMD method in preference to the NOAEL/LOAEL approach. A BMCL$_{05}$ of 56 μg/m^3 was derived based on the incidence of moderate to severe lesions at each exposure level. Irritancy was not the endpoint in this study so a time adjustment was applied using $C^n * T = K$ (n = 3) to adjust the 18 hours of exposure to 1 hour that gave 147 μg/m^3 (see Section 5.6.1 of the TSD). Interspecies uncertainty factors of 2 for toxicokinetic differences with use of a dosimetric adjustment factor (DAF) of 0.85 (dosimetric adjustment factor – described below and in Section 4.4.7.2.2 of the TSD), and √10 for toxicodynamic variability were combined with a combined intraspecies UF of 10 (1 for kinetic and 10 for dynamic variability, reflecting the expectation of greater toxicodynamic variability) for a cumulative UF of 60 and an acute REL of 0.91 ppb.

Study	Cassee et al., 1996b
Study population	11 rats
Exposure method	Nose-only inhalation
Exposure continuity	6 hr/day
Exposure duration	3 days
Critical effects	lesions of the respiratory epithelium
LOAEL	0.25 ppm (0.58 mg/m^3)
NOAEL	not observed
Benchmark concentration (BMCL$_{05}$)	56 μg/m^3
Time-adjusted exposure	C^n*T n = 3
Extrapolated concentration	147 μg/m^3 ($56^3*6/1*3/1)^{1/3}$
Human concentration adjustment	125 μg/m^3 = 147*0.85 (DAF)
LOAEL uncertainty factor (UF$_L$)	not applied
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF$_{A-k}$)	2 (DAF adjustment with analogue chemical)
Toxicodynamic (UF$_{A-d}$)	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF$_{H-k}$)	1
Toxicodynamic (UF$_{H-d}$)	10 (asthma exacerbation in children)
Cumulative uncertainty factor	60
Reference Exposure Level	2.1 μg/m^3 (0.91 ppb)

The DAF is a factor derived by OEHHA based on the modeled comparative flux of formaldehyde in the upper respiratory tracts of rats, rhesus monkeys and humans by Kimbell et al. (2001) (see Section 4.4.7.2.2 of the TSD). Kimbell et al. used three-dimensional,

anatomically realistic, computational flow dynamic models to estimate mass flux across 20 consecutive bins representing the nasal passages. The mean flux at each bin was weighted by the percent of non-squamous epithelium in that bin to derive a weighted average flux for each bin. Averaging across all 20 bins provides an overall estimate of the flux for comparison between species (rat, 13.63 pmol/mm^2; human, 30.80 pmol/mm^2). Peak flux values were also estimated for the rat (2620 pmol/mm^2) and human (2082 pmol/mm^2), and averaged with the mean flux values to estimate the DAF (0.85). The DAF is the ratio of this value for the rat to that for humans. Although acrolein is more reactive than formaldehyde, both compounds appear to have their effects primarily on the respiratory (vs. olfactory) epithelium (Cassee et al., 1996a). This supports the assumption that in applying the DAF to acrolein, acrolein and formaldehyde deposit similarly in the nasal passages. In the absence of acrolein-specific modeling data, any residual uncertainty associated with this assumption is reflected in the use of an interspecies UF$_{A-k}$ of 2.

8.2   Acrolein 8-Hour Reference Exposure Level

Study	Dorman et al., 2008
Study population	360 adult Fischer-344 rats
Exposure method	Discontinuous whole body 0.02 – 1.8 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	65 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.6 ppm
NOAEL	0.2 ppm
Benchmark concentration	not derived
Time-adjusted exposure	C * T = K
Extrapolated 8 hour concentration	71 ppb = (0.2*6 /24*5/7*20/10)
Human concentration adjustment	60 ppb = 71*0.85 (DAF)
LOAEL uncertainty factor (UF$_L$)	1 (NOAEL observed)
Subchronic uncertainty factor (UFs)	√10
Interspecies uncertainty factor	
Toxicokinetic (UF$_{A-k}$)	2 (DAF adjustment with analogue chemical)
Toxicodynamic (UF$_{A-d}$)	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF$_{H-k}$)	1
Toxicodynamic (UF$_{H-d}$)	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	200
Reference Exposure Level	**0.70 μg/m³ 0.30 ppb)**

The 8-hour Reference Exposure Level is a concentration at or below which adverse non-cancer health effects would not be anticipated for repeated 8-hour exposures (see Section 6 in the TSD).

The 8-hour and chronic RELs are based on the observation of lesions in rat respiratory epithelium by Dorman et al. (2008). In this study, a LOAEL of 0.6 ppm and a NOAEL of 0.2 ppm were observed for respiratory lesions in rats. The observation of a NOAEL eliminates the need for a UF for the LOAEL to NOAEL conversion. The critical effect of lesion formation is not a sensory irritancy effect so a time (T) adjustment was applied using C*T = K to extrapolate from the 6 to 24 hours and from 5 to 7 days. This chronic exposure was converted to an 8 hour

exposure with the 8-hr breathing rate conversion of 20/10 and yields an extrapolated 8 hour concentration of 71 ppb. A human concentration of 60 ppb was estimated using a DAF of 0.85. Although the use of the DAF is expected to correct for pharmacokinetic differences between species, an interspecies kinetic UF of 2 was used because the DAF is based on an analogue (formaldehyde). The default interspecies UF_{A-d} of √10 was applied to compensate for the absence of data on pharmacodynamic differences between species. An intraspecies UF_{H-k} of 1 was used since, although the data are only for adult animals, the pharmacokinetic differences between adult and young animals are not expected to be great based on the similar inhalation dosimetry associated with reactive gases in adults and infants (Ginsberg et al., 2005). The potential pharmacodynamic differences among individuals (especially those with and without asthma) and between adults and infants (due to the immaturity of the infants respiratory tract) are expected to be greater. For example, irritant gases more readily stimulate the hyper-reactive airways of asthmatics while enhanced mucus production in response to irritant gases may more easily block the infant's narrower airways. As described in Section 5.2, exacerbation of asthma by acrolein is expected to disproportionately affect children. For these reasons, an intraspecies UF_{H-d} of 10 was employed. The UF_{H-d} of 10 is the default in the absence of human kinetic data. This resulted in a cumulative UF of 200 and an 8-hour REL of 0.70 μg/m³ (0.30 ppb).

These results are supported by studies of Kutzman et al. (1985) and Feron et al. (1978) following exposure of rats to acrolein for 6 hours/day, 5 days/week for 62 days. In these studies, a LOAEL of 0.4 ppm was observed for nasal lesion formation.

Study	Kutzman et al., 1985; Feron et al. (1978)
Study population	96 adult Fischer-344 rats
Exposure method	Discontinuous whole body 0.4 – 4.0 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	62 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.4 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	$C^n * T = K$, where n =1.2
Extrapolated 8 hour concentration	143 ppb = (0.4*6 /24*5/7*20/10)
Human concentration adjustment	122 ppb = 143*0.85 (DAF)
LOAEL uncertainty factor (UF_L)	3 (mild effect; no NOAEL)
Subchronic uncertainty factor (UF_s)	√10
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (DAF adjustment with analogue chemical)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	600
Reference Exposure Level	0.46 μg/m³ (0.20 ppb)

The experimental designs and results from these two studies were essentially identical. As above, the critical effect of lesion formation is not a sensory irritancy effect so a time (T) adjustment was applied using C*T = K to extrapolate to an 8 hour concentration of 143 ppb. A UF of 3 for the use of a LOAEL reflects the expectation that the NOAEL, while not reported in either of these studies, will not be far from the LOAEL. This is based on the steepness of the dose-response in a plot of the nasal histopathology scoring vs acrolein concentration in the Feron paper, and the observation of a NOAEL three-fold lower than the LOAEL in the Dorman study (0.2 vs 0.6 ppm). An adjusted human concentration of 122 ppb was estimated using a DAF of 0.85. The rest of the uncertainty factors were the same as for the crtitical Dorman study   This resulted in a cumulative UF of 600 and an 8-hour REL of 0.46 μg/m³ (0.20 ppb). Thus, this derivation is supportive of the REL derived from Dorman et al. (2008).

8.3   Acrolein Chronic Reference Exposure Level

Study	Dorman et al., 2008
Study population	360 adult Fischer-344 rats
Exposure method	Discontinuous whole body 0.02 – 1.8 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	65 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.6 ppm
NOAEL	0.2 ppm
Benchmark concentration	not derived
Time-adjusted exposure	36 ppb = (0.2*6/24*5/7)
Human concentration adjustment	30 ppb = 36*0.85 (DAF)
LOAEL uncertainty factor (UF_L)	1 (NOAEL observed)
Subchronic uncertainty factor (UF_S)	√10 (exposure 8-12% of lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (DAF adjustment based on analogue chemical)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	200
Reference Exposure Level	**0.35 μg/m³ (0.15 ppb)**

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from continuous chronic exposures (see Section 7 in the Technical Support Document).

The chronic REL was developed using the same study as the 8-hr REL but with a time extrapolation to continuous exposure since the endpoint was not trigeminal irritancy (see Section 1.2.3 in the TSD). It is based on the observed NOAEL of 0.2 ppm for respiratory lesions in rats. The observation of a NOAEL eliminates the need for a UF for the LOAEL to NOAEL conversion. Time adjustment from the experimental to continuous exposure gave 36 ppb (0.2*6 hr/24 hr*5 days/7 days). A DAF of 0.85 gave an equivalent human exposure of 30 ppb. Use of the DAF for an analogue chemical entails an uncertainty factor of 2 as described previously. The

same UFs and rationale as used in the derivation of the 8-hour REL are applied to the chronic REL. The resulting cumulative UF of 200 gave an estimated reference exposure level of 0.35 μg/m³ (0.15 ppb).

These results were supported by those of Kutzman et al. (1985) and Feron et al. (1978)

Study	Kutzman et al., 1985; Feron et al. (1978)
Study population	96 adult Fischer-344 rats
Exposure method	Discontinuous whole body to 0 – 4.0 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	62 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.4 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time adjusted exposure	0.071 ppm = 0.4*6/24*5/7
Human concentration adjustment	60 ppb = 0.071 * 0.85 (DAF)
LOAEL uncertainty factor (UF$_L$)	3 (no NOAEL)
Subchronic uncertainty factor (UFs)	√10 (exposure 8-12% of lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF$_{A-k}$)	2 (with DAF adjustment)
Toxicodynamic (UF$_{A-d}$)	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF$_{H-k}$)	1
Toxicodynamic (UF$_{H-d}$)	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	600
Reference Exposure Level	**0.10 μg/m³ (0.04 ppb)**

The LOAEL of 0.4 ppm was adjusted to a continuous exposure of 0.071 ppm (0.4*6 hr/24 hr*5 days/7 days). Application of a DAF of 0.85 gave a human equivalent concentration of 60 ppb (138 μg/m³). The UFs applied here are the same as those for the Dorman study with the inclusion of a LOAEL to NOAEL UF of 3. The cumulative UF of 600 gives a chronic REL of 0.10 μg/m³ (0.04 ppb). The study by Dorman et al. was selected in preference to these studies because it identified a NOAEL for the critical effect.

The U.S. EPA (2003) based its RfC of 0.02 μg/m³ on the study by Feron et al. (1978) from which a HEC of 0.02 mg/m³ was derived based on a regional gas dosimetric ratio (RGDR) of 0.14 and an adjusted LOAEL of 0.16 mg/m³ (0.14 * 0.16 = 0.02). U.S. EPA applied a total uncertainty factor of 1,000 (3 for interspecies extrapolation from a dosimetrically adjusted dose; 10 for intra-human variability; 3 for the use of a LOAEL; 10 for subchronic to chronic extrapolation). In contrast to the RGDR of 0.14, to better account for differences in rat and human exposures to reactive gases, OEHHA used a DAF of 0.85 based on comparative modeling of gas flux in human and rat nasal passages described above. This, combined with UFs of 6 for interspecies uncertainty (2 for use of the DAF, √10 for toxicodynamic differences), √10 for the use of a subchronic study, and 3 for the use of a LOAEL (vs US EPA's 3, 3, and 10, respectively) account for the difference between the REL and the U.S. EPA RfC.

For comparison, the state of Minnesota Department of Health reports a subchronic Health Risk Value (HRV) for acrolein of 0.2 µg/m^3, a level thought to be without significant risk following inhalation exposure for 13 weeks (MDH, 2002).

8.4   Acrolein as a Toxic Air Contaminant

Acrolein was identified by the ARB as a toxic air contaminant (TAC) in accordance with section 39657(b) of the California Health and Safety Code on April 8, 1993 (Title 17, California Code of Regulations, Section 93001)(CCR, 2007). In view of the differential impacts on infants and children identified in Section 6.2 (more severe effects associated with bronchoconstriction and asthma exacerbation, less ability to escape or avoid exposure), OEHHA listed acrolein as a TAC which may disproportionately impact children pursuant to Health and Safety Code, Section 39669.5(c) .

9. References

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ACUTE TOXICOLOGY SUMMARY FOR ANTIMONY TRIOXIDE

Molecular formula	Molecular weight	Synonyms	CAS #
Sb_2O_3	291.50	antimonious oxide, senarmonite, valentinite, antimony white, antimony peroxide	1309-64-4

I. Acute Toxicity Exposure Levels (for a 1-hour exposure)

Level I (REL) Discomfort or mild effect level	0.004 mg/m^3	Irritation of the skin and mucous membranes may occur following exposures to antimony trioxide above this level.
Level II Disability or serious effect level	No recommendation	
Level III Life-threatening effect level	No recommendation	

II. Physical and Chemical Properties
(From HSDB, 1993 except as noted)

Specific gravity	5.2 @ 25° C
Boiling point	sublimes @ 1,550° C
Melting point	656° C
Vapor pressure	unknown
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in tartaric acid, acetic acid, hydrochloric acid; very slightly soluble in water
Odor threshold	unknown
Odor description	unknown
Metabolites	unknown
Color	white (senarmonite) colorless (valentinite)
Conversion factor	not applicable

III. Major Uses or Sources

The most common use of antimony trioxide is as a textile fire retardant (ATSDR, 1992). Antimony trioxide is also used in pigments, vulcanizing agents and compounds of enamel (Winship, 1987). In the glass industry, antimony trioxide is used as a refining agent and as a glass coloring (Ludersdorf et al., 1987).

IV. Acute Toxicity to Humans

In an occupational study conducted at a facility smelting antimony ore, the prevalence of reported illnesses in male workers exposed to smelting fumes was greater than in workers in other departments of the facility who, presumably, had less exposure (Renes, 1953). Of the men with illnesses, 20% reported dermatitis, 20% rhinitis, 11% laryngitis, and 10% reported tracheitis. Less frequently observed signs of toxicity included bronchiolitis, conjunctivitis, gastritis, gastroenteritis, pharyngitis, pneumonitis, and nasal septal perforations. An average air concentration of several work areas was reported as 4.7 mg Sb/m^3. The lowest measured Sb concentration in the smelter was 0.40 mg/m^3. Airborne arsenic was also measured at the work site. The effects of antimony alone cannot be deduced from this study because of concomitant exposure to other toxicants including arsenic.

Pneumonitis was observed in chest x-rays of men exposed for 2-12 hours to heavy but unquantified concentrations of antimony smelter fumes (Renes, 1953). Most of the workers exposed complained of nasal irritation and epistaxis, sore throat, hoarseness, burning and redness of the eyes, metallic taste, chest pain, headache and shortness of breath. Weight loss, nausea, vomiting, diarrhea, loss of the sense of smell, and chest tightness were reported less frequently.

In contrast to the previous study, Linch and Sigmund (1975) suggest that no adverse effects were reported following acute exposures to concentrations as great as 10 mg/m^3 Sb$_2$O$_3$ during 24 years of operation at one facility.

Antimony trioxide is classified as a probable human carcinogen (group B2 under the USEPA weight-of-evidence classification) based on available data including reports of increased lung cancer mortality in smelter workers following chronic exposure to Sb$_2$O$_3$ (Calabrese and Kenyon, 1991).

Predisposing Conditions for Sb$_2$O$_3$ Toxicity

Medical: Individuals with existing respiratory or cardiovascular disorders may be more sensitive to the toxic effects of acute exposure to high airborne concentrations of Sb$_2$O$_3$ (Sittig, 1980).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

Rats exposed 6 hours per day, 5 days per week for 13 weeks to 0.92 mg/m^3 Sb_2O_3 exhibited proliferation of lung macrophages 28 weeks after the cessation of exposure (Bio/dynamics, 1985). Because of the integral role that macrophages have in the progression of fibrosis, ATSDR (1992) considered proliferation of macrophages to be an adverse health affect and proposed a subchronic LOAEL of 0.92 mg Sb_2O_3/m^3 in rats.

Extensive pneumonitis was observed in guinea pigs exposed initially to 45.4 mg/m^3 Sb_2O_3 for 2 hours/day for 3 weeks and subsequently for 3 hours/day for up to 30 weeks (Dernehl et al., 1945). No other significant pathologic changes were observed.

VI. Reproductive or Developmental Toxicity

No current, reliable studies on the reproductive and developmental toxicity of Sb_2O_3 were located. The only available study reported that women working at an antimony metallurgical plant reported more spontaneous abortions than non-exposed women (Belyaeva, 1967). No range of exposures, or job descriptions of the control group were reported.

The same study reported that rats exposed for 4 hours per day to 209 mg/m^3 Sb_2O_3 for 63 days prior to mating exhibited a reduction in the rate of conception (Balyaeva, 1967). Metaplasia of the uterine endometrium was observed in the animals that failed to conceive, but not in the impregnated animals. Fewer offspring were observed in the pregnant animals whose exposure to Sb_2O_3 continued through gestation, than in control animals.

VII. Derivation of Acute Toxicity Exposure Levels
     (for a 1-hour exposure)

Level I (REL):   0.004 mg/m^3

References: Renes, 1953

Findings: Irritation of the skin and mucous membranes
                was observed in smelter workers exposed to Sb
                for a minimum of two weeks. The lowest
                measured Sb concentration in the smelter was
                0.40 mg/m^3.

Notes: The lowest measured concentration was used as
                a LOAEL. An uncertainty factor of 10 was
                added to estimate a NOAEL from the LOAEL.   An
                additional uncertainty factor of 10 was
                included to account for intraspecies

variability. In the absence of additional data, it is assumed that the toxicity of Sb and Sb_2O_3 are equivalent.

Level II: **No recommendation**

Level III: **No recommendation**

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CHRONIC TOXICITY SUMMARY

ANTIMONY TRIOXIDE

(antimonious oxide, senarmonite, valentinite, antimony white, antimony peroxide)

CAS Registry Number: 1309-64-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 μg/m³** (U.S. EPA RfC)
	This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Pulmonary toxicity; chronic interstitial inflammation in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary

Molecular formula	Sb_2O_3
Molecular weight	169.8 g/mol
Description	White or colorless solid
Vapor pressure	Sublimes at 1550° C
Solubility	Soluble in tartaric acid, acetic acid, hydrochloric acid; very slightly soluble in water
Conversion factor	Not applicable

III. Major Uses and Sources

The most common use of antimony trioxide is as a textile fire retardant (ATSDR, 1992). Antimony trioxide is also used in pigments, vulcanizing agents and compounds of enamel (Winship, 1987). In the glass industry, antimony trioxide is used as a refining agent and as a glass coloring (Ludersdorf *et al.*, 1987).

IV. Effects of Human Exposure

In an occupational study conducted at a facility smelting antimony ore, the prevalence of reported illnesses in male workers exposed to smelting fumes was greater than in workers in other departments of the facility who, presumably, had less exposure (Renes, 1953). Of the men with illnesses, 20% reported dermatitis, 20% rhinitis, 11% laryngitis, and 10% reported

tracheitis. Less frequently observed signs of toxicity included bronchiolitis, conjunctivitis, gastritis, gastroenteritis, pharyngitis, pneumonitis, and nasal septal perforations. An average air concentration of several work areas was reported as 4.7 mg Sb/m^3. The lowest measured Sb concentration in the smelter was 0.40 mg/ m^3. Airborne arsenic was also detected at the work site.

Pneumonitis was observed in chest x-rays of men exposed for 2-12 hours to heavy but unquantified concentrations of antimony smelter fumes (Renes, 1953). Most of the workers exposed complained of nasal irritation and epistaxis, sore throat, hoarseness, burning and redness of the eyes, metallic taste, chest pain, headache and shortness of breath. Weight loss, nausea, vomiting, diarrhea, loss of the sense of smell, and chest tightness were reported less frequently.

In contrast to the previous study, Linch and Sigmund (1975) suggest that no adverse effects were reported following acute exposures to concentrations as great as 10 mg/m^3 Sb_2O_3 during 24 years of operation at one facility.

A cohort of 51 antimony smelter workers employed for 9 - 31 years was investigated by Potkonjak and Pavlovich (1983). Examinations over a 25 year period included chest X-rays, laboratory analysis, pulmonary function tests, and physical examinations. Analysis of airborne dusts revealed 0.82 - 4.72% free silica, 38.73 - 88.86% antimony trioxide, 2.11 - 7.82% antimony pentoxide, and trace amounts of ferric trioxide and arsenic oxide. More than 80% of the particles were < 5 microns in diameter. Workers with duration of employment longer than 9 years exhibited punctate opacities in X-rays, concentrated in the mid-lung region.

V.   Effects of Animal Exposure

Newton *et al.* (1994) exposed rats (65/sex/group) to particles with concentrations of 0, 0.06, 0.51, or 4.50 mg Sb_2O_3/m^3, 6 hours/day, 5 days/week for 1 year. These data are also reported by Bio/dynamics (1990). Animals were sacrificed at 6 and 12 months of exposure, and some were kept for 6 or 12 months after the exposure for a follow-up examination. The eyes, kidneys, liver, prostate, spleen, and urinary bladder were examined in all groups. A mild, dose-dependent ocular irritation was observed at 6 months. At the 12-month follow-up, all surviving rats exposed to Sb_2O_3 had conjunctivitis and cataracts (females only), with a significant dose-response trend. A decreased rate of clearance of particle-laden macrophages was observed in the highest dose-group. Particle-laden macrophages were apparent in all dose groups, but no adverse effects were associated with this observation. An in crease in incidence and severity of pulmonary interstitial and granulomatous inflammation was observed in the highest exposure group. The 0.51 mg Sb_2O_3/m^3 group showed an increased incidence of these lesions, but the effect was not significant when severity of the response was considered.

Rats exposed 6 hours per day, 5 days per week for 13 weeks to 0.92 mg/m^3 Sb_2O_3 exhibited proliferation of lung macrophages 28 weeks after the cessation of exposure (Bio/dynamics, 1985). Because of the integral role that macrophages have in the progression of fibrosis, ATSDR

(1992) considered proliferation of macrophages to be an adverse health affect and proposed a subchronic LOAEL of 0.92 mg Sb_2O_3/m^3 in rats.

Watt (1983) exposed rats and miniature swine to 0, 1.9, or 5.0 mg Sb_2O_3/m^3 6 hours/day, 5 days/week for 1 year. No exposure-related effects on survival, hematology, or clinical chemistry was noted. Lung weights were increased in both species. Nonneoplastic pulmonary effects were observed in all exposed animals and included focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumonocyte hyperplasia, and pigmented macrophages. The severity of these lesions increased with increasing concentration and duration. The LOAEL for pulmonary effects in rats was 1.9 mg/m³.

Extensive pneumonitis was observed in guinea pigs exposed initially to 45.4 mg/m³ Sb_2O_3 for 2 hours/day for 3 weeks and subsequently for 3 hours/day for up to 30 weeks (Dernehl *et al.*, 1945). No other significant pathologic changes were observed

The absorption and retention of antimony following inhalation exposure are primarily a function of solubility and particle size (Newton *et al.*, 1994; Felicetti *et al.*, 1974; Thomas *et al.*, 1973). Clearance of antimony typically is rapid initially, followed by a slower phase. Aerosols generated at lower temperatures (i.e. 100° F) tended to be more water soluble than aerosols generated at higher temperatures, and exposure to these particles resulted in more systemic absorption and retention in the bone. The less soluble and smaller particles generated at higher temperatures were retained longer in the lung.

VI.   Derivation of U.S. EPA RfC

Study	Newton *et al.*, 1994
Study population	Fischer 344 rats (65/sex/group)
Exposure method	Discontinuous inhalation
Critical effects	Chronic pulmonary interstitial inflammation
LOAEL	4.50 mg/m³
NOAEL	0.51 mg/m³
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	1 year
Average experimental exposure	0.091 mg/m³ for NOAEL group
Benchmark Concentration (BMC$_{10}$)	0.87 mg/m³ (0.16 mg/m³ continuity-weighted exposure)
Human equivalent concentration	0.074 mg/m³ (particle with pulmonary respiratory effects, RDDR = 0.48)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	3 (database deficiencies)

Cumulative uncertainty factor   300
Inhalation reference exposure level 0.0002 mg/m^3 (0.2 µg/m^3)

Significant strengths in the antimony REL include (1) the availability of chronic inhalation exposure data, (2) a well-conducted study with extensive histopathological analysis, (3) the demonstration of a dose-response relationship, and (4) the demonstration of consistent adverse effects among multiple studies of several species conducted by independent investigators.

A major area of uncertainty is the lack of adequate human exposure data and the lack of data on reproductive and developmental toxicity.

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Inorganic Arsenic Reference Exposure Levels

1.   Summary

Acute, 8-hour and chronic reference exposure levels (RELs) were derived for inorganic arsenic including arsine. Inorganic arsenic causes a wide variety of toxic effects in humans and experimental animals including effects on development, the vascular system, the nervous system, blood, lung, and skin. The most sensitive acute effects were seen in mice (fetal development) whereas the most sensitive 8-hour and chronic effects were decreased intellectual function in children. The relevant literature evaluated in this assessment was published before April 1, 2008. The key values are summarized below.

1.1   Inorganic Arsenic Acute REL

Reference Exposure Level	**0.2 μg As/m³**
Critical effect(s)	Decreased fetal weight in mice
Hazard Index target(s)	Development (teratogenicity); cardiovascular system; nervous system

1.2   Inorganic Arsenic 8-Hour REL

Reference Exposure Level	**0.015 μg/ As/m³**
Critical effect(s)	Decreased intellectual function in 10 year old children
Hazard Index target(s)	Development; cardiovascular system; nervous system; lung; skin

1.3   Inorganic Arsenic Chronic REL

Reference Exposure Level	**0.015 μg As/m³**
Oral Reference Exposure Level	0.0035 μg/kg bw-day
Critical effect(s)	Decreased intellectual function in 10 year old children
Hazard Index target(s)	Development; cardiovascular system; nervous system; lung; skin

2. Physical & Chemical Properties

Table 2.1 Arsenic and Arsenic Species*

Molecular formula	Molecular weight	Percent As by weight	Synonyms	CAS Registry Number
As	74.92	100%	Arsenic black, metallic arsenic	7440-38-2
As_2O_3 As_4O_6	197.82 395.68	75.7%	Arsenious oxide, arsenic (III) trioxide, arsenic oxide, arsenous acid, arsenous acid anhydride, Crude Arsenic, White Arsenic	1327-53-3
$AsCl_3$	181.28	41.3%	Arsenic butter, trichloroarsine, arsenious chloride	7784-34-1
As_2O_5	229.82	65.2%	Arsenic pentoxide, arsenic anhydride, arsenic oxide, arsenic acid anhydride	1303-28-2
$AsHNa_2O_4$	185.91	40.3%	Arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	7778-43-0
$AsHNa_2O_3$	130.92	57.2%	Arsenous acid disodium salt, arsenious acid sodium salt	7784-46-5
AsH_3	77.94	96.12	Arsine, arsane, arsenic hydride, arsenous hydride, hydrogen arsenide, arsenic trihydride	7784-42-1
$As(OH)_3$	125.94	59.49	Arsenous acid	13464-58-9
$AsO(OH)_3$	141.93	52.78	Arsenic acid, orthoarsenic acid	7778-39-4
As_4S_4	427.92	70.03	Arsenic disulfide, realgar, red arsenic sulfide	
$CH_3AsO(OH)_2$	139.97	53.51	Monomethylarsonic acid	124-58-3
$CH_3As(OH)_2$	123.77	60.41	Monomethylarsonous acid	25400-23-1
$(CH_3)_2AsO(OH)$	137.99	54.28	Dimethylarsinic acid, cacodylic acid	75-60-5
$(CH_3)_2AsOH$	121.99	61.40	Dimethylarsinous acid	55094-22-9
$(CH_3)_3AsO$	136.02	55.06	Trimethylarsine oxide	4964-14-1

*Note: Methylated arsenic species occurring naturally and as metabolites (IARC, 2004)

2.1   Arsenic (Metallic) (ATSDR, 2000)

Description	Yellow, black or gray solid
Molecular formula	see Table 2.1
Molecular weight	see Table 2.1
Specific gravity (water = 1)	5.778 g/cm^3 @ 25°C
Boiling point	613°C (sublimes) at 760 mm Hg
Vapor pressure	7.5 x 10^{-3} mmHg at 280 °C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in nitric acid, insoluble in water
Odor threshold	not applicable
Odor description	odorless
Metabolites	dimethylarsinic acid, methylarsonic acid
Conversion factor	not applicable for As

2.2   Arsenic Trioxide (ATSDR, 2000)

Description	As_2O_3: White solid, glassy, amorphous lumps or crystal
Molecular formula	See Table 2.1
Molecular weight	197.84
Density	As_2O_3: 3.865 g/cm^3
Boiling point	As_2O_3: 460°C
Melting point	As_2O_3: 274°C
Solubility	Oxides: slightly soluble in water 17g/L, insoluble in alcohol, chloroform, ether.
Metabolites	Dimethylarsinic acid, methylarsonic acid

2.3   Arsine (U.S. EPA, 2006a)

Description	Colorless gas
Molecular formula	AsH_3
Molecular weight	77.93
Specific gravity (Water = 1)	1.689 @ 84.9°C
Boiling point	-62.55°C
Melting point	-117°C
Vapor pressure	Greater than 1 atm
Vapor density (Air = 1)	2.695
Solubility	soluble in chloroform and benzene, slightly soluble in water (20 mL/100 mL at 20 C), ethyl alcohol and in alkalis
Odor threshold	0.5 ppm
Odor description	garlic-like or fishy odor
Metabolites	oxidation to arsenite, arsenate, other unidentified (Landrigan *et al*., 1982; Carter *et al*., 2003)
Conversion factor	1 ppm = 3.19 mg/m³ @ 25°C

3.   Occurrence and Major Uses

Arsenic is ubiquitous and is found in small amounts in soils and water throughout the world and also in foods, particularly seafood (NIOSH, 1975). Ore refining processes, including the smelting of copper and lead, are the major sources of release of arsenic dust and inorganic arsenic compounds. Arsenic trioxide is the form of inorganic arsenic most commonly produced. It is used as a raw material for the production of other inorganic arsenic compounds (Asi), alloys, and organic arsenic compounds (Grayson, 1978).

Pesticides have historically constituted the largest single use (50%) of arsenic compounds (HSDB, 1995). The major arsenic herbicides manufactured are monosodium methyl arsonate (MSMA), disodium methyl arsonate (DSMA), and dimethyl arsenic acid (cacodylic acid). Inorganic arsenic compounds are also used as herbicides (arsenite), insecticides (arsenic trioxide, calcium and other arsenates), or rodenticides (sulfides) (ACGIH, 1992). Arsenic trichloride, for example, is used mainly as a chemical intermediate in the production of insecticides, but has other applications in the ceramics and pharmaceutical industries (HSDB, 1995). Arsenic was used as a pesticide to treat tobacco; thus, cigarette smoke was another common source of exposure (U.S.EPA, 1984). The use of arsenic compounds in agriculture has reduced in recent years and U.S. EPA is considering ending their uses under the pesticide reregistration program (U.S. EPA, 2006b).

Arsenic-based wood preservatives have constituted the next largest use (40%) of arsenic compounds (HSDB, 1995). In December 2003 the U.S. EPA terminated all residential uses of wood preservatives containing arsenic limiting such products to restricted use by certified pesticide applicators (U.S. EPA, 2002).

The highly toxic trivalent arsenic compounds, such as arsenic trioxide, are typically introduced into the environment as a result of industrial processes including the smelting of metal ores. Pentavalent arsenic compounds are generally considered to be less toxic and are most frequently found naturally.

Processes such as smelting, galvanizing, soldering, and etching, that require the treatment of metal with strong acids, are possible sources of arsine gas. Acid treatment of metals contaminated with arsenic can result in the release of arsine gas. Arsine is used to provide arsenic as an ingredient in semiconductor manufacture. Combustion of fossil fuels may produce arsine gas.

4.   Toxicokinetics

A knowledge of the metabolism of inorganic arsenic has long been thought to be essential to understanding the mode(s) of action of inorganic arsenic toxicity. Trivalent ($+3$, As^{III}) arsenic species (e.g., arsenite) have often exhibited greater acute toxicity than pentavalent ($+5$, As^V) species (e.g., arsenate). The terms arsenite and arsenate refer to the ionized anions of arsenous acid and arsenic acid, respectively, as they exist in aqueous solution at physiological pH. Since the metabolism of inorganic arsenic in mammalian species generally proceeds via alternate reductive and oxidative methylation steps to mono- (MMA) and dimethyl (DMA) arsenic acids, it was believed that methylation represented detoxication of inorganic arsenic. However, recent

evidence supports the idea that trivalent methylated species are in some cases more toxic than inorganic precursors and may play a key role in arsenic toxicity for selected endpoints. The metabolism of arsine (As^{-III}), while less studied, appears to progress similarly after its oxidation to arsenite (As^{V}) and is in part the basis for including arsine in the RELs for inorganic arsenic.

Several comprehensive reviews of the absorption, distribution, metabolism and elimination of arsenic have been published (Vahter, 1983; Thompson, 1993; ATSDR, 2000; NRC, 2001). Most information on the toxicokinetics of arsenic derives from oral exposure studies. The kinetics of arsenic varies depending on the chemical form of arsenic and on the animal species. The following discussion is limited to the oxidized forms found in water and air and forms that are ingested via the aquatic food chain. These include the inorganic, soluble forms of arsenite (As^{III}) and arsenate (As^{V}), as well as the organic monomethylarsonate (MMA), dimethylarsinic acid (DMA), trimethylarsine (TMA), and or arsenobetaine (in fish).

4.1   Inorganic Arsenic Oxides

Owen (1990) reported inhalation absorption of 32 percent (range 30 to 34 %) from arsenic containing aerosols, however it is uncertain if this figure included the gastrointestinal absorption of arsenic particles from the upper respiratory tract. The International Commission on Radiological Protection Human Respiratory Tract Model (ICRP, 1994) gives total deposition fractions for 10 yr old children inhaling 1 μm activity median thermodynamic diameter particles at 0.31 to 2.03 m^3/hr of 0.42 to 0.58. There are relatively few data on the kinetics of airborne arsenic excretion. Mann *et al*. (1996a) modeled inhalation exposures based on the occupational data of Vahter *et al*. (1986) and Offergelt *et al*. (1992). For simulated occupational exposures of 10 μg/m^3 of arsenic aerosol of MMAD of 5.0 μm, GSD of 2.1, 1.2 L tidal volume and a breathing rate of 16 /min, urinary excretion increased over the work week's exposure from 7 to 25 μg As/g creatinine.

The MMAD refers to the mass median aerodynamic diameter and GSD the geometric standard deviation. These values characterize a distribution of particles in an aerosol. The units refer to the first order rate constant for the absorption of arsenic into the blood plasma from the model lung compartments. The model has separate compartments for the nasopharynx, tracheobroncheal, and pulmonary regions of the lung. Deposition of particles in these lung compartments, in units of μg/hr, depends on breathing rate, tidal volume, concentration of particles in the air, and their aerodynamic diameters. Absorption of deposited particles into blood plasma is first order but depends upon the surface area of the region in question, hence the units of /cm^2-hr.

Model predictions of arsenic metabolites (Asi, MMA, DMA) in postshift urine generally fell within the range of observations for 18 workers in the exposure range of 10-1000 μg As/m^3. After daily inhalation exposure of 100 μg As (III)/m^3 for three weeks, the model predictions for urinary metabolite distribution closely matched observed values (predicted/observed means: Asi, 1.05; MMA, 1.0; DMA, 1.0). From the model, Mann *et al*. (1996b) derived a fitted lung absorption first order rate constant for arsenic trioxide dust of 0.01/cm^2-hr.

In general, investigations that have monitored arsenic excretion of experimental animals following parenteral administration have demonstrated that only a small fraction of the

administered arsenic is excreted in the feces. Thus, to estimate the amount of inorganic arsenic absorbed following oral administration, most kinetic and metabolic studies have monitored the urine. Soluble compounds of inorganic arsenic, whether in the trivalent or pentavalent form, are readily absorbed (80-90 percent) in most animal species following oral administration (Charbonneau *et al*., 1978; Vahter, 1981; Hughes *et al*., 1994; Freeman *et al*., 1995). However, only about 40-50 percent absorption has been reported in hamsters (Yamauchi and Yamamura, 1985; Marafante and Vahter, 1987). Absorption of orally administered inorganic arsenic in humans has been shown to range between 54-80 percent (Tam *et al*., 1979; Buchet *et al*., 1981b; a; Kurttio *et al*., 1998).

Inorganic arsenic compounds are poorly absorbed through the skin (Ca.1-5%); the trivalent is more rapidly absorbed than the pentavalent (Wester *et al*., 1993; Wester *et al*., 2004).

Organic forms of arsenic are also extensively absorbed from the gastrointestinal tract. Experimental studies examining the absorption of MMA, DMA, TMA and arsenobetaine in humans have demonstrated 75-92 percent absorption. At low-level exposures, excretion of arsenic and its metabolites seems to balance absorption of inorganic arsenic. With increasing arsenic intake, there is suggestive evidence that methylation appears less complete. Studies, which examine the effect of dose on excretion patterns, have been conducted in mice and humans (Buchet *et al*., 1981b; a; Vahter, 1981). As the dose of inorganic arsenic increases, the percent of arsenic excreted as DMA decreases, accompanied by an increased excretion in the percent as inorganic arsenic. The percent excreted as MMA remains virtually unchanged. *In vitro* metabolism studies on the methylation of inorganic arsenic have demonstrated that the liver is the site of methylating activity and that S-adenosylmethionine and reduced glutathione are required as methyl donors (Buchet and Lauwerys, 1985; 1987).

While absorption from the gastrointestinal tract is the most important route of exposure for waterborne arsenic, some potential for dermal absorption has been reported. Rahman *et al*. (1994) conducted *in vitro* studies with sodium [^{74}As] arsenate and clipped full-thickness mouse skin in a flow-through system. Doses of 5, 50, 500, or 5000 ng were applied to 0.64 cm^2 of skin as a solid, in aqueous vehicle, or in soil. Absorption of sodium arsenate increased linearly with applied dose from all vehicles. The maximum absorption of 62 percent of applied dose was obtained with the aqueous vehicle and the least (0.3 percent) with soil. Wester *et al*. (1993) evaluated the percutaneous absorption of [^{73}As] arsenate from soil or water *in vivo* in Rhesus monkeys and *in vitro* in human cadaver skin. Water solutions of [^{73}As] arsenate at low (0.024 ng/cm^2) or high (2.1 µg/cm^2) surface concentrations were compared. With topical administration for 24 hr, *in vivo* absorption in the Rhesus monkey was 6.4 ± 3.9 (SD) percent from the low dose and 2.0 ± 1.2 (SD) percent from the high dose. *In vitro* percutaneous absorption of the low dose from water in human skin was 0.93 ± 1.1 percent in receptor fluid and 0.98 ± 0.96 percent in the washed skin; the total was about 1.9 percent. Absorption from soil (0.4 ng/cm^2) was less, at 6.4 percent in the monkey *in vivo* and 0.8 percent in human skin *in vitro*.

The retention and distribution patterns of arsenic are in part determined by its chemical properties. Arsenite (As^{III}) reacts and binds to sulfhydryl groups while arsenate (As^V) has chemical properties similar to those of phosphate. As^V also has affinity for sulfhydryl groups; however, its affinity is approximately 10-fold less than As^{III} (Jacobson-Kram and Montalbano,

1985). The distribution and retention patterns of As^{III} and As^V are also affected by species, dose level, methylation capacity, valence form, and route of administration.

Vahter *et al.* (1984) studied tissue distribution and retention of [74]As-DMA in mice and rats. About 80 percent of an oral dose of 0.4 mg As/kg was absorbed from the gastrointestinal tract. In mice >99 percent of the dose was excreted within 3 d compared to only 50 percent in rats, due largely to accumulation in blood, which delayed excretion. Tissue distribution in mice showed the highest initial (0.5-6 hr) concentrations in kidneys, lungs, intestinal mucosa, stomach, and testes. Tissues with the longest retention times were lungs, thyroid, intestinal walls, and lens.

The effect of dose on arsenate disposition was evaluated in adult female B6C3F$_1$ mice dosed orally with 0.5 to 5000 µg/kg [[73]As]-arsenate in water (Hughes *et al.*, 1994). Urine was collected at several time points over a 48-hr period, and feces at 24 and 48 hr post-exposure. The recovery of As-derived radioactivity in excreta and tissues ranged from 83.1 to 89.3 percent of dose. As-derived radioactivity was detected in several tissues (urinary bladder, gall bladder, kidney, liver, lung) although the sum for each exposure level was very low (<0.5 percent of dose). The principal depot was the liver, followed by the kidneys. As the dose of arsenate increased there was a significant increase in the accumulation of radioactivity in the urinary bladder, kidney, liver, and lungs. The greatest concentration of As radioactivity was in the urinary bladder.

Most studies of arsenic metabolism have involved administration of inorganic arsenic (Asi) as arsenate (As^V) or arsenite (As^{III}) to an experimental animal or a human, and detection of Asi and the methylated metabolites methylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V) in urine, feces, and tissues.

Thompson (1993) conducted an extensive review and analysis of the mammalian metabolic data on arsenic. The metabolism of arsenate can be viewed as a cascade of reductive and oxidative methylation steps leading successively to As^{III}, MMA^V, MMA^{III}, DMA^V, DMA^{III}, $TMAO^V$, and TMA as outlined in Scheme 1. Recently Hayakawa *et al.* (2005) proposed a new metabolic pathway for arsenite, which does not involve oxidative methylation but rather is mediated by As-glutathione complexes, S-adenosylmethionine (SAM) and human arsenic methyltransferase Cyt19. In this pathway arsenic triglutathione (As(SG)$_3$) is converted to monomethyl-(MADG) and dimethyl-(DMAG) conjugates which are hydrolyzed to MMA^{III} and DMA^{III}, respectively. Thus pentavalent methylated metabolites might arise via oxidation of their trivalent forms rather than the reverse as shown in Scheme 1.

Scheme 1. Biomethylation of Arsenic Involving Alternate Reduction of Pentavalent Arsenic to Trivalent Arsenic Followed by Oxidative Addition of a Methyl Group (after Jiang et al. (2003))

$$
\begin{array}{ccccccccc}
 & +2e & & +CH_3^+ & & +2e & & +CH_3^+ & \\
\mathbf{As^VO(OH)_3} & \rightarrow & \mathbf{As^{III}(OH)_3} & \rightarrow & \mathbf{CH_3As^VO(OH)_2} & \rightarrow & \mathbf{CH_3As^{III}(OH)_2} & \rightarrow \\
As^V & & As^{III} & & MMA^V & & MMA^{III} &
\end{array}
$$

$$
\begin{array}{ccccccc}
 & +2e & & +CH_3^+ & & +2e & \\
\mathbf{(CH_3)_2As^VO(OH)} & \rightarrow & \mathbf{(CH_3)_2As^{III}OH} & \rightarrow & \mathbf{(CH_3)_3As^VO} & \rightarrow & \mathbf{(CH_3)_3As^{III}} \\
DMA^V & & DMA^{III} & & TMAO & & TMA^{III}
\end{array}
$$
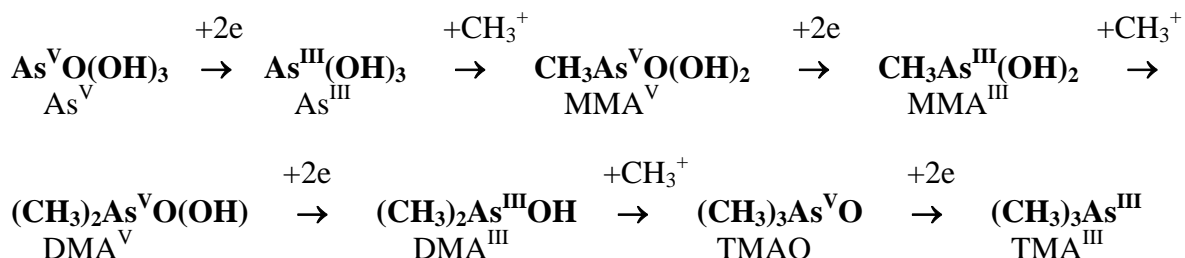
MMA^{III} and DMA^{III} have only recently been detected as stable urinary metabolites in human subjects (Aposhian *et al*., 2000a; Aposhian *et al*., 2000b; Le *et al*., 2000a; Le *et al*., 2000b), and trimethylarsine oxide (TMAO) and trimethylarsine (TMA) are rarely seen and are very minor metabolites in most mammals if found at all. Few data are available on the tissue concentrations of trivalent methylated As species (Kitchin, 2001). Gregus *et al*. (2000) found that in bile duct-cannulated rats, As^{III} and its metabolites were preferentially excreted into bile (22 percent) versus eight percent into urine in two hr. Arsenite appeared in bile rapidly and constituted the large majority in the first 20 min. Thereafter As^{III} declined and MMA^{III} output gradually increased. From 40 min after i.v. As^{III} administration, MMA^{III} was the dominant form of biliary arsenic. Within two hr 9.2 percent of the dose was excreted in the bile as MMA^{III}. Injection of arsenate produced a mixture of As^{V}, As^{III} and MMA^{III} in the bile. Curiously, rats injected with MMA^{V} did not excrete MMA^{III}.

The metabolism results of Styblo *et al*. (1995) in rat liver cytosol *in vitro* seem to support the overall metabolic scheme noted above; MMA^{III} and MMA^{III}-diglutathione complex are more rapidly methylated to the dimethyl forms than MMA^{V}. Thompson also suggests that the data support the presence of two inhibitory loops: (1) competitive inhibition by MMA^{III} of the $As^{III} \rightarrow MMA^{V}$ step catalyzed by monomethyltransferase (MMTase); and (2) possibly noncompetitive inhibition by As^{III} of the $MMA^{III} \rightarrow DMA^{V}$ step catalyzed by dimethyltransferase (DMTase).

Styblo *et al*. (1996) observed 50 μM arsenite inhibition of DMA^{V} production in rat liver cytosol *in vitro*. Healy *et al*. (1998) studied the activity of MMTase in tissues of mice. The activity was determined with sodium arsenite and *S*-[methyl-^{3}H]-adenosyl-L-methionine by measuring the formation of [methyl-^{3}H] monomethylarsonate. The mean MMTase activities (units/mg $\pm$ SEM) measured in cytosol of mouse tissues were: liver, 0.40 ± 0.06; testis, 1.45 ± 0.08; kidney, 0.70 ± 0.06; and lung, 0.22 ± 0.01. When mice were given arsenate in drinking water for 32 or 92 days at 25 or 2500 μg As/L, the MMTase activities were not significantly increased compared to controls. MMTases and DMTases have been partially purified from the livers of rabbits (Zakharyan *et al*., 1995), Rhesus monkeys (Zakharyan *et al*., 1996) and hamsters (Wildfang *et al*., 1998). All of the enzyme preparations exhibited Michaelis-Menten enzyme kinetics with Km values ranging from 8×10^{-4} *M* for hamster DMTase to 1.8×10^{-6} *M* for hamster MMTase. Vmax values ranged from 0.007 pmol/mg protein/hr for hamster DMTase to 39.6 pmol/mg protein/hr for rabbit MMTase. Comparative studies have shown several species to be deficient in methyltransferase activities, notably New World monkeys, marmosets, tamarin, squirrel, chimpanzee, and guinea pig (Vahter *et al*., 1995b; Aposhian, 1997). While comparisons with human arsenic methyl transferase are limited by lack of a purified human enzyme, based on excretion profiles of urinary metabolites the rabbit and hamster appear most pharmacokinetically similar to humans than the other species studied. Walton *et al*. (2003) compared the methylation of arsenite by rat and human primary hepatocytes in vitro (control values in their Tables 1 and 2). For the rat the methylation rate after a 3 hr incubation with 0.1 μM arsenite was 99.3 ± 1.87 pmol CH_3/hr/10^6 cells (mean $\pm$ SD, N =4). The human hepatocytes similarly exposed for 24 hr had a methylation rate of 1.68 ± 0.24 pmol CH_3/hr/10^6 cells, over a 50-fold difference in apparent methylation rate.

While the reduction of arsenate and MMA^{V} can be accomplished nonenzymatically *in vitro*, and arsenate reduction by glutathione occurs in mammalian blood *in vivo* (Vahter and Envall, 1983;

Winski and Carter, 1995), these reductive steps are most likely enzymatically mediated *in vivo*. An arsenate reductase has been partially purified from human liver and described (Radabaugh and Aposhian, 2000). The approximate mass of the enzyme was 72,000. It was specific for arsenite (i.e., did not reduce [^{14}C] MMA^V) and exhibited substrate saturation at about 300 µM. The human arsenate reductase requires a thiol and a heat-stable cofactor and is apparently distinct from those isolated from bacteria (Ji and Silver, 1992; Gladysheva *et al*., 1994; Krafft and Macy, 1998).

Monomethyl arsonate (MMA^V) reductases have been isolated and described for rabbit (Zakharyan and Aposhian, 1999) and hamster (Sampayo-Reyes *et al*., 2000). In the latter study the distribution of MMA^V reductase activity was 91.4 nmol MMA^{III}/mg protein/hr in brain and 61.8 nmol MMA^{III}/mg protein/hr in bladder. Skin, kidney and testis all had less than 15 nmol/mg/hr. Spleen, liver, lung, and heart were all between 15 and 62 nmol/mg/hr. The high activity of MMA^V reductase in brain is curious and may help explain some of the neurotoxic effects of arsenic. Due to relatively low affinity of the MMA^V reductase (K_M = 2.2x10^{-3} M) compared to the methyl transferases (K_M = 5-9x10^{-6} M), the MMA^V reduction is thought to be the rate-limiting step in arsenic metabolism (Zakharyan and Aposhian, 1999). The partially purified human liver MMA^V reductase has been shown to be identical with human glutathione S-transferase Omega class hGSTO 1-1 (Zakharyan *et al*., 2001).

DMA is the main metabolite found in the tissues and urine of most experimental animals administered inorganic arsenic. Humans are also somewhat unique in that MMA has been found to be an important metabolite of inorganic arsenic in addition to DMA. Studies conducted on human volunteers given a single oral dose of inorganic arsenic demonstrated that within 4-7 days, 46-62 percent of the dose was excreted in the urine (Tam *et al*., 1979; Pomroy *et al*., 1980; Buchet *et al*., 1981b; a). Approximately 75 percent of the excreted arsenic is methylated, about one-third as MMA and two-thirds as DMA.

The possibility of genetic polymorphism in arsenic metabolism has been suggested by Vahter *et al*. (1995a), who studied native Andean women in northwestern Argentina who were exposed to a wide range of As concentrations in drinking water (2.5 to 200 µg As/L). The women exposed to the highest As concentration in water exhibited surprisingly low levels of MMA in their urine (2.3 percent of metabolites). The percentage of arsenic urinary metabolites as MMA in typical human urine ranges from 12 to 20. Chiou *et al*. (1997a) studied the relationships among arsenic methylation capacity, body retention, and genetic polymorphisms of glutathione-*S*-transferase (GST) M1 and T1 in 115 human subjects. Percentages of As species in urine (mean ± SE) were: Asi, 11.8 ± 1.0; MMA, 26.9 ± 1.2; and DMA, 61.3 ± 1.4. Genetic polymorphisms of GST M1 and T1 were significantly associated with As methylation. Subjects with the null genotype of GST M1 had an increased percentage of Asi in urine, while those with the null genotype GST T1 had elevated DMA in their urine samples.

Marnell *et al*. (2003) reported six polymorphisms in the MMA^V reductase hGSTO1 gene in DNA isolated from peripheral blood of 75 Mexican subjects. Two subjects with the same polymorphism showed 5 to 10 fold higher concentrations (µg/g creatinine) of Asi in their urine than other subjects.

Yu *et al*. (2003) screened DNA of 22 subjects of European ancestry (EA) and 24 of indigenous American ancestry (IA) for polymorphisms in arsenate reductase and MMA^V reductase genes. For the arsenate reductase gene (hPNP) 48 polymorphic sites were identified while 33 were found in the MMA^V reductase gene (hGSTO1-1). For the EA individuals the MMA^V reductase gene showed greater polymorphism than the arsenate reductase gene whereas the reverse was seen in the IA individuals. In the latter group only one polymorphism had a frequency of > 10%. Meza *et al*. (2005) screened 135 As-exposed subjects from Sonora, Mexico for polymorphisms in arsenic metabolism genes: arsenate reductase (hPNP); MMA^V reductase (hGSTO); and arsenic 3 methyltransferase (CYT19). The subjects were exposed to drinking water with 5.5 to 43.3 ppb arsenic. The screening was based on urinary DMA^V/MMA^V (D/M) ratios. The analysis revealed that all of the variation was due to a very strong association between CYT19 and D/M in children only (7-11 yr). With children removed no significant association was seen in adults (18-79 yr). This developmentally regulated association between CYT19 and arsenic metabolism raises questions about the adequacy of arsenic risk assessment for children.

Several authors have studied the kinetics of As excretion in humans. Tam *et al*. (1979) administered ^{74}As arsenic acid (0.01 µg, ca. 6 µCi) to six adult males (age: 28-60; body weight: 64-84 kg) following an overnight fast. The urine was analyzed at 24 hr intervals for five days following As administration. In the first 24 hr period Asi excretion exceeded that of the methylated metabolites but thereafter the usual DMA > MMA > Asi pattern persisted, with DMA increasing in percentage of cumulative excretion at the later time points. A follow up study (Pomroy *et al*., 1980) followed ^{74}As excretion for periods up to 103 days using a whole body counter, with measurement of excreta for the first seven days. Their results indicate that the excretion data were best represented by a three-component exponential function. The coefficients for the pooled data accounted for 65.7 percent of excretion with a half-life of 2.09 days, 30.4 percent with a half-life of 9.5 days, and 3.7 percent with a half-life of 38.4 days. A four-exponent function showed a better fit to one of the six subjects (half-lives: 0.017, 1.42, 7.70 and 44.1 days).

Physiologically-based pharmacokinetic (PBPK) models employ data from various sources to mathematically simulate the uptake, distribution, metabolism and excretion of toxic chemicals in species of interest. Such models are used in risk assessment to estimate target tissue doses and to facilitate route-to-route and interspecies extrapolations. By contrast, pharmacodynamic (PD) models simulate biological responses to chemical exposures. A number of PBPK models for arsenic disposition and metabolism have been developed for experimental animals and humans (Mann *et al*., 1994; Menzel *et al*., 1994; Mann *et al*., 1996a; 1996b; Yu, 1999; Gentry *et al*., 2004). Although these models are based on somewhat different principles, they all seem to do a fair job in predicting the overall disposition of arsenic in animals and man. However, while the models often incorporate the latest ideas on the metabolism of inorganic arsenic with respect to oxidation state, methylated metabolites, and enzyme inhibition, due to limitations in our understanding of the modes of action of arsenic toxicity, they have yet to include representations of biological responses or pharmacodynamic (PD) capabilities, such as dosimetry linked alterations of DNA methylation, cell signaling pathways, DNA repair inhibition or generation of reactive oxygen species.

As an example of the complexity of arsenic action, Gentry *et al*. (2004) observed that pharmacodynamic changes occurred in mice without changes in PBPK predicted arsenic tissue

dosimetry. These authors used the PBPK model of Mann *et al*. (1996a,b) extended to mice to evaluate possible dosimetry differences between mouse a strain susceptible to arsenic induced tumors (C57Bl/6J) and those that lacked susceptibility (e.g., Swiss CD-1, Swiss CD: NIH(S), C57Bl/6p53 (+/-)). The model was parameterized using published acute mouse data for arsenate, arsenite, MMA and DMA and validated with acute exposure data from the C57Black mouse strain. Model predictions for acute exposure were then compared with data from acute (24 hr) and chronic exposures (26 weeks). No differences were seen in the volume of distribution or tissue-plasma concentration ratios between acute and chronic exposures. Comparison of metabolite profiles in blood, liver and urine also showed little difference between acute and chronic exposures. Model predictions compared well with observed values. The authors concluded "… that pharmacokinetic factors do not provide an explanation for the difference in outcomes across the various mouse bioassays." This conclusion may be overly broad since all the metabolites of arsenic and its metabolic pathways were not included in the PBPK modeling.

Liao et al. (2008) employed PBPK models with age-specific parameters to estimate urinary excretion of methylated arsenic metabolites in children. The results were coupled with skin lesion data from West Bengal, Bangladesh and Taiwan to derive dose-response relationships based on MMA^{III} in urine and concentration and duration of exposure to inorganic arsenic in drinking water using the Weibull (dose and time) model. While MMA^{III} was not specifically modeled a ratio of 7.4/2.8% MMA^{III}/MMA^{V} in total urinary MMA excretion was assumed. Age-specific risks at the ED$_{0.1}$ level (10^{-3} risk) were calculated for 0 -<1, 1-6, 7-12, and 13-18 yr age groups. Hyperpigmentation was a more sensitive endpoint than keratosis and males gave lower ED$_{0.1}$ values than females with values of 2.82, 1.51, 1.08, and 0.91 µg As/L for hyperpigmentation in males in the respective age groups. Age specific median daily drinking water consumption rates of 0.65, 1.29, 1.75, and 2.22 L/d, respectively, were used. Although the authors claim these concentrations as "Recommended Safe" levels, they are specific for 1/1000 risk and the skin lesion endpoint, which is not the most sensitive adverse effect for arsenic in exposed children.

4.2 Arsine

Although most studies of arsenic metabolism have centered on arsenate and arsenite, other forms of arsenic are also metabolized in humans. Apostoli *et al*. (1997) reported on the metabolism of arsine gas (As^{-III}H$_3$) in an occupationally exposed worker. Arsenic species were analyzed in urine over a five-day post-exposure period by liquid chromatography and inductively coupled plasma mass spectroscopy. The As species most excreted were MMA, DMA, As^{III}, arsenobetaine (AsB), and to a lesser extent As^{V}. The data indicate a capability to oxidize As^{-III} to As^{V} species probably via arsenite As (OH)$_3$. Arsenobetaine, an important form of arsenic in food, does not undergo subsequent biotransformation and is excreted via the urine. Curiously, arsenobetaine does not appear to be a metabolite of arsine in rats exposed for 1 hour to 4 to 80 mg/m^3 arsine (Buchet *et al*., 1998). The apparent similarity of the metabolism of arsine and arsenite is important and supports the use of the inorganic arsenic RELs for arsine.

Carter *et al*. (2003) have reviewed the metabolism of arsenic oxides, gallium arsenide and arsine. These authors describe three reactions that appear to occur in aqueous solutions of arsine (-III): (1) the formation of elemental As^0 and hydrogen; (2) reaction of AsH$_3$ with oxidized thiols to form diarsine AsH$_2$-AsH$_2$ (proposed) and reduced thiol RSH; and (3) possible reaction between

arsine and oxygen species, producing arsine hydroperoxide H_2AsOOH (Hatlelid *et al*., 1995; 1996). Relatively few studies of arsine metabolism have been conducted in experimental animals. In vitro studies indicate that arsine was rapidly distributed to red blood cells. In plasma arsine appeared to decompose over a few hours. Arsine apparently undergoes rapid oxidative metabolism although the intermediary metabolites have not been identified and apparently are not identical with those shown above for arsenite metabolism (Scheme 1) (Carter *et al*., 2003). A hypothetical scheme based on the same alternate application of oxidative methylation and reduction steps might look as follows with double arrows indicating four electron oxidation steps and single arrows two electron reduction steps:

$$As^{-III}H_3 \Rightarrow H_2As^I(O)CH_3 \rightarrow H_2As^{-I}CH_3 \Rightarrow HAs^{III}(O)(CH_3)_2 \rightarrow HAs^I(CH_3)_2 \Rightarrow As^V(O)(CH_3)_3$$

Arsine   **TMAO**

According to this scheme the intermediary metabolites would include methylated arsine and arsine oxide species. Alternatively nonmethylative oxidation of arsine could lead to arsenite and arsenate via hydroxylated arsine species. Other metabolites possibly based on the oxidation of elemental As or arising via the postulated arsine hydroperoxide are also possible.

5.   Acute Toxicity of Arsenic and Arsenic Compounds

5.1   Acute Toxicity to Adult Humans

The relative acute toxicity of arsenic compounds decreases as follows: arsine (As^{-III}) > organo-arsine derivatives > arsenites (As^{III}) > arsenoxides ($As^{II}I$) > arsenates (As^V) > pentavalent organic compounds (As^V) > arsonium metals (As^I) > metallic arsenic (As^0), where the Roman numeral indicates the oxidation state (HSDB, 1995).

Acute inhalation exposure may result in severe irritation of the mucous membranes of the upper and lower respiratory tract with symptoms of cough, dyspnea, and chest pain (Friberg *et al*., 1986). These may be followed by garlicky breath and gastrointestinal symptoms including vomiting and diarrhea (HSDB, 1995). Signs of acute poisoning are dermatitis, nasal mucosal irritation, laryngitis, mild bronchitis, and conjunctivitis (Friberg *et al*., 1986). The acute toxic symptoms of trivalent arsenic poisoning are due to severe inflammation of the mucous membranes and increased permeability of the capillaries (HSDB, 1995). Ingestion of 2 grams of As_2O_3 was fatal to an adult male (Levin-Scherz *et al*., 1987).

5.2   Acute Toxicity to Infants and Children

Relatively little data are available on acute toxicity of arsenic compounds to children. Childhood poisonings due to arsenic have been reported in the medical literature, often with little dosimetry. Campbell & Oates (1992) surveyed 200 child poisonings and found of the four deaths reported one was due to arsenic-containing weed killer (probably cacodylic acid). Alternatively, the use of arsenic trioxide in cancer chemotherapy seems well tolerated. George *et al*. (2004) reported the treatment of 11 children with acute promyelocytic leukemia with i.v. 0.15 mg As_2O_3/kg-d (8 treatment cycles over a period of 12 months). The toxic effects noted, including leukocytosis and skin hyperpigmentation, were considered minimal. Relapse-free survival was 81%.

5.3   Acute Toxicity to Experimental Animals

The lethal concentration low (LC_{Lo}) for $AsCl_3$ in the cat for a 20-minute inhalation exposure is 100 ppm (740 mg/m³) (Flury, 1921). In the mouse, the LC_{Lo} of $AsCl_3$ for a 10-minute exposure is 338 ppm (2500 mg/m³) (Flury, 1931).

A single intratracheal instillation of 17 mg As_2O_3/kg in rats resulted in multifocal interstitial pneumonia and focal proliferative bronchiolitis and alveolitis observed at necropsy 14 days post-exposure (Webb *et al*., 1986). The authors suggest that As_2O_3 induced an acute fibrogenic response.

Changes in host resistance from inhalation exposure to As_2O_3 aerosol were examined in female CD1 mice using a streptococcus infectivity model and an assay for pulmonary bactericidal activity (Aranyi *et al*., 1981; Aranyi *et al*., 1985). Mice (100-200/group) were exposed to As_2O_3 aerosol (or filtered air) for 3 hours/day, 5 days/week, for 1, 5 or 20 days. Aerosol exposed and control mice were then combined before challenge with *Streptococcus zoopidemicus* aerosol (4-8 replicate exposures). Statistically significant increases in mortality (P < 0.05) were observed in mice exposed: (1) once to 271, 496, and 940 µg As/m³; (2) 5 times to 519 µg As/m³; and (3) 20 times to 505 µg As/m³. Multiple exposures at a given exposure level did not correlate with increased mortality, suggesting an adaptation mechanism. Single exposures did, however, show a dose-response for increased mortality with increasing level of arsenic exposure. Bactericidal activity was evaluated by measuring the ratio of viable bacteria count to radioactive count in the lung 3 hours after infection with ^{35}S-labeled *Klebsiella pneumoniae*. A single exposure to 271, 496, and 940 µg As/m³, but not 123 µg As/m³, resulted in significantly decreased bactericidal activity. Five exposures to 519 µg As/m³ and twenty exposures to both 245 and 505 µg As/m³ resulted in decreased bactericidal activity. The studies indicate a NOAEL for immunotoxicity of 123 µg As/m³. This study provides a partial mode of action of arsenic-induced increase in mortality due to experimental lung infections with the mouse pathogen *S. zooepidemicus*. The second bactericidal assay with radiolabelled *K. pneumoniae* provides a plausible explanation, namely that arsenic exposure above 123 µg/m³ inhibits normal immune bactericidal response in the lung.

Among the other adverse effects of inorganic arsenic noted in experimental animals, the most interesting and relevant to the 8-hour and chronic RELs are those on the brain and nervous system. These include changes in brain histology and conditioned reflexes, changes in locomotor activity, and decreased acetyl cholinesterase, GAD, and GABA levels in the hypothalamus, brain stem and cerebellum. Arsenic induced alterations of brain structure and function are consistent with the more subtle neuro-developmental effects seen in children exposed to inorganic arsenic at lower environmental levels.

5.4   Developmental and Reproductive Toxicity

Arsenic is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. The oxidation state of arsenic determines the teratogenic potential of its inorganic compounds; trivalent (III) arsenic compounds possess greater teratogenic potential than pentavalent (V) compounds. In hamsters, a single maternal intravenous injection of 20 mg/kg sodium arsenate (V) ($AsHNa_2O_4$) on gestation

day 8 was lethal to 44% of all embryos (Willhite and Ferm, 1984). A smaller dose (10 mg/kg) of sodium arsenite (As^{III}) ($AsHNaO_2$) administered in the same manner resulted in 90% embryonic lethality.

Fetal malformations, including exencephaly, resulted from an intravenous injection of $AsH_3Na_2O_4$ (As^V) into pregnant hamsters on gestation day eight (Ferm and Carpenter, 1968). The reproductive NOAEL in this experiment was 5 mg/kg. A significant reduction in fetal body weight, but no malformations were observed following a maternal dose of 5 mg/kg AsH_2NaO_3 (As^{III}) by the same route on gestation day eleven or twelve (Harrison and Hood, 1981).

A significant increase in pre-implantation mortality followed exposure of pregnant rats to aerosolized As_2O_3 at 1 mg/m³ for 5 months; no maternal toxicity was observed (Kamkin, 1982). At the LOAEL, 0.3 mg/m³, slightly elevated pre-implantation lethality was observed. The validity of this report cannot be evaluated, however, because key experimental details were not reported

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to As_2O_3 at a concentration of 40 mg/m³ for 48 hours (Kamil'dzhanov, 1982). Intravenous injection of radioactive arsenate (As^V) or arsenite (As^{III}) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggests that long term exposure of sperm may occur *in vivo* following acute exposure to As (Danielsson *et al.*, 1984).

Nagymajtenyi *et al.*, (1985) exposed pregnant CFLP mice (8-11 females/group) to As_2O_3 aerosol for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg As_2O_3/m^3 (~0.2, 2.2, and 21.6 mg As/m^3. The aerosol was generated by spraying an aqueous solution of As_2O_3. On the 18th day of gestation the mice were sacrificed and the fetuses removed. The numbers of live and dead fetuses were recorded, weighed, and examined microscopically. Fifty fetuses were stained with Alizarin red-S for skeletal examination. Chromosome preparations were made from livers of 10 fetuses per exposure group. Twenty mitoses in each fetus (200/group) were scored for chromosomal damage and 10 percent of these were karyotyped. The data were analyzed with either Fisher's exact test or in the case of fetal weights with the Dunnett multiple comparison t-test.

A statistically significant decrease in fetal weight was observed in all of the dose groups ($P < 0.05$), with a 3, 9, and 29% reduction in average fetal weight with increasing dose (Table 6.4.1). Significantly delayed bone maturation (ossification defects) was observed only in the highest dose group (sternum 14/50; limbs 32/50, both $p < 0.05$). However, an apparent positive dose-related trend in the number of fetuses with skeletal malformations was observed (2 [control], 3, 7, 31, respectively). A similar dose-related trend in chromosome aberrations in liver cells was also observed in the number of cells with damage (6[control], 10, 13, 24), chromatid gaps, chromatid breaks, chromosome fragments, and chromosome breaks (5[control], 10, 13, 27). Only the number of damaged cells and chromosome breaks at the high dose were significantly different from the control ($p < 0.05$).

Table 6.4.1 Data from Table 1 of Nagymajtényi et al. (1985).

As_2O_3 (mg/m^3)	Number of litters	Living fetuses per mother	Number of fetuses examined	% dead fetuses	Average fetal weight (grams)
28.5±0.3	11	9.6	100	29	0.981±0.04*
2.9±0.04	8	12.8.	100	13	1.146±0.03*
0.26±0.01	8	12.5	100	12	1.225±0.03*
0	8	12.5	100	8	1.272±0.02

* Significantly different from control (p<0.05)

This study demonstrates that inhalation exposure to inorganic arsenic is markedly fetotoxic. Arsenic concentrations of 28.5 mg/m^3 caused a reduction in the number of live fetuses, in fetal weight, and an increase in fetuses with delayed osteogenesis.

Rats exposed to 1 μg As_2O_3/m^3 (0.76 μg As/m^3) for 5 months showed increased preimplantation mortality and delayed ossification in fetuses (Kamkin, 1982). Experimental detail was not presented, thus limiting the usefulness of this study.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to 32.4 mg As_2O_3/m^3 for 48 hours (Kamil'dzhanov, 1982). Similarly, motility was decreased after: (1) a 120-hour exposure to 7.95 mg/m^3; (2) a 252-hour exposure to 1.45 mg/m^3; and (3) an 800-hour exposure to 0.36 mg/m^3.

Holson *et al*. (1999) administered arsenic trioxide (As_2O_3) by whole body inhalation to groups of 25 Crl:CD (SD)BR female rats every day for six hours per day, beginning fourteen days prior to mating and continuing throughout mating. The target exposure levels were 0.3, 3.0, and 10.0 mg As_2O_3/m^3 (measured means: 0.24, 2.6, 8.3 mg As/m^3). Maternal toxicity evidenced by the occurrence of rales, a decrease in net body weight gain, and decreased food intake during pre-mating and gestation exposure, was observed only at the high dose. The NOAEL for maternal toxicity was 2.6 mg As/m^3 (3.4 mg As_2O_3/m^3). No treatment-related malformations or developmental variations were observed at any exposure level. The NOAEL for developmental toxicity was 8.3 mg As/m^3 (11 mg As_2O_3/m^3). The median mass aerodynamic diameter of particle sizes generated in the exposure chambers ranged from 1.9 to 2.2 μm for the three doses indicating that the dusts were respirable. However there were no blood or urine arsenic analytical data to assess delivered doses.

Nemec *et al*. (1998) evaluated the developmental toxicity of inorganic arsenic in mice and rabbits. CD-1 mice (25/dose group) and New Zealand White rabbits (20/dose group) were gavaged with aqueous arsenic acid (H_3AsO_4) doses of 0, 7.5, 24, or 48 mg/kg-d on gestation days (GD) six through 15 (mice) or 0, 0.19, 0.75, or 3.0 mg/kg-d on GD six through 18 (rabbits). The

animals were examined at necropsy (GD 18, mice; GD 29, rabbits). Treatment related maternal toxicity including mortality (2/25) was observed only in the highest dose administered to mice. Effects on maternal weight gain were noted only on GD 6-9 (P < 0.01) and GD 15-18 (P < 0.05) of the mid dose and on GD 6-9 (p < 0.05) of the low dose. While overall maternal weight gains were statistically significantly reduced only at the top dose there was an apparent negative trend in decreased GD18 body weights with increasing dose (56.2 g control, 54.9 g, 52.7g, 46.7g, respectively). While the authors identified a NOAEL for maternal toxicity of 7.5 mg/kg-d, the apparent negative trend noted above suggests that this may be a LOAEL (4.0 mg As/kg-d).

Statistically significant adverse effects on offspring growth or survival were seen only at the highest dose of 48 mg/kg-d. However, there was an apparent negative trend in the number of live fetuses per litter with increasing dose (12.3 control, 11.6, 11.0, 6.6, respectively). An increased incidence of resorptions per litter was seen in the 48 mg/kg-d dose group (P ≤ 0.01), (mainly early resorptions). Early and total resorptions showed an apparent positive trend (6.4% total control, 6.1%, 9.6%, 41.9%, respectively). Mean fetal weight showed an apparent negative trend (1.3 g control, 1.32 g, 1.23 g, 0.99 g, respectively). There were no statistically significant dose-related increases in the overall incidence of fetal malformations; however, the mean percent of litter malformation was about three-fold higher in the 48 mg/kg-d dose group than in the lower doses and control. The NOAEL for developmental toxicity would appear to be 7.5 mg/kg-d (4.0 mg As/kg-d).

Maternal toxicity in rabbits, including mortality, slight body weight loss, and clinical signs (decreased urination and defecation, occasional prostration and ataxia), occurred only at the high arsenic acid dose of 3.0 mg/kg-d. The number of does with decreased urination and defecation appeared to be slightly higher in the mid- and low-dose groups, but these effects may not have been treatment related and no effects on body weight were seen. At sacrifice on GD 29 maternal body weight appeared to be reduced in the high dose group. A significant loss in mean maternal gravid body weight occurred during the first six days of high-dose treatment (GD 6-12) (p ≤ 0.01). This effect persisted and was significantly different from controls for the entire treatment interval (GD 6-18). There were no statistically significant increases in the incidences of any developmental parameters, including malformations. Fetal survival, mean fetal weight, and sex ratio on GD 29 were not affected by the treatment. The number of live fetuses per litter was reduced and resorptions per litter increased in the high-dose group. The latter findings were mainly due to one doe with a totally resorbed litter. The overall values were the range from laboratory historical controls. The authors identified a NOAEL of 0.75 mg/kg-d (0.4 mg As/kg-d) for both maternal toxicity and developmental toxicity.

Stump *et al*. (1999) administered either sodium arsenate (As[V]) i.p. or arsenic trioxide (As[III]) i.p. or by gavage on GD 9 to 25 Crl:CD (SD) BR rats. The doses of sodium arsenate were 0, 5, 10, 20, and 35 mg/kg (0, 1.2, 2.4, 4.8, 8.4 mg As/kg). The doses of arsenic trioxide were: i.p. 0, 1, 5, 10, and 15 mg/kg (0, 0.8, 3.8, 7.6, and 11.4 mg As/kg); and by gavage (p.o.) 0, 5, 10, 20, 30 mg/kg (0, 3.8, 7.6, 15.2, 22.7 mg As/kg). Sodium arsenate (i.p.) caused decreased maternal food consumption (GD 9-20), decreased body weights and body weight gains at the highest dose of 35 mg/kg. Decreased food consumption was also seen in the 20 mg/kg dose group at GD 9-10 and GD 9-20. Arsenic trioxide (i.p.) resulted in excessive mortality in the highest dose-group (19/25) and significant reductions in maternal food consumption, body weight at GD20, body weight change, and net body weight in the next highest dose-group (10 mg/kg). Arsenic trioxide (p.o.)

resulted in less mortality in the highest dose-group (7/25). Clinical signs were noted in the 20 and 30 mg/kg dose-groups including changes in fecal consistency and decreased defecation. Food consumption (GD 9-10) was decreased in a dose-dependent manner across As treatment groups. The study identified single dose maternal effects NOAELs of 2.4 mg As/kg for sodium arsenate (i.p.) and 3.8 mg As/kg for arsenic trioxide i.p. A LOAEL of 3.8 mg As/kg was identified for arsenic trioxide p.o.

Intraperitoneal administration of sodium arsenate or arsenic trioxide caused neural tube and ocular defects (exencephaly, microphthalmia/anophthalmia, and other craniofacial defects) in the offspring of treated rats. These effects were statistically significant only at doses causing maternal toxicity or mortality (35 and 10 mg/kg, respectively). Oral administration of arsenic trioxide caused no treatment-related malformations. The study identified single dose developmental NOAELs of 2.4 mg As/kg for sodium arsenate i.p., 3.8 mg As/kg for arsenic trioxide i.p., and 15.2 mg As/kg for arsenic trioxide p.o.

DeSesso *et al*. (1998), in a comprehensive review of the developmental toxicity of inorganic arsenic, concluded that cranial neural tube defects (NTDs) were induced in rodents only when exposure occurred early in gestation, at high maternally toxic doses, and by parenteral routes of administration. They argued that such NTD effective doses are unlikely to be achieved by the oral, inhalation, or dermal routes in rodents, and that inorganic arsenic does not represent a realistic developmental risk in humans subjected to any environmentally relevant exposure scenarios.

Male and female Charles River CD mice (10/group) were treated with 0 or 5 ppm arsenite in drinking water continuously through three generations (Schroeder and Mitchener, 1971). Endpoints examined included the interval between litters, the age at first litter, the ratio of males to females, the number of runts, stillborn offspring, failures to breed, and congenital abnormalities. The study showed an alteration in the number of small litters in the arsenic exposed group.

Female CD-1 mice (8-15/group) were treated by oral gavage with 0, 20, 40, or 45 mg sodium arsenite/kg on a single day of gestation between days 8 and 15 (Baxley *et al*., 1981). Maternal mortality, fetal malformations, and increased prenatal death were observed among animals treated with 40 and 45 mg sodium arsenite/kg.

Pregnant golden hamsters (>10/group) were treated by oral gavage with a single administration of 0, 20, or 25 mg/kg sodium arsenite on one of gestational days 8-12 (Hood and Harrison, 1982). Prenatal mortality was increased among animals receiving 25 mg/kg on gestational days 8 and 12 and fetal weights were decreased among animals receiving 25 mg/kg on gestational day 12. One dam died following administration of 20 mg/kg.

Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggested that long term exposure of sperm to arsenic may occur *in vivo* following acute exposure (Danielsson *et al*., 1984).

6.   Chronic Toxicity of Arsenic and Arsenic Compounds

6.1   Chronic Toxicity to Adult Humans

Arsenic in drinking water is carcinogenic to humans (Group 1, IARC, 2004). Arsenic compounds show limited to sufficient evidence of carcinogenicity in experimental animals (IARC, 2004). The U.S. Environmental Protection Agency has classified arsenic as Group A; a human carcinogen, based on sufficient evidence from human data including increased lung cancer mortality in multiple human populations exposed primarily through inhalation, increased mortality from multiple internal organ cancers (liver, kidney, lung, bladder), and increased skin cancers observed in populations exposed to arsenic in drinking water (IRIS online file www.epa.gov/iris/subst/0278.htm). Since this document deals with noncancer risks, the carcinogenicity of arsenic is not covered here in any detail (see OEHHA (1999)).

Smelter workers, exposed to concentrations of arsenic up to 7 mg As/m^3, showed an increased incidence in nasal septal perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (Lundgren, 1954).

In a case-control study, copper smelter workers (n = 47) exposed to arsenic for 8-40 years (plus 50 unexposed controls matched for age, medical history, and occupation) were examined by electromyography and for nerve conduction velocity in the arms and legs (Blom *et al*., 1985). The workers were found to have a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocities in three peripheral nerves (upper and lower extremities). Slightly reduced nerve conduction velocity in 2 or more peripheral nerves was reported as "more common" among arsenic exposed workers. Minor neurological and electromyographic abnormalities were also found among exposed workers. Occupational exposure levels were estimated to be 0.05-0.5 mg As/m^3, with As_2O_3 the predominant chemical form. Except for three arsenic exposed workers who had long-term exposure to lead, exposure to other heavy metals was insignificant.

The smelter workers described by Blom *et al*. (1985) (number of controls reduced to 48) were further examined for prevalence of Raynaud's phenomenon and for vasospastic tendency by measurement of finger systolic pressure at 10°C and/or 15°C relative to that at 30°C (FSP%) (Lagerkvist *et al*., 1986). The FSP% was found to covary with the duration of exposure to arsenic, and the prevalence of Raynaud's phenomenon was significantly increased among exposed workers. Daily arsenic uptake was estimated at less than 300 μg/day and was confirmed with urinary excretion data.

Hyperpigmentation and hyperkeratinization were observed in workers exposed to 0.4 - 1 mg/m^3 inorganic arsenic for two or more years (Perry *et al*., 1948).

Most of the relevant epidemiological data on arsenic adverse effects comes from studies of arsenic exposure via drinking water. These studies are relevant because arsenic exerts similar toxic effects once it enters the body. For example, arsenic causes lung cancer in humans by both oral and inhalation routes. The adverse effects summarized below include skin lesions(keratosis and altered pigmentation), vascular effects on the heart, brain and peripheral vasculature, peripheral neuropathy, and lung disease.

6.1.2.1 Skin Effects

Mazumder *et al*. (1998) investigated arsenic-associated skin lesions of keratosis and hyperpigmentation in 7683 exposed subjects in West Bengal, India. While water arsenic concentrations ranged up to 3400 µg/L, over 80% of the subjects were consuming water with < 500 µg/L. The age-adjusted prevalence of keratosis was strongly related to water As concentration, rising from zero in the lowest exposure level (< 50 µg/L) to 8.3% for females drinking water containing >800 µg As/L, and from 0.2 to 10.7% in males, respectively. A similar dose-response was observed for hyperpigmentation: 0.3 to 11.5% for females; and 0.4 to 22.7% for males. Overall males had 2-3 times the prevalence of both keratosis and hyperpigmentation than females apparently ingesting the same doses of arsenic per body weight. Subjects that were more than 20% below standard body weight for their age and sex had a 1.6-fold increase in the prevalence of keratoses, suggesting that malnutrition may play a role in increasing susceptibility.

Rahman *et al*. (2006) evaluated arsenic exposure and age- and sex-specific risk for skin lesions in a population-based case-referent study in Bangladesh. The entire population over four years of age of Matlab, Bangladesh (N = 166,934) was screened for skin lesions. Skin lesions were classified as hyperpigmentation (melanosis), hypopigmentation (leukomelanosis), or keratosis. A total of 504 cases with skin lesions were identified. A randomly selected referent group of 1830 subjects was included in the study. Arsenic exposure was assessed by personal history of tube well use since 1970 or year of birth if later. Water samples from all functioning tube wells were measured for arsenic concentration by hydride-generation atomic absorption spectroscopy. A dose-response relationship was observed for increased skin lesions and arsenic exposure for both sexes (P < 0.001). For males using the metric of As µg/L the highest exposure quintile ($\geq$ 300 µg/L) gave an adjusted odds ratio (OR) of 9.56 (95% CI = 4.20-21.8). Females gave a corresponding OR of 6.08 (3.06-15.5). The cumulative As exposure metric (µg/L x years) gave OR's of 10.4 and 9.19, respectively. In an analysis with males and females combined, adjusted for age and socioeconomic status, males had significantly higher risk of As-related skin lesions than females, when females' lowest average exposure quintile was used as the reference. For the highest quintile, the males OR was 10.9 (5.8-20.4) and the females OR was 5.78 (3.10-10.8), P = 0.005.

Dermatitis and irritation of the mucous membranes have been observed in arsenic-exposed workers (Vallee *et al*., 1960). Hepatic fatty infiltration, central necrosis, and cirrhosis were observed in two patients who ingested As_2O_3 (1% in Fowler's solution) for three or more years (Morris *et al*., 1974). Daily consumption of 0.13 mg As/kg in contaminated well water resulted in the chronic poisoning and death of four children; at autopsy, myocardial infarction and arterial thickening were noted (Zaldivar and Guillier, 1977).

6.1.2.2 Vascular Disease

Vascular diseases have long been noted to be associated with chronic arsenic exposures among German vineyard workers (Grobe, 1976) and inhabitants of Antofagasta, Chile (Borgono *et al*., 1977). Peripheral vascular diseases have been reported to be associated with the occurrence of arsenic in well waters in Taiwan (Chen and Wu, 1962; Chi and Blackwell, 1968; Tseng, 1977; Chen *et al*., 1988). Concentrations in one study were characterized as 0.10 – 1.8 ppm (Yu *et al*.,

1984). The term arseniasis or arsenosis connotes vascular disease associated with chronic exposure to arsenic, specifically blackfoot disease (BFD). BFD is characterized by progressive narrowing of the peripheral arteries, particularly those of the lower extremities. This can lead to ulceration, gangrene and amputation. The etiology of BFD is unclear but arsenic is thought to be the principal cause. The term arsenicosis refers to arsenic induced skin lesions ranging in severity over four stages, seven grades and 20 sub-grades from diffuse melanosis (skin pigmentation or depigmentation) to aggressive skin and internal malignancy (Saha, 2003).

Wu *et al*. (1989) found significant trends of mortality rates from peripheral vascular diseases and cardiovascular diseases with concentrations of arsenic in well water. However, no significant association was observed for cerebrovascular accidents. Engel and Smith (1994) evaluated arsenic in drinking water and mortality from vascular disease in 30 U.S. counties from 1968 to 1984. Mean As levels in drinking water ranged from 5.4 to 91.5 µg/L. Standardized mortality ratios (SMRs) for diseases of arteries, arterioles, and capillaries (DAAC) for counties exceeding 20 µg/L were 1.9 (90% C.I. = 1.7-2.1) for females and 1.6 (90% C.I. = 1.5-1.8) for males. SMRs for three subgroups of DAAC including arteriosclerosis and aortic aneurysm were also elevated as were congenital abnormalities of the heart and circulatory system.

Tseng *et al*. (1996) studied the dose relationship between peripheral vascular disease (PVD) and ingested inorganic arsenic in blackfoot disease endemic villages in Taiwan. A total of 582 adults (263 men and 319 women) underwent Doppler ultrasound measurement of systolic pressures on bilateral ankle and brachial arteries and estimation of long-term arsenic exposure. The diagnosis of PVD was based on an ankle-brachial index of < 0.9 on either side. Multiple logistic regression analysis was used to assess the association between PVD and As exposure. A dose-response relationship was observed between the prevalence of PVD and long-term As exposure. The odds ratios (95% confidence intervals) after adjustment for age, sex, body mass index, cigarette smoking, serum cholesterol and triglyceride levels, diabetes mellitus and hypertension were 2.77 (0.84-9.14), and 4.28 (1.26-14.54) for those who had cumulative As exposures of 0.1 to 19.9 and ≥ 20 (mg/L) x yr, respectively. A follow up study (Tseng *et al*., 1997) indicated that PVD was correlated with ingested As and not with abnormal lipid profiles. The lipid profiles studied were total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), apolipoprotein AI, and apolipoprotein B. Other lipids such as modified LDL, subclasses of LDL and HDL, and other lipoproteins such as lipoprotein (a), which may track as better indicators of atherosclerosis, were not included. Also, the roles of platelet aggregation and coagulation profiles were not studied.

Chen *et al*. (1996) evaluated the dose-response relationship between ischemic heart disease (ISHD) mortality and long-term arsenic exposure. Mortality rates from ISHD among residents in 60 villages in an area of Taiwan with endemic arseniasis from 1973 through 1986 were analyzed for association with As concentrations in drinking water. Based on 1,355,915 person-years and 217 ISHD deaths, the cumulative ISHD mortalities from birth to age 79 yr were 3.4%, 3.5%, 4.7%, and 6.6% for the median As concentrations of < 0.1, 0.1-0.34, 0.35-0.59, and ≥ 0.6 mg/L, respectively. Multivariate-adjusted relative risks (RRs (95% C.I.)) associated with cumulative arsenic exposure from well water were 2.46 (0.53-11.36), 3.97 (1.01-15.59), and 6.47 (1.88-22.24) for 0.1-9.9, 10.0-19.9, and 20+ (mg/L)-yr, respectively, compared with those without As exposure.

Chiou *et al.* (1997b) evaluated the dose-response relationship between prevalence of cerebrovascular disease and ingested arsenic among residents of the Lanyang Basin in northeast Taiwan. A total of 8102 adults from 3901 households were recruited for the study. Arsenic in well water of each household was determined by hydride generation and atomic absorption spectrometry. Logistic regression analysis was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals for various risk factors of cerebrovascular disease. A significant dose-response relationship was observed between As concentration in well water and prevalence of cerebrovascular disease after adjustment for age, sex, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption. The dose-response relationship was even more prominent for cerebral infarction with multivariate-adjusted odds ratios (95% C.I.) of 1.0, 3.4 (1.6-7.3), 4.5 (2.0-9.9), and 6.9 (3.0-16), respectively, for those who consumed well water with As concentrations of 0, 0.1-50.0, 50.1-299.9, and > 300 μg/L. For cumulative arsenic exposures of <0.1, 0.1-4.9, and ≥ 5.0 (mg/L)-yr, the odds ratios were 1.00, 2.26, and 2.69 for cerebrovascular disease and 1.00, 2.66, and 3.39 for cerebral infarction, respectively. All of the values above for As exposed groups were significantly greater than unexposed at P < 0.05.

Chen *et al.* (1995) also investigated the association between long-term exposure to inorganic arsenic and the prevalence of hypertension. A total of 382 men and 516 women were studied in villages where arseniasis was endemic. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, or a history of hypertension treated with antihypertensive drugs. The long-term arsenic exposure was calculated from the history of artesian well water consumption obtained through subject questionnaires and the measured arsenic concentration in well water. Residents in villages where long-term arseniasis was endemic had a 1.5-fold increase in age- and sex-adjusted prevalence of hypertension compared with residents in nonendemic areas. The duration of well water consumption, average As water concentration, and cumulative As exposure were all significantly associated with hypertension. For the cumulative As exposure in (mg/L)-yr, the percent prevalence values were: 0, 5.0%; 0.1-6.3 (mg/L)-yr, 4.9%; 6.4-10.8 (mg/L)-yr, 12.8%; 10.9-14.7 (mg/L)-yr, 22.1%; 14.8-18.5 (mg/L)-yr, 26.5%; > 18.5 (mg/L)-yr, 29.2%.

As part of a study of arsenic exposure via drinking water and mortality outcome in Millard County, Utah, Lewis *et al.* (1999) found a statistically significant association with mortality from hypertensive heart disease. Median drinking water concentration of arsenic ranged from 14 to 166 μg/L for the 946 subjects in the study. The standard mortality ratios (SMR) without regard to specific exposure levels were SMR = 2.20 (95% C.I., 1.36-3.36) for males and SMR = 1.73 (95% C.I., 1.11-2.58) for females. When analyzed by cumulative exposure groups of low (< 1.0 (mg/L)-yr), medium (1.0-4.9 (mg/L)-yr), and high (≥ 5.0 (mg/L)-yr), there was no apparent dose response relationship. However the cumulative dose estimates in this study were lower than in the Chen *et al.* (1995) discussed above so the results of the two studies are not inconsistent.

Chen *et al.* (2006) conducted a cross-sectional analysis of the association of arsenic exposure from drinking water and blood pressure in 10,910 subjects. Time-weighted well arsenic concentrations (TWA) based on current and past well usage were derived. Odds ratios (OR's) for high pulse pressure (systolic – diastolic pressure ≥ 55 mmHg) by increasing TWA quintiles (≤ 8, 8.1-40.8, 40.9-91.0, 91.1-176.0, 176.1-864.0 μg/L) were: 1.00 (referent); 1.39 (95% C.I. 1.14, 1.71); 1.21 (0.9, 1.49); 1.19 (0.97, 1.45); 1.19 (0.97,1.46). OR's for systolic hypertension (≥ 140 mmHg) suggested a similar but weaker association. Participants with lower than average

intake of B vitamins and folate showed somewhat higher OR's. No associations were apparent for TWA and diastolic hypertension.

In a study related to those above, Lai *et al*. (1994) studied inorganic arsenic ingestion and the prevalence of diabetes mellitus. A total of 891 adult residents of villages in southern Taiwan where arseniasis is endemic were included in the study. Diabetes status was determined by an oral glucose tolerance test and a history of diabetes regularly treated with sulfonylurea or insulin. Cumulative arsenic exposure in ppm-yr was determined from the detailed history of drinking artesian well water. There was a dose-response relation between cumulative arsenic exposure and prevalence of diabetes mellitus. The relation remained significant after adjustment for age, sex, body mass index, and activity level at work by a multiple logistic regression analysis giving multivariate-adjusted odds ratios of 6.61 and 10.05, respectively, for exposures of 0.1-15 ppm-yr and > 15.0 ppm-yr versus an unexposed group. In an effort to confirm this association between diabetes mellitus and arsenic observed for drinking water in Taiwan, Rahman and Axelson (1995) reviewed 1978 case-control data from a Swedish copper smelter. Twelve cases of diabetes mellitus (death certificate) were compared with 31 controls without cancer, cardiovascular and cerebrovascular disease. The odds ratios for diabetes mellitus with increasing arsenic exposure categories were 1.0 (reference level), 2.0, 4.2, and 7.0 with the 95% confidence level including unity. The trend was weakly significant, p = 0.03. Albeit with limited numbers, the study provides some support for a role of arsenic exposure in the development of diabetes mellitus.

6.1.2.3 Neurological Disease

Hafeman *et al*. (2005) evaluated the association between arsenic exposure and peripheral neuropathy in a cross-sectional study of 137 adults in Bangladesh. Exposure measures included individual arsenic water concentration, cumulative arsenic index (CAI), and urinary arsenic concentration. Experimental measures were primarily vibrotactile threshold testing of the index finger (IVT) and toe (TVT) and secondarily tapping speed, grip strength, ankle reflex, and proprioception. The cumulative arsenic index and urinary arsenic were both significantly associated with elevated TVT (P = 0.02 and P = 0.009, respectively) after adjustment for age and gender. While dose-response relations were difficult to define, a linear regression analysis of TVT (vibration units) versus the continuous measures of urinary arsenic and CAI gave slopes of 0.02 and 0.0025 TVT units/50 µg As/mg urinary creatinine, respectively. The association between IVT and arsenic exposure was not statistically significant. No association was found between any measure of arsenic exposure and grip strength, tapping speed, ankle reflex, or proprioception.

6.1.2.4 Lung Disease

Several studies have reported effects of arsenic exposure through drinking water on the lung. Mazumder et al. (2000) reported increasing respiratory symptoms, including cough, shortness of breath, and chest sounds, with increasing arsenic concentrations in the drinking water in people residing in West Bengal, India. The effects seen were marked in individuals who also had arsenic related skin lesions. In a later study also in West Bengal, these investigators also reported a large increase (OR = 10; 95% CI 2.7-37) in bronchiectasis in individuals with skin lesions compared to those without arsenic-related skin lesions (Mazumder et al., 2005).

Von Ehrenstein *et al*. (2005) studied the relation between lung function, respiratory symptoms, and arsenic in drinking water among 287 adults, including 132 with arsenic-induced skin lesions in West Bengal, India. Arsenic levels in drinking water and the number of male subjects with or without skin lesions were: 0-99 µg/L, 9, 36; 100-399 µg/L, 66, 34; ≥400 µg/L, 18, 15, respectively. For respiratory symptoms of "shortness of breath at night" and "morning cough", the odds ratios (ORs) for men with skin lesion versus those without was 2.8 with 95% confidence intervals (C.I.) of (1.1, 7.6) and (1.2, 6.6), respectively. For men with skin lesions, the average forced expiratory volume in one second (FEV_1) was reduced by 256.2 mL (95% C.I.; 113.9, 398.4) P < 0.001. Average forced vital capacity (FVC) was reduced by 287.8 mL (95% C.I.; 134.9, 440.8) P < 0.001. In men a 100 µg/L increase in arsenic level was associated with a 45.0 mL decrease (95% C.I.; 6.2, 83.9) in FEV_1 (P = 0.02) and a 41.4 mL decrease (95% C.I.; -0.7, 83.5) in FVC (P = 0.054). The findings were adjusted for age, height and smoking in both males and females. Women participating in the study (N = 109) had a lower risk of developing skin lesions than men and exhibited few respiratory symptoms.

6.2   Chronic Toxicity to Infants and Children

The adverse effects of inorganic arsenic exposure reported in children include skin lesions, neurodevelopmental effects (IQ and related effects), lung disease expressed in later years, and reproductive effects (decreased birth weight, spontaneous abortion, neonatal death).

As noted above Mazumder *et al*. (1998) observed a dose-response for arsenic-associated skin lesions in a cross-sectional survey of 7683 subjects in West Bengal, India. The study population was divided by age decades such that the effect on young children (≤ 9 yr) and adolescents (10-19 yr) could be analyzed separately. The prevalence of keratosis in females and males was 0.2 and 0.5 percent in young children and 1.0 and 1.7 percent in adolescents, respectively. The comparable values for hyperpigmentation were 1.7 and 2.0 percent and 2.2 and 3.5 percent, respectively. Overall 1149 young children and 1599 adolescents were surveyed. The low- to mid-dose quantal responses for combined skin lesions in young children using the mid points of the arsenic concentration ranges (µg/L) were: 25, 0/414; 75, 0/95; 125, 4/118; 175, 2/50; 275, 6/161; 425, 11/101. For the adolescents the comparable values were: 1/730; 2/147; 2/107; 7/110; 26/213; 9/58.

The adverse effects of inorganic arsenic on the developing intellectual function of exposed children have been reported in several studies summarized in this section. While some of the studies have deficiencies, as a group they indicate that arsenic exposure, like lead exposure, presents a risk to children. The neurodevelopmental endpoint has been selected by OEHHA as the critical effect for deriving 8-hour and chronic RELs for inorganic arsenic.

Calderon *et al*. (2001) conducted a cross-sectional study to examine the effects of chronic exposure to lead (Pb) and arsenic (As), and also nutrition, on the neuropsychological development of children. Two populations of children aged six to nine years (N = 41, 39) with differing As exposure levels (63 vs. 40 µg/g) but similar Pb exposures (8.9 vs. 9.7 µg Pb/dL blood, respectively) were compared using the Wechsler Intelligence Scale for Children (WISC) Revised Version for Mexico. After controlling for significant potential confounders verbal IQ was observed to decrease with increasing urinary arsenic (P < 0.01). Language, verbal comprehension and long-term memory also appeared to be adversely affected by increasing

arsenic exposure (concepts and knowledge factors, P < 0.05 each). Blood lead was significantly associated with a decrease in attention (sequential factor, P < 0.05). However since blood lead is an imprecise measure of lead burden there could be some residual confounding in this study.

The relationship between arsenic exposure via drinking water and neurological development as indicated by intelligence (IQ) was assessed in Thailand (Siripitayakunkit *et al*., 1999) in 529 children aged six to nine years using a cross-sectional design. Arsenic levels in hair were used to assess exposure and the WISC test for children was used to assess IQ. The range of arsenic concentrations in hair was 0.48 to 26.94 μg/g (mean = 3.52, SD = 3.58). The mean IQ of the study was 90.44 (range 54 to 123). Most of the IQs were classified as average (45.7%) or dull normal (31.6%). Approximately 14% and 3% of the children were in the borderline and mental defective groups, respectively. The percentage of children in the average IQ group decreased significantly from 57 percent to 40 percent with increasing arsenic exposure. The percentage in the lower IQ group increased with increasing As (23% to 38%) and in the low IQ group (zero to six percent). In a comparison of IQ between children with As hair levels ≤ two ppm or > two ppm, arsenic was found to explain 14 percent of the variance in IQ after controlling for father's occupation, mother's intelligence score, and family income. Arsenic levels in hair above 2 ppm were associated with a 0.75-point decrease in IQ below the grand mean and As levels above 5 ppm with a two point decrease. Although the cross-sectional study design does not allow for establishment of the time precedence of exposure to arsenic, the investigators stated that the subjects of the study were born in a period of chronic arsenic poisoning and that this cohort has been continuously exposed since birth due to their non-mobility. The study suffers from small numbers of children exposed to low arsenic (hair arsenic ≤ 1 ppm) so this group could not be compared to the high arsenic children. Also the possible exposure to chemical confounders like lead was not discussed.

In a parallel cross-sectional study (Siripitayakunkit *et al*., 2001) the 529 children (above) were subjected to the Motor-Free Visual Perception Test (MVPT) and the Visual-Motor Integration Test (VMI). The visual perception score of each child was compared with the score of children in a control sub-district of the same age. The cutoff point for poor perception was the mean minus one standard deviation (SD) in each age level. Among arsenic-exposed children, 21 percent had poor visual perception and 17.6 percent had poor VMI. The comparable values in the control population were 16.5 percent and 15.8 percent, respectively. Potential confounders were controlled by multiple classification analysis. Only five percent of the variance in visual perception of children was significantly explained by arsenic (P = 0.01). The grand mean perception score was 20.57 and the adjusted values at low, medium and high hair As were 20.92, 20.51, and 20.03, respectively. Alternatively, these authors did not find an effect of arsenic on visual-motor integration.

Like the study of IQ decrements noted above, this study has the advantage of associating an adverse effect in children with a metric of chronic arsenic exposure, hair arsenic concentration. Disadvantages include a limited level of reporting and possible confounding with exposure to other metals.

Tsai *et al*. (2003) performed a cross-sectional study of the effect of arsenic exposure on the development of cognitive function among adolescents. Forty-nine 13-year old students were divided into low and high exposure groups and were compared with 60 13-year old unexposed

children. Four neurobehavioral tests were conducted: continuous performance test (CPT); symbol digit (SD); pattern memory (PM); and switching attention (SA). Exposure in terms of As concentration in drinking water averaged 0 (<0.15), 131.2, and 185.0 ppb for control and exposure groups, respectively. Average cumulative arsenic exposures were 0, 252.1, and 768.2 mg (e.g., 184.99 ppb x 1008.6 cm^3/d x 11.28 yr x 365 d/yr x 10^{-3}). Neurobehavioral analysis revealed significant dose-response effects of arsenic exposure on CPT (P = 0.005), PM (P = 0.009) and SA (P = 0.0001), but not on SD (P = 0.23). A multiple linear regression analysis of the dose-response relationship between cumulative arsenic exposure and neurobehavioral endpoints showed a strong arsenic effects for CPT (low exposure group, P = 0.001), PM (high exposure group, P = 0.003) and SA (high and low exposures, P = 0.0001). This study is limited by low numbers but seems in line with other findings of As-induced CNS effects. The authors note that "the central nervous system of child and adolescents might be more vulnerable than adult to neurotoxicant". Although no dose-response relationship between As exposure and nerve conduction velocities was observed, the authors could not exclude the possibility of peripheral nerve dysfunction.

Wasserman *et al*. (2004) conducted a cross-sectional study of intellectual function in 201 As-exposed 10-year old children in Bangladesh. Children's intellectual function was assessed with tests drawn from the Wechsler Intelligence Scale for Children version III including Verbal, Performance, and Full-Scale raw scores. Children provided urine for arsenic and creatinine and blood samples for blood lead and hemoglobin measurements. After adjustment for sociodemographic covariates such as maternal education, height and head circumference, and waterborne levels of manganese (Mn), As in drinking water was associated with reduced intellectual function, in a dose-dependent manner. Children exposed to water arsenic of > 50 µg/L had significantly lower Performance and Full-Scale scores than did children with water As levels < 5.5 µg/L. Using the Full-Scale raw score, As water concentrations of 10 and 50 µg/L were associated with decrements of 3.8 and 6.4 points, respectively. The relationships between urinary arsenic concentration (µg As/g creatinine) and child intellectual function were not statistically significant but were in the expected (negative) direction (Full-Scale, P = 0.09; Performance, P = 0.14; Verbal, P = 0.11). Since there was no standard of intelligence for use in Bangladesh these decrements could not be directly equated with U.S. standard IQ points. However, "other simpler predictors of child intellectual function, such as maternal education and child height and head circumference, were significantly related to intellectual raw scores in the expected directions." In this study, as in others of this type exposure is inferred from water concentration.

Smith *et al*. (1998) studied lung and urinary bladder cancer mortality in a region of northern Chile (Region II, Antofagasta) where the residents were exposed to arsenic in their drinking water. Arsenic levels ranged from a population weighted average of 570 µg/L between 1955 and 1969 to 100 µg/L by 1980. Standardized mortality ratios (SMRs) were estimated for Region II as follows. Census data were used to calculate the person-years at risk during 1989-1993 by 10-year age groups, for men and women separately. National mortality data were obtained for 1991, the midpoint of the study period, and age- and sex-specific mortality rates were calculated for each cause of death of interest for the rest of Chile excluding Region II. The expected number of deaths was then calculated for Region II by multiplying the rest of the Chile 1991 age- and sex-specific mortality rates by the person-years at risk for residents in Region II for the period 1989-

1993. Standardized mortality ratios were estimated by dividing observed deaths by expected deaths. Statistical tests of significance were based on the Poisson distribution, and 95 percent confidence intervals were calculated using exact methods.

The SMRs (observed/expected deaths) for bladder, kidney, liver, and skin cancers, and all other cancers combined, were not related to age in either sex. However, lung cancer mortality ratios were particularly high in younger men aged 30-39 yr (SMR = 11.7, 95 percent C.I. 6.4-19.6, P < 0.001). The estimated SMRs were not as elevated in all groups. The values for the subsequent 10-year age groups were: 5.9; 4.9; 2.9; 4.0; 2.8; and 3.8 for the total with a 95%CI of 3.5-4.1. Also observed was a decreasing trend in chronic obstructive pulmonary disease deaths (COPD), with higher rates among younger men, particularly those aged 30-39. Four COPD deaths were reported among men (0.8 expected), and six deaths among women (0.1 expected). These ten individuals who died of COPD would have been young children at the time of peak arsenic water levels in 1955-1970. Smoking was accounted for but not in men and women separately.

In a later study Smith *et al*. (2006) reported increased mortality from lung cancer and bronchiectasis in young adults following arsenic exposures *in utero* and in early childhood. For subjects born just before the high exposure period (1950-1957) and exposed in early childhood the SMR for bronchiectasis was 12.4 (95% C.I., 3.3-31.7; P < 0.001). For those born during the high exposure period (1958-1970) with likely *in utero* and early childhood exposure the SMR for bronchiectasis was 46.2 (C.I., 21.1-87.7; P < 0.001). The authors conclude that "exposure to arsenic in drinking water during early childhood or *in utero* has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults form both malignant and nonmalignant lung disease."

Additional evidence supporting a link between childhood arsenic exposure and subsequent lung disease comes from autopsies of children in the affected area. The results of five autopsies of children, who died in 1968 and 1969 in Antofagasta and showed skin lesions and other evidence of arsenic poisoning, also showed lung abnormalities in four of the children. Two of these cases exhibited interstitial fibrosis (Rosenberg, 1974). Also, a survey of 144 children in Antofagasta with skin pigmentation due to arsenic exposure reported a history of bronchopulmonary disease 2.5-fold more frequent than children with normal skin (15.9 vs. 6.2 percent, respectively) (Borgono *et al*., 1977).

Chronic exposure to arsenic has been associated with decreased birth weight and an increased rate of spontaneous abortion in female smelter workers. However, this association is confounded by the presence of other toxicants in the smelting process, including lead (Nordstrom *et al*., 1979). Anemia and leukopenia have been reported in infants ingesting approximately 3.5 mg As/day in contaminated milk over a period of 33 days (Hammamoto, 1955).

Premature birth and subsequent neonatal death was reported in a single individual following ingestion of arsenic (Lugo *et al*., 1969).

Ihrig *et al*. (1998) conducted a hospital-based case-control study of stillbirths and environmental arsenic exposure using an atmospheric dispersion model linked to a geographical information system. They collected data on 119 cases and 267 controls in a central Texas area including a facility with 60-year history of arsenic-based agricultural product manufacture. Four exposure

groups were categorized (0; < 10 ng/m^3; 10-100 ng/m^3; and > 100 ng/m^3). For the period 1983-93 they fit a conditional logistic regression model including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. Effects were only seen in the Hispanic group with the medium exposure group having a prevalence odds ratio and 95% confidence interval of 1.9 (0.5-6.6) and the high exposure group 8.4 (1.4-50.1). The authors postulate a possible influence of a genetic polymorphism affecting folate metabolism in Hispanic populations possibly leading to increased neural tube defects and stillbirths. Small numbers limits this study; for example, there were only seven cases in the high exposure group and five of these were Hispanic.

Von Ehrenstein *et al*. (2006) studied pregnancy outcomes, infant mortality, and arsenic exposure via drinking water in West Bengal, India. The reproductive histories of 202 women were reviewed including measurements of 409 drinking water wells. The total number of pregnancies was 660 and the number of live births plus stillbirths was 558. Odds ratios for spontaneous abortion, stillbirth, neonatal mortality (death in the first month) and infant mortality (death in the first year) were estimated by logistic regression. Exposure to arsenic concentrations $\geq$ 200 μg/L during pregnancy was associated with a six-fold increased risk of stillbirth after adjustment for potential confounders (OR = 6.07; 95% C.I. 1.24-24.0, p = 0.01). The odds ratio for neonatal death was 2.81 (95% C.I. 0.73-10.8). No significant associations were found for arsenic exposure and spontaneous abortion (OR = 1.01; 95% C.I. 0.38-2.70) or overall infant mortality (OR = 1.33; 95% C.I. 0.43-4.04). Arsenic related skin lesions were observed in12 women who had increased risk of stillbirth (OR = 13.1; 95% C.I. 3.17-54.0).

6.3   Subchronic and Chronic Toxicity to Experimental Animals

Female albino rats (20 per group) were exposed to 0, 1.3, 4.9, or 60.7 μg As$_2$O$_3$/m^3 as aerosol continuously for 3 months (Rozenshtein, 1970). Decreased whole blood sulfhydryl group content, histological changes in the brain, bronchi, and liver, changes in conditioned reflexes, and changes in chronaxy ratio were observed in both the high- and mid-dose groups. Among animals in the high dose group, eosinophilia, decreased blood cholinesterase activity, decreased serum sulfhydryl content, and increased blood pyruvic acid were observed. No significant changes were observed in the low-dose group.

Male mice (8-10 per group) were exposed to 0, 0.5, 2.0, or 10.0 ppm sodium arsenite in drinking water for 3 weeks followed by a 28-day recovery period (Blakley *et al*., 1980). The primary immune response of the spleen (as indicated by changes in IgM-production assayed by plaque-formation) was suppressed at all dose levels. The secondary immune response was also suppressed at all dose levels as indicated by a decrease in the number of IgG producing cells.

Male Sprague-Dawley rats (7-28 per group) were exposed to 0, 40, 85, or 125 ppm sodium arsenate in drinking water for 6 weeks (Brown *et al*., 1976). Rats from all arsenic exposed groups showed increased relative kidney weights, decreased renal mitochondrial respiration, and ultrastructural changes to the kidney.

Male ddY mice (number not stated) received 0, 3, or 10 mg As$_2$O$_3$/kg/day orally for 14 days and were examined for changes in concentrations of monoamine-related substances in various brain regions and for changes in locomotor activity (Itoh *et al*., 1990). Locomotor activity was

increased in the low-dose group and decreased in the high-dose group. Several monoamine-related compounds were altered in both dose groups in the cerebral cortex, hippocampus, hypothalamus, and corpus striatum. The study indicates an effect of arsenite on brain chemistry but is inconclusive with respect to dose response.

Male and female Wistar rats (7-10 per group) were treated from age 2 to 60 days by oral gavage with daily administration of 0 or 5 mg As/kg body weight (as sodium arsenate) (Nagaraja and Desiraju, 1993; 1994). After 160 days, body weights, brain weights, and food consumption were decreased in the arsenic exposed group. Acetylcholinesterase (AChE) and GAD activity and GABA levels were decreased in the hypothalamus, brain stem, and cerebellum during the exposure period; all but AChE activity returned to normal during the post-exposure period. Changes in operant conditioning were also observed among the exposed animals.

Female Holtzman rats (>5 per group) were treated with 0, 100, 500, 1000, 2000, or 5000 ppm As_2O_3 in feed for 15 days (Wagstaff, 1978). Hexibarbitone sleeping time was altered in all arsenic exposed groups. Body weight and feed consumption were decreased among animals in the groups exposed to ≥ 500 ppm As_2O_3. Clinical signs of toxicity observed among arsenic exposed animals included roughened hair, diarrhea, and decreased physical activity.

Male Sprague-Dawley rats and C57 black mice (12 per group) were treated with 0, 20, 40, or 85 ppm sodium arsenate in drinking water for up to 6 weeks (Woods and Fowler, 1978). Among arsenic exposed rats, heme synthetase activity was decreased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, hepatic ALA synthetase activity was decreased and urinary uroporphyrin and coproporphyrin were increased. Among exposed mice, heme synthetase activity was decreased and uroporphyrinogen I synthetase activity was increased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, urinary uroporphyrin and coproporphyrin were increased.

Administration of 3.7 mg As_2O_3/kg/day to Rhesus monkeys for 12 months did not result in any neurologic change detectable by an EEG (Heywood and Sortwell, 1979). Two of the 7 animals exposed to this concentration died before the conclusion of the 52-week period. Of the surviving animals, two were retained for a 52-week recovery period after which they were sacrificed and necropsied. No significant changes in organ weights or gross appearance were noted.

7.   Toxicity of Arsine

7.1 Toxicity to Adult Humans

Numerous case reports of accidental arsine poisoning exist in the literature, but reliable estimates of concentrations during acute human intoxication do not exist. This is due in large part to the insidious nature of arsine toxicity - arsine is a colorless gas, has a mild odor at low concentrations, produces no mucous membrane irritation, and usually results in delayed symptoms of toxicity (Klimecki and Carter, 1995). In mammalian systems, arsine primarily targets the erythrocyte and causes hemolysis and methemoglobinemia with acute exposure (NRC, 1984). Jaundice, hemoglobinuria, anuria, hepatic and renal damage, anoxia, and anemia are secondary effects resulting from hemolysis. Before the advent of dialysis, there were no reports of patients surviving if renal failure developed (Buchanan, 1962). Other acute symptoms reported include

headache, weakness, dizziness, dyspnea, nausea, vomiting, diarrhea, and abdominal cramping (Klimecki and Carter, 1995). Central and peripheral nervous systems may be affected by acute arsine exposure, leading to agitation, disorientation, hallucinations, psychopathologic abnormalities, and peripheral nerve degeneration (Frank, 1976; Klimecki and Carter, 1995). The psychopathologic and peripheral abnormalities are thought to be secondary to the conversion of arsine to arsenate or arsenite. The first signs and symptoms of toxicity, hemoglobinuria and/or nausea, are usually delayed 2 to 24 hours following exposure (Kleinfeld, 1980).

A case report documents hemolytic anemia, hematuria, and renal failure following intermittent exposure to arsine gas over 2.5 hours (Parish *et al*., 1979). Symptoms of gastrointestinal distress, headache, and malaise were also reported following this exposure. The concentration of arsine gas sampled 3 days after exposure was 0.1 ppm (0.3 mg/m³), but the concentration at the time of poisoning was unknown. Another typical accidental poisoning resulted when 2 men were exposed to arsine gas in a metal smelting works (Coles *et al*., 1969). Symptoms included nausea, vomiting, red urine, generalized aching, shivering, epigastric pain, and jaundice. However, the more severely affected worker developed symptoms within 1 hour of exposure while the other did not develop symptoms for 24 hours. The more severely affected worker developed acute renal failure that required peritoneal dialysis.

In an occupational study, the highest average concentration of arsine recorded in a battery formation area of a battery manufacturing plant was 20.6 µg/m³ (0.006 ppm) (Landrigan *et al*., 1982). Elevated levels of urinary arsenic were observed in some workers but effects on the hematopoietic system were apparently not examined.

A study by Williams *et al*. (1981) collected personal and area air samples after 2 workers exhibited symptoms of arsine poisoning while restoring a large 19th century painting. Symptoms included headaches, nausea, weakness, vomiting, and red urine. The control-corrected air concentration of arsine ranged from 0.010 to 0.067 mg/m³. While these concentrations are below the OSHA PEL (permissible exposure level) 8-hour TWA (time weighted average) of 0.2 mg/m³, the results may indicate that these workers are sensitive responders or that humans in general may be more sensitive to the effects of arsine than experimental animals. However, the air samples may not represent the actual concentration of arsine that caused the symptoms of poisoning in the workers since the workplace air was not analyzed for arsine until after symptoms were reported. The study also notes that 'appreciable concentrations' of lead and arsenic were found in the workplace air.

No studies were identified addressing the chronic toxicity of arsine in humans.

7.2   Toxicity to Infants and Children

No studies were identified allowing quantitative assessment of arsine toxicity in infants and children. Arsine's mode of toxic action is not completely understood but appears to involve binding to erythrocyte sulfhydryl groups followed by intracellular ion loss and hemolysis (Rael *et al*., 2000). Clinical treatment of arsine poisoning usually involves exchange transfusion. It seems plausible that infants and children would be more sensitive to the irreversible hematotoxicity of arsine than adults due to their greater breathing rate per unit body weight.

7.3   Toxicity to Experimental Animals

A number of studies were reviewed to understand the time-concentration relationship of arsine lethality. The most complete and relevant study was the IRDC (1985), which allowed determination of 1% and 5% lethality benchmark doses for exposure durations of 0.5 to 4 hours in rats. The most important acute non-lethal effects noted were hemolysis and reticulocytosis (Peterson and Bhattacharyya, 1985). Longer term effects of arsine also involved significant changes in hematological parameters (hemoglobin and mean corpuscular volume) (Blair, 1990).

LC_{50} values (estimate of concentration resulting in 50 percent mortality of exposed animals) reported by Gates (1946) are as follows: 120-210 ppm (380-670 mg/m³) for 10 minutes in rats, 110 ppm (350 mg/m³) for 30 minutes in dogs (equivalent to 190 ppm (610 mg/m³) for 10 minutes), and 200-300 ppm (640-960 mg/m³) for 10 minutes in rabbits. An LC_{50} in mice was reported as 31 ppm (99 mg/m³) for a 50-minute exposure (Levvy, 1947). The survival time of the fatalities (4 days) was reported to be more or less independent of exposure concentration (2500 mg/m³ to 25 mg/m³) and exposure duration.

The study by Levvy (1947) in mice varied exposure durations for each given concentration of arsine. Because the mortality data were not presented in conventional form by the standard LC_{50} method, the data were normalized to a 1-hour exposure using the modified form of Haber's equation (as described in Section 5.7.1 of the TSD):

$$C^n \times T = K,$$

where C = concentration, T = time, K = a constant determined at a given C, T and the exponent n is a constant determined experimentally. The exponent "n" of 1.8 was determined by varying the term n in a log-normal probit analysis (Crump and Howe, 1983; Crump, 1984) until the lowest chi-square value was achieved. Fifty-four data points were used to estimate the exponent n because these points were of sufficient duration ($\geq$ 5 minutes) and resulted in the best chi-square fit for the line and obvious heterogeneity (Table 7.3.1). This relationship indicates that the toxicity of arsine varies approximately with the product of the square of concentration times time rather that simply concentration times time.

Table 7.3.1 Arsine Mortality in Mice: Results from Levvy (1947) and 1-Hour Adjusted Concentrations Using Haber's Equation (C^n x T = K, where n = 1.8).

Concentration (ppm)	Exposure Duration (min)	Mortality (no. died/total)	1-Hour Adjusted Concentration (ppm)
157*	10	30/30	58
	5	28/30	39
	2.5	17/30	27
	1.7	0/30	22
78.4*	15	21/30	36
	9	10/30	27
31.4	70	30/30	34
	50	15/30	28

* Shaded rows include data used for determination of the ED_{05} and BD_{05}

Craig and Frye (1988) reported a 4-hour LC_{50} of 42.6 ppm in rats. However, when the rats were separated by sex for statistical purposes, there was slightly greater mortality among females than males (38.9 ppm LC_{50} for females vs. 46.8 ppm LC_{50} for males). No abnormalities were seen at necropsy except red discharge from nose, mouth, and genitalia at the higher concentrations. A concentration-related suppression of body weight gain was observed during the first week of the 14-day post-observation period.

The most comprehensive arsine lethality study was undertaken by IRDC (1985). LC_{50}s of 240, 178, and 45 ppm were determined in rats (10 rats/sex/group) for 30 minute, 1 hour, and 4-hour exposures, respectively. Deaths generally occurred within 3 days following 30-minute exposure to arsine. As in the previous study (Craig and Frye, 1988), there was slightly greater mortality in females than males. Adverse effects noted during exposure included dyspnea, while effects noted post-exposure included a concentration-related increase in hematuria, dark material around the head or the anogenital area, and pallor of ears, eyes, and feet. The higher concentrations resulted in weight loss immediately following exposure, suppressed weight gain during the first week and compensatory weight gains during the second week post-exposure. Necropsy on animals that died showed red, yellow or orange fluid in the bladder, stomach, or intestine, and discoloration of the kidneys, lungs, and liver.

Data in the IRDC (1985) report were used to determine the exponent "n" in the equation C^n x T = K. This was done by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The value of "n" for extrapolation to 1-hour exposure was dependent on exposure duration. For extrapolation from 30 minutes to 1-hour exposure, n = 2.2; for extrapolation from 4-hours to 1-hour exposure, n = 1.0.

Table 7.3.2 contains the studies which provided adequate raw mortality data from which a maximum likelihood estimate corresponding to 5% lethality (ED_{05}) and benchmark dose at the 95% lower confidence interval of the ED_{05} and ED_{01} (BD_{05} and BD_{01}, respectively) could be determined.

Table 7.3.2 Animal Lethality Benchmark Dose Determinations in ppm for Arsine

Reference	Species	Exposure Time (min)	LC_{50} 60 min[1]	ED_{05} 60 min[1]	BD_{05} 60 min[1]	BD_{01} 60 min[1]
IRDC, 1985	rat	30	175	120	105	86
	rat	60	178	112	88	66
	rat	240	181	118	101	80
Craig and Frye, 1988	rat	240	170	125	102	84
Levvy, 1947	mice	varied[2]	29	20	16	13

[1]   Exposure time was extrapolated to 60 minutes, if needed, using a modification of Haber's equation ($C^n * T =$ K). For rats, n = 2.2 for extrapolation from 30 minutes to 1-hour, or n = 1.0 for extrapolation from 4 hours to 1-hour; for mice, n = 1.8.

[2]   Lethality data for 5 exposure durations were pooled and normalized to a 1-hour exposure using the equation C^n x T = K (see Table 1).

In other experimental animal studies, a reduction in hematocrit as a function of arsine concentration was observed in mice following a 1-hour exposure (Peterson and Bhattacharyya, 1985). A LOAEL of 9 ppm (29 mg/m³) and a NOAEL of 5 ppm (16 mg/m³) were reported. The demarcation between the NOAEL and LOAEL for this non-lethal effect was well defined, not only among the exposure groups (5 ppm vs. 9 ppm), but also among individual mice in each exposure group (Peterson, 1990). Hematologic recovery of the surviving mice was gradual but nearly complete within 11 days after exposure (Peterson and Bhattacharyya, 1985). The study also reported a NOAEL of 15 ppm (100% survival) and LOAEL of 26 ppm (100% lethality) for lethality.

A continuous benchmark dose analysis of these data was performed. The full data set on hematocrit reduction 24 hours after exposure gave a BMD_{05} of 7.81 ppm and a $BMDL_{05}$ of 5.2 ppm (quadratic continuous model fit P= 0.16). The only other data sets that were adequately fit were the 24 hour increase in reticulocyte count (%) with the 11 and 26 ppm outliers removed (power continuous model, P = 0.50) and the 5 days values with the 9 ppm outlier removed (cubic continuous model, AIC = 61.8). Several response levels were evaluated including 25% relative, 1 and 2 % absolute increases and 1 and 2 standard deviations. The latter SD levels were closest to the minimal significant increase levels and exceeded the control plus one control SD values of 0.88 ppm (24 hr) and 2.0 (5 days). For a 1 SD response level at 24 hours the $BMD_{1SD} = 3.29$ ppm and the $BMDL_{1SD} = 2.17$ ppm. The values for 2SD were $BMD_{2SD} = 4.69$ ppm and $BMDL_{2SD} = 3.50$ ppm. For the 5 days data set the $BMD_{2SD} = 4.32$ ppm and the $BMDL_{2SD} = 2.70$ ppm. Reticulocytosis may be a more sensitive indicator of adverse hematologic effects of arsine exposure than hematocrit reduction.

A subchronic study in male and female rats and female mice (Fowler *et al*., 1989) supports the sharp increase in dose-response noted by Peterson and Bhattacharyya (1985). All treatment groups exposed to arsine (6 hr/day, 5 days/week) at concentrations of 10 ppm and above showed 100 percent mortality within 4 days while those exposed to 5 ppm or less showed no mortality or overt signs of toxicity. Other effects observed included a dose-related increase in spleen weight and a slight increase in liver weight. Blood samples taken at necropsy showed a slight dose-

related decrease in hematocrit and a marked dose-related increase in the activity of red blood cell ALAD (δ-aminolevulinic acid dehydratase).

In a 90-day study, male and female mice were exposed to 0, 0.025, 0.5, and 2.5 ppm arsine gas for 6 hours/day, 5 days/week (Blair *et al*., 1990). After 5, 15, and 90 days, blood was collected for hematologic analysis. Exposure to 2.5 ppm had significant effects on all hematological parameters for nearly the entire exposure period, while 0.5 ppm caused only a few significant changes in hematological parameters at day 90 of exposure (decreased hemoglobin in males and increased MCV in females). Exposure to 0.025 ppm was without effect.

A continuous benchmark dose analysis was performed on the data sets of Blair *et al*. 1990. Adequate fits to the hematocrit data were obtained with the linear and quadratic models with $BMDL_{025}$ (relative risk) values ranging from 0.128 to 0.894 ppm (P values for model fits of 0.11 to 0.96). Absolute reticulocyte count increases gave continuous $BMDL_{10}$'s ranging from 0.22 to 0.68 ppm with linear and quadratic models (P values of 0.31 to 0.99). However, due to the poor dose spacing, essentially a missing dose level between 0.025 and 0.5 ppm, these results are considered inconclusive in determining an alternative NOAEL to 0.025 ppm.

7.4   Developmental and Reproductive Toxicity

In an unpublished study, workers in one semiconductor plant were reported to have a 39% rate of miscarriage, almost twice the national average (Sanger, 1987). Workers were exposed to unidentified levels of arsine gas, but other possible exposures were not identified.

A developmental toxicity study exposed pregnant rats and mice to 0.025, 0.5, or 2.5 ppm (0.079, 1.5, or 7.9 mg/m³) arsine for 6 hours per day on gestation days 6 through 15 (Morrissey *et al*., 1990). The rats exposed to 2.5 ppm exhibited a significant increase in fetal body weight, but no other endpoints of developmental toxicity were observed. The incidence of malformations observed in arsine exposed mice at 0.025 ppm (exencephaly) and at 2.5 ppm (unfused eyelids) was not significantly different from control mice.

8.   Derivation of Reference Exposure Levels

8.1   Acute Reference Exposure Level for Inorganic Arsenic

Study	Nagymajtenyi *et al*., 1985
Study population	pregnant mice
Exposure method	maternal inhalation exposure
Exposure continuity	
Exposure duration	4 hours per day on gestation days 9, 10, 11, and 12
Critical effects	decreased fetal weight
LOAEL	0.26 mg/m³ As_2O_3 (0.197 mg As/m³)
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	n/a
Human Equivalent Concentration	n/a
LOAEL uncertainty factor (UF_L)	10 (no NOAEL)
Subchronic uncertainty factor (UF_s)	n/a
Interspecies Uncertainty Factor	
Toxicokinetic (UF_{A-k})	$\sqrt{10}$ (animal study)
Toxicodynamic (UF_{A-d})	$\sqrt{10}$ (animal study)
Intraspecies Uncertainty Factor	
Toxicokinetic (UF_{H-k})	$\sqrt{10}$ (remaining interindividual variation: study considered effects on fetus or infant)
Toxicodynamic (UF_{H-d})	$\sqrt{10}$ (interindividual variation)
Cumulative uncertainty factor	1,000
Reference Exposure Level	**0.0002 mg As/m³ (0.20 µg As/m³,)**

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 in the Technical Support Document). The most appropriate study for the basis of an acute REL for arsenic is Nagymajtenyi *et al*. (1985). This study was selected since it measured a sensitive toxicological endpoint with a relevant route of exposure, and the experimental design and reporting were considered adequate (as specified in the Non-cancer Risk Assessment technical support document, Section 4.1.1). It involved a significant number of animals exposed by inhalation to three dose levels plus a control. Unfortunately, no NOAEL was obtained. However, a significant dose-related reduction in fetal weight and increased incidences of intrauterine growth retardation, skeletal malformations, and hepatocellular chromosomal aberrations were observed in mice following maternal inhalation exposure to 200 µg As/m³ (260 µg As_2O_3/m³) for 4 hours on gestation days 9, 10, 11, and 12 (p<0.05). The most sensitive effect, decreased fetal weight, was observed at 200 µg As/m³, so 200 µg As/m³ was taken as a LOAEL. Maternal toxicity data were not reported. This study is used as the basis of the acute REL:

0.2 mg/m³/1000 = 0.0002 mg/m³ = 0.2 µg As/m³ (equivalent to 0.065 ppb arsine gas)

No temporal adjustment was made for the critical study since the critical period of exposure for a developmental effect may be very short relative to the study duration (OEHHA, 2007). The study concentration with appropriate uncertainty factors is a "not to exceed" value. An uncertainty factor of 10 (UF_L) was used to account for the lack of a no observed adverse effect level (NOAEL). A second uncertainty factor of 10 was used to account for interspecies differences between the test species and humans. This factor is the product of two components addressing pharmacokinetic (UF_{A-k}) and pharmacodynamic (UF_{A-d}) differences, each assumed to be the $\sqrt{10}$. A final uncertainty factor of 10 was applied to address human interindividual differences in pharmacokinetics (UF_{H-k}) and pharmacodynamics (UF_{H-d}) also assumed to be $\sqrt{10}$ each. The overall uncertainty of extrapolating from 4-hour exposures in mice (LOAEL) to no anticipated effects in humans is 1000 as noted in table above and the calculation of the acute REL. The rationale for the choice and value of uncertainty factors used by OEHHA is provided in the Non-cancer Risk Assessment technical support document (Section 4.4.3).

Inorganic arsenic (oxides) are listed as developmental toxicants under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The studies reviewed in this document support the conclusion that exposure to inorganic arsenic may affect fetal weight, spontaneous abortion, neonatal death and postnatal neurological development.

In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. In the absence of certainty, OEHHA takes the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant, particularly when viewed from a population perspective.

8.2   Inorganic Arsenic 8-Hour Reference Exposure Level

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures which might include daily occupational, in-home or in-school exposures. (see Section 6 in the Technical Support Document).

Due to the possibility of repeated exposure and the relatively slow clearance of arsenic compounds, the 8-hour REL is taken to be equivalent to the chronic REL. The half-life of the initial exponential phase of excretion of arsenic after a single dose is typically between one and two days, but there are also several much slower excretion processes. So a single exposure to arsenic would take several days to be cleared, mainly via urinary metabolites. Repeated exposures can significantly prolong the clearance of arsenic as the internal dose accumulates, so that in terms of internal dosimetry it would be difficult to distinguish repeated periodic exposure from chronic exposure scenarios. An individual exposed daily via air and/or drinking water might show very similar urinary arsenic excretion to another individual exposed only periodically at work, school etc.

8.3   Inorganic Arsenic Chronic Reference Exposure Level

Study	Wasserman *et al.* (2004); Tsai *et al.* (2003)
Study population	201 children 10 years of age
Exposure method	drinking water
Exposure continuity	continuous
Exposure duration	9.5 to 10.5 years
Critical effects	Decrease in intellectual function, adverse effects on neurobehavioral development
LOAEL	0.23 μg As/m^3 based on est. LOAEL of 2.27 μg/L (Wasserman *et al.*, 2004; see Section 8.3.1.1)
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	none, exposure considered continuous
Human equivalent concentration	n/a
LOAEL uncertainty factor (UF$_L$)	3 (LOAEL estimated by quantitative analysis of study data)
Subchronic uncertainty factor (UFs)	1 (default: duration >8% of lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF$_{A-k}$)	1 (default: human study)
Toxicodynamic (UF$_{A-d}$)	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF$_{H-k}$)	√10 (remaining interindividual variation: study considered effects on 10 year-old but not infant)
Toxicodynamic (UF$_{H-d}$)	√10 (default, interindividual variation)
Cumulative uncertainty factor	30
Inhalation Reference Exposure Level	**0.015 μg As/m^3**
Oral Reference Exposure Level	0.0035 μg/kg-d

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document).

8.3.1.1 Child Based Values

A number of studies have indicated potentially greater toxicity of arsenic exposure during childhood (see below). Although some PBPK modeling has been applied to inorganic arsenic and its methyl metabolites, the modes of toxic action and relevant internal dosimetry are not sufficiently understood at present to use this modeling directly in REL development. In this section we compare quantitative analyses of dose-responses and LOAELs in key studies involving arsenic exposures in children. Health protective exposure levels derived from these analyses will be compared with similar analyses from studies in adults in the following section.

The study of Wasserman *et al.* (2004) indicated a dose-response of decreasing Full-Scale intellectual function raw scores with increasing drinking water arsenic exposure in 10-year olds. The values in their Fig.2 give an exact fit to a quadratic model ($Y = Y_0 + aX + bX^2$; Y_0 intercept = 0, a = -0.443, b = 0.0063, R^2 = 1.0) with a low dose slope of –0.44 points/μg/L. Assuming an adverse effect level of one point loss, then the corresponding arsenic concentration can be calculated as:

-1point/-0.44 point/µg/L = 2.27 µg/L.

This level might be equivalent to a LOAEL. Further, assuming water intake of 1 Liter/day (L/d) and essentially complete intestinal absorption, this can be converted to an intake of 2.3 µg/d. If we assume a drinking water intake based on the 95% upper confidence level (UCL) for U.S. children aged 1 to 10 years of 1564 mL/day the intake would be somewhat higher at 3.6 µg/d (OEHHA, 2000; Table 8.3). Since 10-year old males would inhale about 9.9 m^3/d (OEHHA, 2000), if airborne arsenic were 100% absorbed, this oral effect level would be equivalent to an inhalation level of 2.3 µg/day/9.9 m^3/day = 0.23 µg/m^3. Assuming a more realistic inhalation absorption of 50 % would give a value of 0.46 µg/m^3. Applying a 3-fold UF for an estimated LOAEL based on a quantitative dose response analysis (a higher value would be used without a dose response analysis) and 10-fold for inter-individual variation since only 10-year olds were studied, a health protective air concentration of 0.015 µg/m^3 can be calculated. An oral value based on the average study body weight of 21.9 kg and 100% oral absorption would be 2.3 µg/d/21.9 kg = 0.105 µg/kg-day. Applying the same overall uncertainty factor of 30 the oral health protective value would be 0.105 µg/kg-day/30 = 0.0035 µg/kg-day.

The data of Tsai *et al*. (2003) for 13 year old children gave dose response relationships for arsenic exposure metrics of ppb As in drinking water and cumulative arsenic intake (mg) vs. the pattern memory (PM) and switching attention (SA) endpoints (ms). A continuous benchmark response analysis for ppb As vs. ms test duration was conducted for PM (BMD_{05} = 49.75; $BMDL_{05}$ = 31.2 ppb) and SA (BMD_{05} = 28.81; $BMDL_{05}$ = 19.73 ppb) both using a linear model. For cumulative As intake the PM endpoint data were similarly fit by a linear model (BMD_{05} = 194.1; $BMDL_{05}$ = 122.7 mg) and the SA data by a polynomial (quadratic) model (BMD_{05} = 39.1; $BMDL_{05}$ = 25.4 mg; see Fig. 1). The SA endpoint appears to be the most sensitive. Based on the SA $BMDL_{05}$ of 19.7 ppb and 1 L/d drinking water intake a minimum effect level of 19.7 µg/d is estimated. If we assume a drinking water intake, based on the 95% UCL for U.S. children aged 11 to 19 years of 2.143 L/d the intake would be 2-fold higher at 42.2 µg/day (OEHHA, 2000; Table 8.3). Using uncertainty factors of 10 for interindividual variation and 3 for extrapolation from a minimum to a no effect level, a health protective intake of 19.7 µg/d/30 = 0.658 µg/d is calculated. Assuming inhalation of 10 m^3/d and 50 % absorption (default) this value can be converted to an inhalation value of 0.658 µg/day/(0.50 x 10 m^3/day) = 1.32 µg/m^3. Using the SA cumulative $BMDL_{05}$ of 25.4 mg As and 10 years exposure, an effect level of 25.4 mg/(10 yr x 365days/yr) = 6.96 µg/day is calculated. Using the same assumptions and UFs as above, an inhalation value of 0.044 µg/m^3 can be derived based on As concentration. The cumulative dose metric is a more accurate estimate of arsenic exposure than As water concentration, so the value of 0.046 µg/m^3 or 0.05 µg/m^3 (rounded) is preferred over the concentration based value. An oral value based on an average body weight for a 13-14 year old child (OEHHA, 2000) of 50 kg is 6.96 µg/day/50 kg = 0.139 µg/kg-d. Applying the same overall uncertainty factor of 30 would give 0.139 µg/kg-day/30 = 0.0046 µg/kg-day.

The quantal responses for skin lesions in young children ($\leq$ 9 yr) and adolescents (10-19 yr) from Mazumder *et al*. (1998) were subjected to benchmark dose analysis. For young children, the quantal linear model adequately fit the data (X^2 = 6.1, P = 0.30) with a BMD_{01} = 54.4 µg/L and a $BMDL_{01}$ = 39.3 µg/L. For adolescents, the best fitting model was the log probit (X^2 = 0.77, P = 0.68) with a BMD_{01} = 77.3 µg/L and a $BMDL_{01}$ = 47.4 µg/L. These values are similar to the

analysis of all age groups combined (above) and application of a 10-fold UF for intraspecies variation seems adequate for these data. Thus the health protective intake for children for skin effects would be in the range of 3.9 to 4.7 µg/d for one liter/day water intake. For conversion to inhalation equivalent, young children are assumed to inhale 9.9 m^3/day and drink 1 liter/day and adolescents to inhale 14 m^3/day and drink 1.5 liter/day (OEHHA, 2000). It is further assumed that 50 percent of inhaled arsenic is absorbed via the pulmonary and gastro-intestinal routes. The resulting health protective values would be 0.68 to 0.79 µg/m^3.

A study in Thailand (Siripitayakunkit *et al*., 1999) related drinking water arsenic exposure, indicated by hair arsenic, to IQ in 529 six to nine year old children. A continuous benchmark dose response analysis of this data set gave a BMD_{05} = 0.035 µg As/g hair and $BMDL_{05}$ = 0.0155 µg As/g (polynomial model). A slope of –3.2 IQ points/µg/g was derived from the $BMDL_{05}$. Using the conversion factor of 0.01µg As/g hair/µg As/Liter of water (Kurttio *et al*. 1998), a decrease of 1 IQ point would be equivalent to chronic consumption of 30 µg As/L water (OEHHA, 2004). At one liter/day water consumption the 30 µg/d value is over an order of magnitude higher than the analogous estimate indicated by the Wasserman *et al*. (2004) study above. An inhalation value was derived as above: 30 µg/day/(10 m^3/day x 0.50 x 30UF) = 0.20 µg/m^3.

The visual perception data from Siripitayakunkit *et al*. (2001) was subjected to continuous benchmark dose analysis. The $BMDL_{035}$ of 2.40 µg/g hair (polynomial model) was near the low level mean minus one SD score (20.5), presumably an adverse effect level on visual perception as defined by the authors. The linear model gave a higher value (3.69 µg/g) but did not fit the data as well in the low exposure range. Using the conversion factor above, one liter per day water consumption, and a 30-fold cumulative UF results in a presumptive health protective intake of 8 µg/d for this endpoint (2.40 µg/g ÷ 0.01 µg/g/µg/Liter x 1 Liter/day ÷ 30UF = 8.00 µg/d). An inhalation value was derived as above: 8.0 µg/day/(10 m^3/day x 0.50) = 1.6 µg/m^3.

Chronic arsenic exposure appears to have adverse effects on intellectual development and visual perception in children. While the quantitation of these effects and the toxicological significance of the criteria selected are somewhat uncertain, OEHHA thinks they are sufficient to support a chronic reference exposure level (cREL). It is uncertain whether neurological effects are the most sensitive caused by chronic arsenic exposure in children. Additional studies in exposed children are needed to adequately quantify adverse effects. The values above are summarized in Table 8.3.1. The child-based values range from 0.015 to1.6 µg/m^3. The geometric mean of the three cognitive endpoint values (0.015, 0.20, 0.05) is 0.053 µg/m^3.

Table 8.3.1. Inhalation Values Derived from Human Child Studies

Study	Toxic Endpoint	Criterion	Value	Derived cREL, $\mu g/m^3$
Wasserman *et al*. (2004)	Intellectual function	One point loss	2.27 µg/d	0.015
Siripitayakunkit *et al*. (1999)	IQ	One point loss	-3.2 IQ/µg/g hair As	0.20
Siripitayakunkit *et al*. (2001)	Visual perception loss	LOAEL	240 µg/d	1.6
Mazumder *et al*. (1998)	Skin Lesions	LED_{01}	39-47 µg/d	0.68-0.79
Tsai *et al*. (2003)	Neurobehavioral effects	LED_{05}	7 µg/d	0.05
Smith *et al*. (2006)	Bronchiectasis mortality	LED_{01}	213 µg/d	1.4

Figure 8.3.1 Switching attention (ms) in 13-year old children versus cumulative arsenic intake in mg (Tsai et al., 2003).

Polynomial Model with 0.95 Confidence Level

10:14 12/20 2005
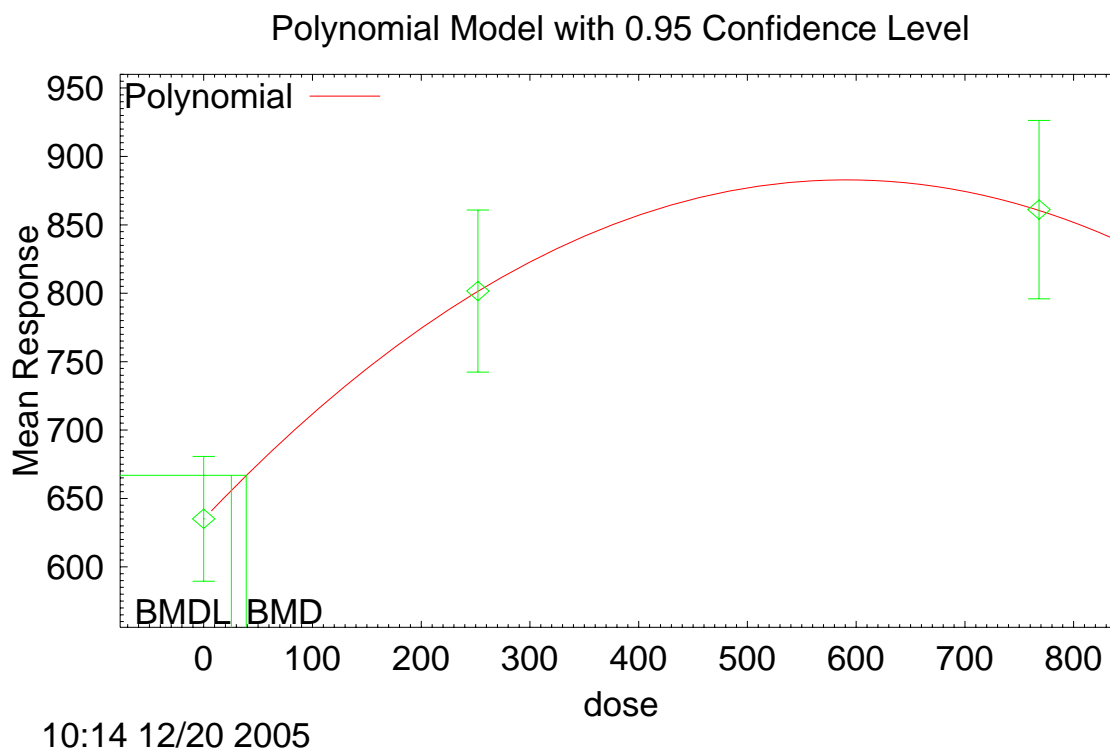
Inorganic arsenic is apparently more potent in its neurotoxic effects in humans than in experimental animals. The values of 2.27 µg/day in Wasserman *et al* (2004) and 7 µg/day in Tsai *et al* (2003) for cognitive effects in 10-13 year-old children are much lower than brain

effects seen in animals e.g., 5 mg/kg-day in rats (Nagaraja and Desiraju, 1993; 1994) and 3.7 mg/kg-day in Rhesus monkeys (Heywood and Sortwell, 1979).

The bronchiectasis data from Smith et al. (2006) were subjected to benchmark dose analysis. A control value based on a background incidence rate of 0.04% (1/2500) and exposure of 40 µg As/L x 10 yr were used together with observed incidence values of 4/651 (90 µg As/L x 10 yr) and 9/488 (870 µg As/L x 13 yr). No statistically significant model fits were obtained. The best fitting model was the log probit ($X^2 = 4.95$, P = 0.026) which gave an LED_{01} ($BMDL_{01}$, 1% response) of 2.77 (mg/L) x yr. This value can be converted to an inhalation value of 1.42 µg/m^3 (2.77mg yr/L x 1000 µg/mg/(13 yr x 10 m^3/d x 30UF x 0.5) = 1.42 µg/m^3). This value has been added to Table 8.3.1 for comparison only due to the poor model fit.

8.3.1.2 Adult Based Values

In this section we review toxicological criteria from studies in adults that may serve as the basis for a chronic REL for inorganic arsenic or otherwise provide supporting information.

Studies in experimental animals show that inhalation exposure to arsenic compounds can produce immunological suppression, developmental defects, and histological or biochemical effects on the nervous system and lung, thus providing supportive evidence of the types of toxicity observed in humans. Among the inhalation studies, the lowest adverse effect level (LOAEL) was quite consistent:

> 245 µg As/m^3 for decreased bactericidal activity in mice (Aranyi et al., 1985);
> 200 µg As/m^3 for decreased fetal weight in mice (Nagymajtenyi et al., 1985); and
> 270 µg As/m^3 for decreased sperm motility in rats (Kamil'dzhanov, 1982).

Reports of human inhalation exposure to arsenic compounds, primarily epidemiological studies of smelter workers, indicate that adverse health effects occur as a result of chronic exposure. Among the targets of arsenic toxicity are the respiratory system (Lundgren, 1954), the circulatory system (Lagerkvist et al., 1986), the skin (Perry et al., 1948), the nervous system (Blom et al., 1985), and the reproductive system (Nordstrom et al., 1979). Occupational exposure levels associated with these effects ranged from 50 to 7000 µg As/m^3. These epidemiological studies suffer, however, from confounding as a result of potential exposure to other compounds, which limits their usefulness in the development of the chronic REL.

A single study showed effects occurring at 4.9 µg As_2O_3/m^3 (Rozenshtein, 1970). However, lack of detail with respect to endpoints and experimental design limits this study's usefulness for developing a Reference Exposure Level.

The cerebrovascular disease (CVD) and cerebrovascular infarct (CI) data of Chiou et al. (1997b) were subjected to benchmark dose analysis (BMD). The data were best fit using the quantal linear regression (QL) dose-response equation. Since the responses were of the order of 0.1 to 2 percent, the values calculated were for the 1 percent response (ED_{01}) and its 95% lower confidence limit (LED_{01}), rather than the usual 5 percent response values for the analysis of animal study data.

The values for CI were marginally better fit by the dose-response equation than those for CVD. Also the QL models gave better fits to the unadjusted data sets for both endpoints. The unadjusted ED_{01} and LED_{01} values with goodness of fit P value meeting the acceptable fit criterion of $P \geq 0.1$ were 359 and 189 µg/L for CVD and 268 and 166 µg/L for CI, respectively. Using the cumulative dose metric these values were 5.1, 3.0, 5.9, and 3.5 (mg/L)-yr, respectively. Due to the severity of these and other endpoints analyzed below, the uncertainty in the dose assignments (range mid-points instead of averages), and the fact that the chosen points of departure or LEDs were generally two-fold or more above concurrent control levels, the LED_{01} should be considered equivalent to a LOAEL for the purposes of risk assessment. Due to the severity of the CI endpoint, a 100 UF was used to derive a health protective water concentration of 0.1 to 0.3 µg/L based on the two dose metrics. For CVD with a 30 UF the corresponding values were 0.28 to 1.3 µg/L (for details of analysis see OEHHA, 2004). Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding inhalation values for these vascular effects would be for CI 0.10 to 0.33 µg/m^3 and for CVD 0.28 to 1.26 µg/m^3.

BMD analysis of the ISHD data from Chen *et al*. (1996) showed that these data were well fit by the QL dose-response equation (ED_{01} = 8.27 (mg/L)-yr, X^2 = 0.26, P = 0.88). The LED_{01} of 5.53 (mg/L)-yr should be considered an effect level for this endpoint. In this analysis the cumulative arsenic dose metric of (mg/L)-yr and resultant benchmark doses were divided by 70 yr to yield comparable lifetime drinking water concentrations of arsenic. Using a cumulative uncertainty factor of 100, a health protective concentration of 0.16 µg/L can be derived (OEHHA, 2004). Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption the corresponding health protective inhalation value for ISHD would be 0.16 µg/m^3.

The Chen *et al*. (1995) data on the association of hypertension (HT) and cumulative arsenic intake via drinking water were subjected to BMD analysis. The QL dose-response equation fit the unadjusted data well but was somewhat less than adequate for the adjusted prevalence values. The acceptable criterion for the X^2 goodness of fit test for the benchmark dose is $P \geq 0.10$. In the case of arsenic induced hypertension, the 10 percent effect level was chosen due to the higher background and greater dose response range compared to other human studies evaluated where 1% or 5% response levels were used. For HT the LED_{10} is considered an appropriate LOAEL for risk assessment. In the case of the adjusted data set, removal of the highest cumulative dose allows an acceptable fit of the QL equation with an LED_{10} of 7.4 (mg/L)-yr. The data of Rahman *et al*. (1999) were also analyzed. Both crude and adjusted data sets were well fit by the QL model with P values much greater than 0.1. The unadjusted LED_{10} value of 6.3 (mg/L)-yr from Bangladesh is quite similar to comparable value of 7.2 (mg/L)-yr from the Taiwan study (OEHHA, 2004). Health protective drinking water concentrations with a cumulative uncertainty factor of 30 ranged from 0.55 to 0.68 µg/Liter. Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption the corresponding health protective inhalation value for HT would be 0.55 to 0.70 µg/m^3.

The data of Chen *et al*. (2006) indicate a supralinear dose-response. The data were analyzed for benchmark response using metrics of time weighted average (TWA) and cumulative arsenic exposure of TWA times years of exposure or (mg/L)-yr. Systolic hypertension quantal responses of the first four quintiles of the overall population (N = 8726) were fit by the log-logistic model

of BMDS (v 1.4.1). The $BMDL_1$ values (1% response) of 71.5 µg/L and 0.66 (mg/L)-yr were obtained (X^2 = 3.8, P = 0.15, d.f. = 2). The pulse hypertension data were similarly fit using the longer-term exposure subpopulation (N = 6319). In this case the 10% response level was used for $BMDL_{10}$'s of 0.49 µg/L and 0.004 (mg/L)-yr (X^2 = 4.45, P = 0.11, d.f = 2). TWA BMDLs for systolic and pulse hypertension in arsenic exposed subpopulations with lower intakes of B vitamins were also evaluated. The $BMDL_{10}$ values for populations with low dietary folate ranged from 62 to 405 µg/L TWA. The results indicate a higher sensitivity of the pulse hypertension effect to low level arsenic than the systolic hypertension effect. The supralinearity of dose-response makes comparison with earlier studies problematic. For example, projected 10^{-4} extra risk levels for pulse and systolic hypertension from this study are at least an order of magnitude less than values seen earlier with Chen *et al*. (1995) or Rahman *et al*. (1999) although cumulative arsenic exposures were 5-10 times higher in the latter studies (Table 6). A cREL estimated from the 0.49 µg/L value above would be 0.0033 µg/m^3 (0.49 µg/L x 2L/d/(20m^3/d x 0.5 absorption x 30UF).

Similarly, the diabetes mellitus (DM) data of Lai *et al*. (1994) and Rahman *et al*.(1998) were analyzed. In this case, the QL dose-response model adequately fit both unadjusted and multivariate-adjusted prevalences. EDs and LEDs were determined for the 1 and 5 percent response levels. The LED_{05} for the adjusted values appear the best choice for a chronic criterion for arsenic-induced diabetes mellitus, i.e., 8.8 (mg/L)-yr from Lai *et al*. and 0.21 mg/L from Rahman *et al*. The health protective drinking water derived from these values with a cumulative UF of 30 were 0.84 and 1.4 µg/L, respectively (OEHHA, 2004). Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation values for diabetes mellitus would be 0.85 to 1.4 µg/m^3.

In addition to the values noted above, an estimated LOAEL of 20 (mg/L)-yr for peripheral vascular disease from Tseng *et al*. (1996) was also included in this analysis. Using a cumulative UF of 30, a drinking water value of 1.9 µg/L was derived (OEHHA, 2004). Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation value for peripheral vascular disease would be 1.9 µg/m^3. The study of Wang *et al*. (2002) on arsenic induced carotid atherosclerosis (subclinical) also gave an estimated LOAEL of 20 (mg/L)-yr and would yield the same health protective values.

The arsenic-induced skin keratosis and hyperpigmentation data of Mazumder *et al*. (1998) were analyzed as above (OEHHA, 2004). For both male and female skin keratosis data sets, adequate fits were obtained by the QL model with lower bound values (LED_{01}) of 49.6 µg/L for males and 124 µg/L for females. Adequate fits could not be obtained for both hyperpigmentation data sets with the models available in the benchmark dose program; however, the dose-response graphs appeared to be linear in the lower exposure groups with respective LED_{01}s of 18.9 and 34.7 µg/L. It appears that a single dose level outlier (125 µg/L) was largely responsible for the failure of the statistical test. Mazumder also included an assessment of skin keratosis and hyperpigmentation prevalence by dose per body weight. Using the dose metric of µg/kg-day, the skin hyperpigmentation data were still unable to be fit by the BMDS models. Therefore only the skin keratosis endpoint appears suitable for the development of a health protective value for

arsenic-induced noncancer effects. Using a cumulative UF of 30, a drinking water value of 1.7 µg/L was derived. Assuming 20 m^3/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation value for skin keratosis would be 0.34 µg/m^3.

The skin lesion data of Rahman *et al*. (2006) was analyzed for benchmark response. The unadjusted data reported in Rahman's Table 3 was used with the mid points of the exposure concentration ranges (e.g., 5, 30, 100, 224, 450 µg/L) and the mean As exposures in Rahman's Table 4 (e.g., 9.8, 59.3, 127, 199, 344 µg/L). For the unadjusted male data, no adequate fit could be obtained. The female data was adequately fit by the quantal linear (P = 0.43) and log-logistic (P = 0.51) models. The latter giving a BMDL$_{10}$ of 6.28 µg/L with mid-point based exposure estimates, and the former giving a BMDL$_{10}$ of 108.2 µg/L with mean As concentrations. Similarly, for the cumulative As dose metric of (mg/L)-yr no adequate fit was obtained with the male data, while the female data were best fit by the log-probit model (P = 0.86) for a BMDL$_{10}$ of 2.80 (mg/L)-yr. Using the age and asset adjusted data with the average As concentrations, an adequate fit to the male data could be obtained with the multistage model if the top dose group was removed, BMDL$_{10}$ = 96.0 µg/L (X^2 = 0.60, P = 0.74). The female adjusted data set gave a lower BMDL of 65.4 µg/L despite the authors' finding that the males were more sensitive. This may simply reflect the difficulty of fitting the male data. In almost all cases, the BMDL values are lower (indicating higher risk) than seen in the earlier study by Mazumder *et al*. (1998) analyzed above.

The Von Ehrenstein et al. (2005) study of decrements in lung function related to arsenic exposure via drinking water reported slopes of -45.0 mL forced expiratory volume in 1 second (FEV$_1$) and -41.1 mL forced vital capacity (FVC) per 100 µg/L increase in arsenic concentration for exposed men. Assuming low dose linearity these values can be converted to inhalation values of 0.044 µg/m^3 (FEV$_1$) and 0.048 µg/m^3 (FVC) corresponding to respective 1 mL losses in lung function (e.g., 45/100 = 2.22 µg/L/mL decrement; 2.22 µg/L/mL x 2L water/d /(20m^3/d x 10UF x 0.5) = 0.044 µg/m^3/mL).

The inhalation values derived from oral human exposure studies above are summarized in Table 8.3.2. With the exception of the very low value derived from the pulse hypertension endpoint, the derived health protective inhalation values range over approximately forty fold from 0.044 to 1.7 µg/m^3. These adult values exceed the child-based values (range 0.015 to 1.6 µg/m^3). Therefore the proposed chronic REL value of 0.015 µg/m^3 is derived from the child arsenic exposure studies evaluated above and the adult studies provide supporting information.

Table 8.3.2 Inhalation Values Derived from Adult Human Drinking Water Studies

Study	Toxic Endpoint	Criterion	Value	Derived chronic REL, ($\mu g/m^3$)
Chiou *et al.* (1997b)	Cerebrovascular disease	LED_{01}	378 µg/d	1.26
Chiou *et al.* (1997b)	Cerebrovascular infarct	LED_{01}	332 µg/d	0.33
Chen *et al.* (1996a)	Ischemic Heart Disease Mortality	LED_{01}	5.53 (mg/L)-yr	0.16
Chen *et al.* (1995)	Hypertension	LED_{10}	5.8 (mg/L)-yr	0.55
Chen *et al.* (2006)	Systolic and pulse hypertension	SHT LED_{01} PHT LED_{10}	71.5 µg/L 0.49 µg/L	1.43 0.0033
Lai *et al.* (1994)	Diabetes mellitus	LED_{05}	8.8 (mg/L)-yr	0.85
Rahman *et al.* (1998)	Diabetes mellitus	LED_{05}	0.21 mg/L	1.4
Mazumder *et al.* (1998)	Skin keratosis	LED_{01}	50 µg/L	0.33
Rahman *et al.* (2006)	Skin keratosis or altered pigmentation	LED_{10}	65.4 µg/L	0.44
Tseng *et al.* (1996)	Peripheral vascular disease	est. LOAEL	20 (mg/L)-yr	1.69
Wang *et al.* (2002)	Carotid atherosclerosis	est. LOAEL	20 (mg/L)-yr	1.69
Von Ehrenstein *et al.* (2005)	Lung Function decrements	-1 mL FEV_1 -1 mL FVC	2.22 µg/L 2.42 µg/L	0.044 0.048

In addition to being inhaled, airborne arsenic can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for arsenic of 0.0035 µg/kg-day is also proposed. (From section 8.3.1.1, 2.3 µg/kg-d/(21.9 kg x 30UF) = 0.0035 µg/kg-d).

9.   Arsine Based Calculations

The NAC/NRC (National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances/National Research Council Subcommittee on Acute Exposure Guideline Levels) derived an Acute Exposure Guidance Level-2 (AEGL-2, disabling) of 0.17 ppm (500 $\mu g/m^3$) for one-hour exposure to arsine based on the hemolysis mouse data of Peterson and Bhattacharyya (1985) (Thomas and Young, 2001). Due to the steepness of the dose response the derivation of an AEGL-1 (Non-disabling) was considered inappropriate. Also the reliance on animal data was considered more "scientifically valid than AEGLs estimated from limited anecdotal human data". The panel used a total UF of 30 (10 for interspecies differences and 3 for intraspecies differences).

Based on the same study data, OEHHA calculated a continuous $BMDL_{1SD}$ of 2.17 ppm (6.9 mg/m^3) for reticulocytosis. When this value was adjusted with uncertainty factors of 10 for interspecies and 30 for intraspecies differences (including 10 for the intraspecies toxicokinetic sub-factor, as proposed in OEHHA, 2007 draft) the potential acute reference exposure level (aREL) for a one hour exposure was 2.17 ppm/300 = 0.0072 ppm (23 $\mu g/m^3$).

Despite the additional 10-fold margin of safety and more sensitive endpoint incorporated in the OEHHA derivation summarized above, there is still residual uncertainty in this comparison aREL value for arsine. There is particular concern with respect to the lack of adequate human data, given that rodents appear more resistant to the effects of acute exposure to various inorganic forms of arsenic than humans. The analogy between arsine and other inorganic forms of arsenic is supported by the observation that arsine exposure in humans and experimental animals results in similar metabolites excreted in urine as result from other inorganic arsenic exposure (Landrigan *et al*., 1982; Buchet *et al*., 1998). A further source of concern with a REL based on the Peterson and Bhattacharyya (1985) study is that while the margin of exposure for hemolysis is greater than 1000, the margin for total lethality is less than 4000. Although a steep dose-response slope for acute lethality is not unprecedented, it is a problematic feature when combined with the uncertainty in animal-to human extrapolation noted above. Thus, OEHHA staff have low confidence in using the Peterson and Bhattacharyya study as a basis of an aREL value for arsine and instead will rely on the aREL based on arsenic trioxide inhalation in mice (0.2 $\mu g/m^3$ arsenic, equivalent to 0.065 ppb arsine), which is sufficiently protective for all inorganic arsenic species.

A comparison of various possible values for an 8-hour REL for arsine is shown in Table 8.3.3. Adjustment of the one-hour NOAEL from Peterson and Bhattacharyya (1985) to eight hours using the modified Haber equation for mice gives a value of 1.6 ppm (4.98 mg/m^3)/300UF = 0.053 ppm (17 $\mu g/m^3$). This value is much higher than the values observed by Williams *et al*. (1981) in workers exposed to arsine concentrations estimated at 0.01 to 0.07 mg/m^3. The adverse effects noted included headache, nausea, weakness and vomiting. Although based on only a couple of subjects, the Williams *et al*. study would indicate an 8-hour value of about 0.04 mg/m^3/30 UF = 0.001 mg/m^3 or 1$\mu g/m^3$. Alternatively, the 90-day study of Blair *et al*. (1990) gives a NOAEL for hematologic effects in mice of 0.025 ppm arsine at 6 hours/day, 5 days/week. Applying the same 300 UF as above gives 0.083 ppb or 0.26 $\mu g/m^3$. This latter figure seems more in line with the limited human observations and more suitable for potentially

repeated 8-hour exposures to arsine. The intraspecies extrapolation includes additional uncertainty factors (PK + PD UF) for exposure of infants and children to arsine.

Table 8.3.3. Development of Health Protective Values for Arsine

Study	Toxic Endpoint	NOAEL/LOAEL/ BMDL	Derived REL µg/m³
Peterson and Bhattacharyya, 1985	Reticulocytosis in mice 1 hour exposure	$BMDL_{1SD}$ 2.17 ppm 6.9 mg/m³	Acute 23
Peterson and Bhattacharyya, 1985	As above with 8-hour adjustment	1.6 ppm 4.98 mg/m³	8-hour 17
Williams et al., 1981	Headache, nausea, weakness, and vomiting in exposed workers	0.01 to 0.07 mg/m³, average 0.04 mg/m³ LOAEL.	8-hour 1.0
Blair et al., 1990	Hematologic effects	NOAEL 0.025 ppm 6 hr/day	8-hour 0.26

PBPK modeling of arsenic species in experimental animals and humans is presently considered inadequate to apply directly to the derivation of RELs for repeated arsine exposures.

Arsine exposure at atmospheric concentrations that caused adverse maternal effects did not adversely affect endpoints of developmental toxicity in mice or rats (Morrissey et al., 1990). In the absence of neurodevelopmental studies with arsine, it is assumed that such an effect would be comparable to those of other inorganic forms of arsenic. In view of the observed effect levels for hematological effects noted in the animal studies, both 8 hour and chronic effects of arsine are considered to be adequately covered by the respective cREL for inorganic arsenic based on neurodevelopmental effects observed in children (i.e., 0.015 µg/m³ arsenic, equivalent to 0.005 ppb arsine)). In view of the concern over neurodevelopmental effects for all inorganic forms of arsenic, OEHHA concludes that it is appropriate to apply this value for 8-hour and chronic exposures to arsine.

10. Arsenic as a Toxic Air Contaminant that Disproportionately Impacts Children

In view of the neurodevelopmental toxicity studies discussed above, it is clear that infants and children are more susceptible to the toxicity of arsenic than adults. OEHHA recommends that inorganic arsenic and arsine be identified as a Toxic Air Contaminant the disproportionately impacts children under the California Health and Safety Code Section 39699.5.

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ARSENIC (INORGANIC)

CAS No: 7440-38-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	74.92
Boiling point	613 °C (sublimes)
Melting point	817 °C @ 28 atm
Vapor pressure	1 mm Hg at 372 °C
Air concentration conversion	1 ppm = 2.21 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.2 E+1 (mg/kg-day)$^{-1}$
[Human occupational exposure lung tumor incidence (Enterline *et al*., 1987a);.
relative risk model, adjusted for interaction with tobacco smoking (CDHS, 1990).]

Oral slope factor: 1.5 E+0 (mg/kg-day)$^{-1}$
[Human skin cancer incidence (Tseng *et al*., 1968, 1977), time- and dose-related
formulation of the multistage procedure (U.S. EPA, 1988).]

III. CARCINOGENIC EFFECTS

Human Studies

Inhalation

Cancer mortality has been studied among workers employed in three major smelters in the U.S., in (1) Tacoma, Washington, (2) Anaconda, Montana, and (3) Garfield, Utah. Smelter workers in Sweden (Ronnskarverken) and in Japan (Sagnoseki-Machi) and cohorts of both miners and smelter workers in China have also been studied.

Enterline and Marsh (1982) and Enterline *et al*. (1987a) examined the longest follow-up period for the Tacoma, Washington cohort. The 1982 report used cumulative doses based on urinary arsenic measurements. Standardized mortality ratios (SMRs) for respiratory cancer ranged from 170 for those receiving the lowest intensity and shortest duration of exposure, to 578 for those with the highest intensity and with 20-29 years duration of exposure. A strong dose-response relationship was evident only when the analysis was limited to the 582 retired workers in the cohort. In the 1987 reanalysis, Enterline and colleagues incorporated newly available historical air sampling data (Enterline *et al*., 1987a); in this study, the dose-response relationship appears more clearly.
The Anaconda, Montana cohort was also the subject of numerous publications. Lee-Feldstein (1983, 1986) divided the 8,045 men of the full study group into nine subcohorts based on arsenic exposure and year of first employment. When considering only those men who had been in their

maximum exposure category for at least 12 months, each of the nine subcohorts, except for one subgroup which had a very small sample size, showed significantly elevated respiratory cancer rates relative to the combined male population of Idaho, Montana and Wyoming (Lee-Feldstein, 1983). Lee-Feldstein (1983) also investigated the association of sulfur dioxide (SO_2) with respiratory cancer in this cohort. Findings from this study could not conclude that arsenic trioxide was the primary environmental agent causing the excessive respiratory cancer seen in the study group.

In another study, Lee-Feldstein (1986) incorporated quantitative exposure estimates based on industrial hygiene data collected between 1943 and 1958. In all but the latest-employed cohort, a statistically significant linear dose-response relationship was observed between arsenic exposure and the directly standardized death rate (DSDR) for respiratory cancer. Lee-Feldstein (1986) reiterated that the latest-employed cohort may not have been followed long enough to display a dose-related mortality pattern, and the men in this cohort may have experienced prior exposures which confound the relationship between arsenic exposure and respiratory cancer mortality. Also, men who were younger at the start of employment were at greater risk for lung cancer than those who began employment later in life. Further analysis of the same cohort by Welch *et al.* (1982) and Higgins *et al.* (1985) confirmed the linear dose-response relationship between exposure and respiratory cancer.

The Garfield, Utah smelter was studied by Rencher *et al.* (1977), who found a three- to five-fold increase in the proportion of deaths due to lung cancer among smelter workers when compared to workers in the mine or concentrator. Similar results were reported by Tokudome and Kuratsune (1976) who studied 839 copper smelter workers in Japan. A dose-response effect on respiratory cancer was observed using either duration of employment or intensity of exposure. For the same duration of employment, risks were greater among those employed in earlier periods.

Workers at the Ronnskarverken smelter in Sweden experienced lung cancer mortality at about five times the rate of residents of the county (Wall, 1980). Pershagen *et al.* (1981) conducted a nested case-control study within this cohort, focusing on the interrelationship of smoking, arsenic and lung cancer. For smokers and nonsmokers, the age-standardized rate ratios (SRRs) were 3.0 and 2.9. Among roaster workers, the most heavily exposed in this plant, the SRRs were 4.4 and 4.5. Exposures were not quantified in this analysis.

Other studies of cancer incidence and mortality among workers at the Ronnskar smelter in Sweden confirmed the excess lung cancer risk (Sandstrom *et al.*, 1988; Jarup *et al.*, 1989a,b). An analysis of age-adjusted rates by calendar year showed a decline in lung cancer starting in the mid-1970s, possibly due to lower exposures, earlier notification of health problems, and/or changing smoking habits (Sandstrom *et al.*, 1988). However, among the most recently hired cohort, lung cancer incidence was greater than expected.

Taylor *et al.* (1989) conducted a case-control study among tin miners in China to examine the relationship between arsenic exposure and lung cancer. After adjusting for tobacco use and radon exposure, the risk of lung cancer for subjects in the highest quartile of arsenic exposure

was 22.6-fold higher than for those in the lowest quartile. Duration but not intensity of exposure appeared to be a predictor of lung cancer risk.

Another report from China covers a cohort consisting of workers employed at two copper smelters, one arsenic smelter and a mine (Wu, 1988). Wu reported that nearly 19,000 person-years were followed, resulting in 40 lung cancer deaths.

Enterline *et al*. (1987b) analyzed data from eight smelters with fairly low levels (relative to the Anaconda, Tacoma, and Ronnskar smelters) of arsenic. When data from the six smelters were combined and examined, the results suggested an increasing trend in risk with increasing exposure ($p = 0.06$). A significant effect was observed for cumulative exposure to arsenic and for smoking.

Reports on cancer and insecticide manufacturing exposures to arsenic were by Ott *et al*. (1974), Baetjer *et al*. (1975b; as cited in Mabuchi *et al*., 1979), Mabuchi *et al*. (1979), and Sobel *et al*. (1988). A study of orchardists who potentially sprayed arsenic-containing pesticides is reviewed by Wicklund *et al*. (1988). The report by Mabuchi *et al*. (a more extensive follow-up of the same cohort Baetjer analyzed) found a sharp increase in the lung cancer SMR with increasing duration of employment among those predominantly exposed to arsenic, although no increase was observed for those with exposure to arsenic only. However, more than 99 percent of this latter group were employed for five years or less.

Ott *et al*. (1974) observed a marked increase in respiratory cancer mortality with increasing cumulative dose in workers previously employed in an insecticide manufacturing plant. Sobel *et al*. (1988) updated the study by Ott *et al*. by 9 additional years of follow-up and by tracing more than 99% of those who had been lost to follow-up in the study by Ott *et al*. The 9 follow-up years yielded a non-statistically significant respiratory cancer SMR of 116.

A case-control study of deaths among orchardists (Wicklund *et al*., 1988) found no association between exposures to arsenic-containing pesticides and respiratory cancer, after controlling for smoking.

In summary, for smelter workers, the association between respiratory cancer mortality and arsenic exposure is a consistent, replicable finding of substantial magnitude with a clear dose-response relationship, and high statistical significance. The mortality data on workers employed in the manufacturing of insecticides provide further evidence that arsenic acts as a respiratory tract carcinogen.

Oral

Chronic exposure to high levels of arsenic in drinking water has been identified as increasing skin cancer incidence in humans (US EPA, 1988, 1995).

In a region on the southwest coast of Taiwan, artesian well water with high arsenic concentrations ranging from 0.01-1.82 ppm had been in use for more than 45 years (Tseng *et al*., 1968, 1977). 40,421 inhabitants of 37 villages of the regions were examined for skin lesions,

peripheral vascular disorders and cancers. The study identified 7,418 cases of hyperpigmentation, 2,868 of keratosis (Type A/benign), 428 of skin cancer (squamous cell carcinoma, basal cell carcinoma, *in situ* squamous cell carcinoma, and Type B keratoses/intraepidermal carcinomas) and 360 cases of Blackfoot disease. The incidence rates for keratosis and skin cancer were 183.5 and 10.6/1000, respectively. A control population of 7,500 people did not exhibit any of the above disorders.

The above exposed population was divided into "low", "mid" and "high" exposure groups based upon the well-water arsenic concentration in each village (<0.3, 0.3-0.6, and >0.6 ppm, respectively). A dose-response relationship was identified for the prevalence of skin cancer and Blackfoot disease (no dose-response data was presented for hyperpigmentation and keratosis). The prevalence of both disease was also found to increase with age. Males were found to have higher prevalence rates than females (male to female ratios for skin cancer and Blackfoot disease were 2.9 and 1.3, respectively).

Additional studies of chronic human arsenic exposure resulting in increased skin cancer or internal organ cancer incidence have been identified and reviewed (Fierz, 1965; Borgono and Greiber, 1972; Cebrian *et al*., 1983; Yue-Zhen *et al*., 1985; Chen *et al*., 1985, 1986; reviewed by US EPA, 1988).

Animal Studies

There were two animal inhalation studies on the carcinogenicity of arsenic available at the time the document *Report to the Air Resources Board on Inorganic Arsenic. Part B. Health Effects of Inorganic Arsenic Compounds* was written (CDHS, 1990). Berteau *et al*. (1977, 1978) exposed mice to a respirable aerosol of arsenic(III) (containing approximately 27 mg arsenic(III)/m^3) for 40 minutes/day for 26 days and 20 minutes/day thereafter. Inhaled doses were approximately 1.3 mg arsenic/kg/day and 0.69 mg arsenic/kg/day. No evidence of neoplasia was observed grossly in exposed animals.

In an inhalation study of arsenic trioxide, Glaser *et al*. (1986) exposed 20 rats for 18 months, at approximately 60 μg arsenic/kg/day and 40 rats at approximately 20 μg arsenic/kg/day. No tumors were observed in exposed animals. The report lacked important methodological details, including sampling to verify exposure levels. Also, the study tested fewer animals than required by standard cancer bioassay protocols.

In an arsenic (III) trioxide-treated group of 47 male hamsters, Pershagen *et al*. (1984) found three carcinomas: two of bronchi or lungs (an adenocarcinoma, and an anaplastic carcinoma) and one of larynx or trachea (a squamous cell carcinoma). These carcinomas were not statistically significant when considered in relation to the concurrently treated controls but were statistically significant when considering additional controls from the same colony ($p = 0.01$, one-tailed test). In female hamsters, benign lung tumors (adenomas) were induced by intratracheal instillation of a suspension of solid arsenic trioxide in a phosphate buffer (Ishinishi *et al*., 1983; Ishinishi and Yamamoto, 1983), but Ohyama *et al*. (1988) did not induce lung tumors in male hamsters similarly treated with arsenic trioxide or gallium arsenide.

Arsenic (V) has also induced tumors in animals. Calcium arsenate injected intratracheally induced lung adenomas in male hamsters (Pershagen and Bjorklund, 1985) and leukemia and lymphoma were produced by sodium arsenate by subcutaneous injection in mice (Osswald and Goerttler, 1971).

Among oral studies, only one study reported positive findings. Tumors, including adenocarcinomas of the skin, lung, and lymph nodes, were noted in mice given Fowler's solution (potassium arsenite), but the report lacks experimental details necessary for critical assessment (Knoth, 1966; as reviewed in U.S. EPA, 1984).

Other oral studies reported that arsenite (3 μg arsenic/l in drinking water) reduced the total tumor incidence in male and female white Charles River CD mice (Kanisawa and Schroeder, 1967), and enhanced the growth rate of "spontaneous" (common) mammary tumors in female inbred C3H mice (Schrauzer and Ishmael, 1974; Schrauzer *et al.*, 1978).

## IV.	DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

The International Agency for Research on Cancer (IARC) evaluated arsenic in 1980 and classified "arsenic and arsenic compounds" in Group 1, which includes the "chemicals and groups of chemicals (which) are causally associated with cancer in humans." Ingestion of arsenic is associated with cancer at sites different from those associated with arsenic inhalation: ingestion is associated with skin cancer, while inhalation results in lung neoplasms.

In contrast, arsenic has not conclusively produced carcinogenesis in animals. Arsenic produces tumors in animals, but these tumors are rarely malignant. The few reports of carcinogenic effects of arsenic compounds in animals are seriously flawed. The hypothesis that arsenic may act as a tumor promoter has been tested but not proven in animals.

CDHS (1990) used human data for its cancer risk assessment of arsenic because (1) these data showed a strong, consistent association with increased respiratory cancer in epidemiologic studies, (2) quantitative exposure measurements were made in several of these studies, and (3) clear dose-response relationships were observed. No risk assessment has been conducted using animal data because the cancer bioassays using relevant routes of exposure have been negative and because no adequate inhalation bioassay has been published.

The quantitative cancer risk assessment for arsenic considered data from the occupational mortality studies of smelter workers in Anaconda, Montana by Welch *et al.* (1982), Higgins *et al.* (1985) and Lee-Feldstein (1986), and in Tacoma, Washington by Enterline *et al.* (1987a).

Oral

US EPA (1995) conducted a review of the available literature and identified the studies by Tseng *et al*. (1968, 1977) as the key references for quantifying ingested arsenic cancer potency. US EPA stated that these studies demonstrate a causal association between arsenic ingestion and an elevated risk of skin cancer. These data were considered reliable for the following reasons: 1) the study and control populations (40,421 and 7,500, respectively) were large enough to provide reliable estimates of the skin cancer incidence rates; 2) a statistically significant elevation in skin cancer incidence in the exposed population compared to the control population was observed many years after first exposure; 3) a pronounced skin cancer dose-response by exposure level was demonstrated; 4) the exposed and control populations were similar in occupational and socioeconomic status, with ingestion of arsenic-contaminated drinking water the only apparent difference between the two groups, and 5) over 70% of the observed skin cancer cases were pathologically confirmed.

Methodology

Inhalation

Data from the Anaconda and Tacoma smelters show nonlinear relationships between cumulative dose and the relative risk (or SMR) for death from lung cancer. These dose-response curves are concave downward (their slopes remain positive but decrease as exposure increases). Notwithstanding this observation, the staff of DHS used linear models for this risk assessment. In these models, the dose of arsenic was measured as cumulative $\mu g/m^3$-years; the response was measured as the relative increase in risk over the background (risk ratio). In addition, the models assume that the mechanism of carcinogenesis is a nonthreshold process.

The data from Enterline *et al*. (1987a), Higgins *et al*. (1985), and Lee-Feldstein (1986) were fitted to the model. The regression model used to achieve a linear extrapolation is described by the equation:

$$E[obs_i] = [\alpha + \beta(d_i)] \times Exp_i$$

where $E[\cdot]$ represents the expectation of a random variable, d_i represents the average cumulative dose of arsenic (in $\mu g/m^3$-years) for exposure group i, obs_i represents the observed number of deaths in exposure group i, Exp_i represents the expected number of deaths in group i based on the standard population, α represents the risk ratio predicted for a cumulative dose (d) of zero, and β is the slope parameter (in $[\mu g/m^3\text{-years}]^{-1}$).

To calculate unit risk, the staff of DHS selected the MLE (maximum likelihood estimate) slope and upper 95% confidence limit (UCL) based on use of the four lowest exposure groups from the Enterline *et al*. (1987a) analysis.
A risk assessment was also conducted using an adjustment for the strong interaction between arsenic and smoking observed in several occupational cohorts. The prevalence of smoking was independent of the level of arsenic exposure in the Anaconda cohort (Welch *et al*., 1982), but may have been higher than in the general population. Also, there appeared to be no reason for

smokers to be distributed differently among the exposure levels in the Tacoma cohort, hence smoking was assumed to be independent of arsenic exposure in this cohort as well.

Each dose-specific crude SMR was adjusted taking the low-dose SMR in each study as the baseline. Next, a nonsmokers' SMR and a smokers' SMR were derived. From the nonsmokers' SMR, observed and expected deaths among nonsmokers were inferred. Finally, a regression model was fitted to the inferred nonsmokers' data to find the slope of the line relating cumulative arsenic dose to excess relative risk. This procedure was applied to the data of Enterline *et al.* (1987a) under the assumption that the interaction between smoking and arsenic varies as a function of dose, and that the joint effects at low doses are multiplicative.

The MLE for β was 2.30×10^{-4} using the data on nonsmokers from the study by Enterline *et al.* (1987a). An 95% UCL was estimated and used in evaluating unit risks.

Risks were evaluated separately by sex and for four smoking categories: never, former, light (< 1 pack/day) and heavy smokers. Unit risks for these categories range from 400 to 8,400 per million persons, with upper bounds ranging from 630 to 13,000 per million.

The staff of DHS recommended that the range of risk for ambient exposures to arsenic be based on the 95% UCL predicted from fitting a linear model to the human data adjusted for interaction with smoking. The staff of DHS further recommended that the overall unit risk, 3.3×10^{-3} per $\mu g/m^3$, be considered the best estimate of the upper bound of risk.

Oral

A generalized multistage procedure with both linear and quadratic dose assumptions was used to predict the prevalence of skin cancer as a function of arsenic concentration in drinking water (d) and age (t), assuming exposure to a constant dose rate since birth. F(t,d) represents the probability of developing skin cancer by age t after lifetime exposure to arsenic concentration d. The procedure used is expressed as follows: $F(t,d) = 1 - \exp[-g(d) H(t)]$, where g(d) is a polynomial in dose with non-negative coefficients, and H(t) is $(t-w)^k$, where k is any positive real number, and t > w for induction time w. The cancer potency calculation was based on skin cancer incidence data for Taiwanese males (Tseng *et al.*, 1968) because their skin cancer prevalence rates were higher than the females studied. The calculation was also based on several assumptions listed below.

1. The mortality rate was equal for both diseased (skin cancer) and nondiseased persons.

2. The population composition (with respect to skin cancer risk factors) remained constant over time, implying that there was no cohort effect.
3. Skin cancers were not surgically removed from diseased persons.

The population at risk was classified into 4 age groups (0-19, 20-39, 40-59 and $\geq$ 60 years of age) and three dose groups (0 - 0.3, 0.3 - 0.6 and > 0.6 ppm drinking water arsenic concentration) for males and females separately from the reported prevalence rates (Tseng *et al.*, 1968, 1977) as percentages. The assumption was made that the Taiwanese persons had a constant arsenic

exposure from birth, and that males and females consumed 3.5 L and 2 L drinking water/day, respectively. The multistage procedure was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic. Both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water/day, adjusted for U.S. population survivorship by life-table analysis, ranged from 1 E-3 to 2 E-3 for an arsenic intake of 1 μg/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5 E-5 $(\mu g/L)^{-1}$; the corresponding cancer potency value is 1.5 E-0 $(mg/kg/day)^{-1}$.

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ACUTE TOXICITY SUMMARY

METALLIC COPPER AND COPPER COMPOUNDS

Molecular formula	Molecular weight	Synonyms	CAS Registry Number
Cu	63.55	copper	7440-50-8
CuO	79.54	cupric oxide, copper oxide, copper (I) oxide	1317-38-0
$CuSO_4$	159.60	copper sulfate, blue vitrol, copper (II) sulfate, cupric sulfate, blue copper, blue stone	7758-98-7

I.   Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level   **100 μg/m³**
Critical effect(s)   respiratory system defense mechanism
Hazard Index target(s)   Respiratory System

II.   Physical and Chemical Properties (for metallic copper except as noted)
(HSDB, 1994)

Description   reddish metal
Density   8.94 g/cm^3 @ 25°C
Boiling point   2595°C
Melting point   1083°C
Vapor pressure   1 mm Hg @ 1628°C
Flashpoint   not applicable
Explosive limits   not applicable
Solubility   soluble in nitric acid; very slightly soluble in
                                              hydrochloric acid and ammonium hydroxide
Odor threshold   not applicable
Odor description   odorless
Metabolites   no data found
Conversion factor   not applicable

III.   Major Uses or Sources

Copper (Cu) is a widely used structural metal, particularly where high electrical and thermal conductivity are needed (ATSDR, 1990). Copper fumes are generated in copper and brass foundries, in smelters, and in the welding of copper-containing metals. Copper compounds are found in fungicides and other agricultural products, ceramics, and pyrotechnics. Airborne sources of copper include combustion of fuels and other materials containing copper.

Copper sulfate ($CuSO_4$), the most common copper salt, is used as a fungicide, as a component of electroplating solutions, as a chemical intermediate for other copper salts in dyes, and in the tanning of leather (ATSDR, 1990).

Copper oxide (CuO) is another common copper salt. It is used in insecticides, fungicides, and catalysts (HSDB, 1994). CuO is also used in fuel additives, cement, and wood preservatives.

IV.   Acute Toxicity to Humans

Following occupational exposures to copper dust, commonly reported reactions include metallic or sweet taste, upper respiratory tract irritation, and nausea (Whitman, 1962). An unpublished letter regarding occupational exposure to copper fumes reported that levels of 0.02-0.40 mg/m³ copper did not "cause complaints" while exposure to 1.0-3.0 mg/m³ copper for "short periods of time" resulted in a "sweet taste in the mouth" but no nausea (Whitman, 1957).

Inhalation exposure to copper fumes, usually from welding or smelting operations, may result in "metal fume fever." This condition results in headache, dryness of the mouth and throat, chills, fever, and muscle aches, usually beginning 4-8 hours after exposure to the oxides of various metals, including copper. Symptoms and signs spontaneously subside within 24-36 hours (ATSDR, 1990; Seaton and Morgan, 1984). Symptoms consistent with metal fume fever were reported by workers in a facility with airborne copper dust at concentrations of 0.03-0.12 mg/m³ (Gleason, 1968). Upper respiratory irritation has been reported, in addition to symptoms consistent with metal fume fever (fever, dyspnea, chills, headache, nausea, myalgia, cough, shortness of breath, a sweet metallic taste, and vomiting), in factory workers exposed to copper fumes for 1 to 10 hours as a result of cutting pipes known to contain copper (Armstrong *et al*., 1983). The sweet taste experienced by workers from the Whitman (1957) report above is consistent with the onset of symptoms of metal fume fever.

Factory workers exposed to copper dust, CuO, and several other copper salts reported symptoms of eye, nose, and throat irritation, anorexia, and nausea (Askergren and Mellgren, 1975; Suciu *et al*., 1981). Occasional diarrhea was also reported by these workers.

Predisposing Conditions for Copper and Copper Compound Toxicity

Medical: Persons with Wilson's disease, a genetic disorder affecting copper homeostasis, may be more sensitive to the effects of copper exposure (Schroeder *et al*., 1966; ATSDR, 1990). Persons with glucose-6-phosphate dehydrogenase deficiency, anemic, allergic, liver or kidney conditions moght be more sensitive (Reprotext, 1999). Infants and children less than 1-year of age may be more sensitive to the effects of copper exposure because homeostatic mechanisms for clearing copper from the body are not yet developed

Chemical: Persons exposed to molybdenum might be less sensitive to copper, since molybdewnum is antagonistic to copper toxicity (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

Rats were dosed by intratracheal instillation with 2.5, 5, 10, 20, 30, 50, and 100 mg Cu/rat and pulmonary clearance of CuO was measured over time (Hirano *et al*., 1993). The CuO particles were cleared from the lung with a half-time of 37 hours.

A 54% and 70% increase in mortality in male and female mice, respectively, over controls was observed following challenge with aerosolized streptococci after a 3-hour exposure to 0.56 mg/m³ Cu as $CuSO_4$ (Drummond *et al*., 1986). Pulmonary bactericidal activity was not measured for this exposure group.

The effects of copper sulfate (and other metal sulfate) aerosols on respiratory defense mechanisms were studied in male hamsters (Skornik and Brain, 1983). Pulmonary macrophage phagocytic rates were measured by determining the in vivo uptake of radioactive colloidal gold 1, 24, or 48 hours after a single 4-hour inhalation exposure to 0, 0.3, 3.2, 4.0, 5.8 and 7.1 mg Cu/m³. When hamsters were exposed for 4 h to greater than or equal to 3.2 mg Cu/m³, macrophage endocytosis was significantly reduced 1 h after exposure compared with that in unexposed control animals. The reduction was dose-dependent. At 24 h after exposures to the higher concentrations of Cu the percent of gold ingested by pulmonary macrophages remained depressed but less than at 1 hour. (By 48 h, the rate of macrophage endocytosis in hamsters returned to control levels except in hamsters exposed to 3.2 and 5.8 mg Cu/m³.)

VI.   Reproductive or Developmental Toxicity

Copper is known to be spermicidal (U.S.EPA, 1987). Copper absorbed from copper intrauterine loops or wires has been shown to prevent mammalian embryogenesis. Conversely, terata have been observed in the offspring of experimental animals deficient in dietary copper.

Inhibited spermatogenesis and testicular atrophy were observed in male rats exposed to 0.1-1.0 mg/m³ CuO (Ginoian, 1976). The same study also reported that the number of fetuses was reduced in a dose-related manner in females exposed to CuO. Because the original article was not available for review, key experimental details, including duration of exposure, are unknown.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 100 μg/m³

Study	ACGIH, 1991; Gleason, 1968; Whitman, 1957, 1962
Study population	workers
Exposure method	inhalation
Critical effects	metal fume fever
LOAEL	unkown
NOAEL	1 mg Cu/m³
Exposure duration	unknown
Extrapolated 1 hour concentration	no extrapolation
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.1 mg Cu/m³ (100 μg/m³)

The ACGIH-TLV is based on an unpublished letter which reported that exposure to 1 - 3 mg/m³ copper fume for "short periods" resulted in a "sweet taste in the mouth" and that exposure to 0.02 - 0.4 mg/m³ did not result in any symptoms (Whitman, 1957). However, it was not clear from the letter if or how actual copper levels were measured. Another author reported that symptoms of metal fume fever were observed in workers exposed for an unspecified number of weeks to 0.03 - 0.12 mg/m³ copper dust (Gleason, 1968). The latter exposure was not designed to determine the level of copper responsible for the symptoms; it was meant to justify the implementation of exhaust controls. Therefore, the air samples were not directly compared to worker exposure or worker symptoms.

The current REL is based on the ACGIH-TLV of 1 mg/m³ copper dust. The TLV of 1 mg/m³ is a NOAEL based on the report of Whitman (1957) indicating that exposure to copper dust was detectable by taste but that no other symptoms occurred following exposure to 1 - 3 mg/m³ for an unknown duration. An uncertainty factor of 10 was applied to the NOAEL to account for variability in individual response. No time extrapolation was applied because the duration of exposure was not clearly specified by either of the available reports. Because of the limitations of the existing data, reevaluation of the REL for copper is recommended when better methods or data are available.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists an IDLH of 100 mg/m³ but it is based on studies of lethality by the oral route in animals and man.

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CHRONIC TOXICITY SUMMARY

COPPER AND COPPER COMPOUNDS

Molecular Formula	Synonyms	Molecular Weight	CAS Reg. No.
Cu	copper	63.55	7440-50-8
$CuCl_2$	copper chloride	134.45	7447-39-4
CuO	cupric oxide; copper oxide; copper (I) oxide	79.54	1317-38-0
$CuSO_4$	copper sulfate; blue vitrol; copper (II) sulfate; cupric sulfate; blue copper; blue stone	159.61	7758-98-7

I. Chronic Toxicity Summary

Inhalation reference exposure level   **0.02 µg Cu/m³**

Critical effect(s)   'Metal fume fever'; cold-like symptoms in humans

Hazard index target(s)   Respiratory system

II. Chemical Property Summary (from HSDB, 1995, except as noted)

Molecular formula   see above

Molecular weight   see above

Description   Cu: reddish lustrous metal
CuCl₂: yellow-brown powder
CuO: brownish/black crystalline powder
CuSO₄: blue crystals

Vapor pressure   1 mm Hg @ 1628°C

Solubility   Cu: insol. in H_2O; sol. in HNO_3, hot H_2SO_4; sl. sol. in HCl, NH_4OH
$CuCl_2$: 706 g/l H_2O; sl. sol. in alcohol (Beliles, 1981)
CuO: insol. H_2O; sol. in NH_4Cl, KCN (Beliles, 1981)
$CuSO_4$: 14.3 g/100 ml H_2O @ 0°C; 75.4 g/100 ml @ 100°C; 1.04 g/100 ml CH_3OH @ 18°C

Conversion factor   Not applicable

III. Major Uses and Sources

Copper is a widely used structural metal, particularly in applications where high electrical and thermal conductivity are required, and is the major component of bronze and brass (ACGIH, 1992). Copper fume may be generated in copper and brass foundries, smelters, and in the welding of copper containing metals. Copper compounds are also found in fungicides and other agricultural products, ceramics, and pyrotechnics. Copper sulfate ($CuSO_4$) is the most common salt of copper and is used as a fungicide, a component of electroplating solutions, and as a chemical intermediate for other copper salts and dyes and in the tanning of leather. Copper oxide (CuO) is another common copper compound used in insecticides, fungicides, catalysts, fuel additives, cement, and wood preservatives.

IV. Effects of Exposures to Humans

Workers employed in sieving copper dust and copper electroplating were examined over a period of four years, with 100, 97, 75, and 97 workers examined in the four consecutive years beginning in 1970 (Suciu *et al.*, 1981). Maximum concentrations to which workers in sieving operations were exposed declined from a high of 464 mg/m^3 in 1971 to 111 mg/m^3 two years later and ultimately to 7-22 mg/m^3 through health protective measures. Normal serum copper levels, based upon measurement of 20 control workers, were found to fall between 80 and 120 μg/100 ml serum. Among exposed workers, 37-46% per year had serum copper levels over 120 μg/100 ml serum. Neuro-physiological findings included changes in EEG, memory deficiencies, paresthesia and pain, cardiovascular changes, digestive disorders, respiratory problems, and endocrine disorders. In the study, however, symptom incidence was not compared with a control group.

Exposure to copper dust was reported in workers polishing copper plates (Gleason, 1968). Three men reported symptoms of warmth or chills and head stuffiness (the classic signs of 'metal fume fever') "some weeks" after the beginning of a copper plate polishing operation. Air samples showed that concentrations in the operation area ranged from 0.030 to 0.120 mg Cu/m^3, depending on location. Aluminum was also detected as a "major" or "minor" component of the dust, depending on location. Microscopic analysis of the dust showed it was of "extreme fineness". Copper dust levels in the air were reduced to 0.008 mg/m^3 when a local exhaust ventilation system was installed. As a result, symptoms among the workers subsided.

Similar symptomatology, including fever, dyspnea, chills, headache, and nausea, was also reported among 26 workers involved in the cutting of brass pipes (Armstrong *et al.*, 1983). Elevated urinary copper levels were reported in the workers and symptoms appeared an average of 4 hours after exposure.

The nasal mucosa of 16 metal workers, 10 of whom were exposed to complex copper salt dust, and 9 construction workers were examined (Askergren and Mellgren, 1975). The dust to which the workers were exposed was predominantly comprised of 26% copper hydroxide nitrate ($Cu(NO_3)_2 \cdot 3Cu(OH)_2$), 25% copper hydroxide sulfate ($CuSO_4 \cdot 3Cu(OH)_2$), 22% copper silicate

($CuSiO_3$), and 17% CuO. Exposure levels were not quantitated. Potential duration of exposure among the 10 sheet metal workers ranged from 1 to 60 months. Workers exposed for longer periods showed atrophic changes to the nasal mucosa, as indicated by increased vascularity with more prominent superficial blood vessels. This effect was also observed with some frequency among the other non-exposed workers. The construction workers also showed other changes in nasal mucosa (livid mucosa and mucoid secretion).

V. Effects of Exposures to Animals

Male and female CD_1 mice (47 or 48/sex/group) were exposed for 3 hours/day, 5 days/week to 0.12 mg Cu/m^3 for one week or 0.13 mg Cu/m^3 for 2 weeks in the form of $CuSO_4$ and examined for changes in host defense (Drummond *et al.*, 1986). Significantly increased mortality and decreased mean survival time were reported in mice exposed to copper for two weeks followed by challenge with an aerosol of *Streptococcus zooepidemicus*. Decreased bactericidal activity of alveolar macrophages (as % *Klebsiella pneumoniae* killed) was observed in female mice exposed for one week and both male and female mice exposed for two weeks. Two week exposure produced a significant decrease in normal tracheal epithelium in female mice and extensive areas of alveolar thickening.

Eight male rabbits were exposed to 0.6 ± 0.3 mg Cu/m^3 in the form of $CuCl_2$ for 6 hr/day, 5 days/week for 4-6 weeks, with an equal number of control rabbits exposed to filtered air only (Johansson *et al.*, 1983; Johansson *et al.*, 1984; Lundborg and Camner, 1984). The rabbits were sacrificed within 3 days of the last exposure (2 per day, 3 days/week). Examination of the lungs revealed no changes in gross appearance and no statistical difference was found between exposed and control animals with respect to histological lesions (Johansson *et al.*, 1984). Type II cells of the lung were found to be slightly increased in the exposed animals, although only the volume density of the type II cells was found to be increased significantly. Total lung phospholipid was also unchanged. Extracted alveolar macrophages from copper exposed animals had slightly increased lamellated inclusions, although no increase in cell number, protrusions, oxidative metabolic activity, particle uptake, or bactericidal activity was observed (Johansson *et al.*, 1983). Lysozyme activity in lung lavage fluid and in alveolar macrophages and their conditioned medium was unchanged between treated and control animals (Lundborg and Camner, 1984).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Gleason, 1968
Study population	Three workers
Exposure method	Occupational inhalation exposure
Critical effects	'Metal fume fever'; cold-like symptoms
LOAEL	0.030-0.120 mg/m^3
NOAEL	0.008 mg/m^3
Exposure continuity	8 hrs/day × 5 days/week
Exposure duration	Unspecified ("some weeks")
Average experimental exposure	0.002 mg/m^3 for NOAEL group
Human equivalent concentration	0.002 mg/m^3 for NOAEL group
Subchronic uncertainty factor	10
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.02 µg/m^3

Data indicate that the inhalation of copper produces adverse effects in occupationally exposed humans. The most useful data come from the study of Gleason *et al.* (1968) showing the appearance of symptoms similar to 'metal fume fever' among workers exposed to copper dust levels in the range of 0.03 to 0.12 mg Cu/m^3. Symptoms ceased when dust levels were reduced to 0.008 mg Cu/m^3. Thus, this level can be taken as a NOAEL in the development of the chronic REL. Adjusting the dose for work-week exposure results in an average experimental exposure of 0.002 mg Cu/m^3. An uncertainty factor of 10 was applied to adjust for the less than chronic exposure and a factor of 10 was applied to adjust for potentially sensitive human subpopulations. The resulting chronic REL is 0.02 µg Cu/m^3. Other uncertainties associated with the study include: (1) the presence of other compounds in the work environment, (2) the small study size, (3) limited breadth and reporting of toxic endpoints, and (4) limited reporting of experimental detail.

Evidence from animal studies also suggests that inhalation of copper has adverse effects on the respiratory system and increases susceptibility to bacterial infection (Johansson *et al.*, 1983; Johansson *et al.*, 1984; Drummond *et al.*, 1986). In a relatively large study (47 or 48 animals/group) of mice exposed to CuSO$_4$, decreased host resistance and histological changes to respiratory epithelium were observed following two-week exposure (Drummond *et al.*, 1986). The LOAEL for the study was observed at 0.13 mg Cu/m^3 (only a single dose level was examined for two different time periods). This exposure level is considerably above the chronic REL derived from the human data. The use of this study for the derivation of the chronic REL would result in a value below that derived from the human data primarily because of uncertainty associated with using animal data, the relatively short exposure duration, and the absence of a NOAEL. However, the cumulative uncertainty associated with the human study is more

acceptable than that associated with the animal study. Therefore the data from the Gleason *et al.* (1968) study have been used for the derivation of the chronic REL.

The strengths of the inhalation REL include the use of human exposure data and the observation of a NOAEL. Major areas of uncertainty are the lack of reproductive toxicity data, the lack of chronic inhalation exposure studies, the uncertainty in estimating exposure, the potential variability in exposure concentration, and the limited nature of the study.

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CHRONIC TOXICITY SUMMARY

1,4-DICHLOROBENZENE

(p-dichlorobenzene; di-chloricide; p-dichlorobenzol; Paradow; Paramoth; Parazene; p-chlorophenyl chloride)

CAS Registry Number: 106-46-7

I.   Chronic Toxicity Summary

Inhalation reference exposure level	**800 μg/m³** (100 ppb)
Critical effect(s)	General effects (reduced body weights and food consumption) in rats
	CNS effects (tremors) in rats
	Respiratory/dermal effects (nasal and ocular discharge) in rats
	Liver effects (increased liver weight) in rats, and Kidney effects (increased kidney weight) in rats.
Hazard index target(s)	Nervous system; respiratory system; alimentary system; kidney

II.   Chemical Property Summary (HSDB, 1997; CRC, 1994)

Description	White crystals, monoclinic prisms
Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01 g/mol
Boiling point	174°C
Melting point	52.7°C
Vapor pressure	10 torr @ 54.8°C
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	1 ppm = 6.0 mg/m³ at 25°C

III.   Major Uses and Sources

Commercial grade 1,4-dichlorobenzene (1,4-DCB) is available in the USA as a technical grade liquid, typically containing a small percentage (>0.1% by weight) of meta (1,3-DCB) and ortho (1,2-DCB) isomers; as a solution in solvent or oil suspension; or as crystalline material pressed into various forms (HSDB, 1997). Besides its role as an intermediate in the synthesis of various organics, dyes and pharmaceuticals, 1,4-dichlorobenzene is used as a space or garbage deodorizer for odor control. The insecticidal and germicidal properties of 1,4-dichlorobenzene are used to control fruit borers and ants, moths, blue mold in tobacco seed beds, and mildew and mold on leather or fabrics. In 1996, the latest year tabulated, the statewide mean outdoor

monitored concentration of 1,4-DCB was approximately 0.15 ppb (CARB, 1999). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 30,577 pounds of dichlorobenzene (CARB, 2000).

IV.   Effects of Human Exposure

Case reports of human exposure to 1,4-DCB include malaise, nausea, hepatic manifestations (yellow atrophy and cirrhosis), proteinuria, bilirubinuria, hematuria, and anemia. A woman exposed to 1,4-DCB for 6 years developed central nervous system effects, including severe cerebellar ataxia, dysarthria, weakness in all limbs, and hyporeflexia (U.S. EPA, 1985).

No epidemiologic studies of 1,4-DCB exposures were located.

V.   Effects of Animal Exposure

Rats, rabbits and guinea pigs were exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/m^3) 1,4-DCB by inhalation 7 hours/day, 5 days/week for 6-7 months (Hollingsworth *et al.*, 1956). High dose animals showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Liver and kidney changes included cloudy swelling and centrilobular cellular degeneration (liver). In another inhalation study in rats animals were exposed to 0, 75 or 500 ppm (0, 451 or 3006 mg/m^3) for 5 hours/day, 5 days/week for 76 weeks (Riley *et al.*, 1980). The authors found increased kidney and liver weights in the high dose group. Thus 75 ppm was a NOAEL. Studies with oral exposure to 1,4-DCB, including the NTP (1987) chronic bioassay study (maximum dose of 300 mg/kg-day), have also found an increased incidence of renal and hepatic lesions (cellular degeneration and focal necrosis).

Three inhalation reproductive studies, one in rabbits (Hayes *et al.*, 1985), one in mice (Anderson and Hodge, 1976), and one in rats (Chlorobenzene Producers Assn., 1986), found minimal reproductive effects. In rabbits exposed on days 6-18 of gestation to 100, 300, and 800 ppm 1,4-DCB, only the differences in percentage of implantations resorbed and in percentage of litters with resorptions were significantly increased and only in the 300 ppm group (Hayes *et al.*, 1985). No reduction in reproductive performance was observed in mice exposed to 0, 75, 225, or 450 ppm 1,4-DCB for 6 hours/day for 5 days (Anderson and Hodge, 1976).

In a two-generation reproductive study (Chlorobenzene Producers Association, 1986), Sprague-Dawley rats P1 (28/sex/group) were exposed to 0, 50, 150 or 450 ppm (0, 301, 902, or 2705 mg/m^3) of 1,4-DCB vapor, 6 hours/day, 7 days/week for 10 weeks, and then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks and then mated. No developmental abnormalities were observed in pups examined. At 450 ppm significant decreases in live births, pup weights, and pup survival were seen in both the F1 and F2 generations. Non-reproductive effects observed in the parental males in the 150 and 450 ppm groups included significantly increased liver and kidney weights. All dose levels caused hyaline droplet nephrosis in post-pubescent males; but this change was associated with the formation of

alpha-2u-globulin, an abnormality considered specific for male rats with no relative human significance (U.S. EPA, 1991). The Chlorobenzene Producers Association reproductive study was chosen by the U.S. EPA to derive the RfC.

VI.   Derivation of Chronic Reference Exposure Level

Study	Chlorobenzene Producers Association, 1986
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm)
Critical effects	Reduced body weights and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hr/day for 7 days/week
Average experimental exposure	13 ppm for NOAEL group (50 x 6/24)
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	10 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 ppb, 0.8 mg/m^3, 800 µg/m^3)

The chronic REL for 1,4-dichlorochlorobenzene is also the U.S. EPA RfC. OEHHA agrees with the U.S.EPA analysis. A 3-fold subchronic uncertainty factor (instead of 10) was used by U.S. EPA because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980). Ten weeks are also greater than 8% of a rat's two-year lifetime and thus in accord with OEHHA's use of a subchronic UF of 3 (OEHHA, 2000).

For comparison, Riley *et al*. (1980) found a chronic NOAEL of 75 ppm for kidney and liver effects in rats, which is equivalent to 11.2 ppm continuous exposure. Use of an RGDR of 1 and a total UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 0.4 ppm.

VII.   Data Strengths and Limitations for Development of the REL

The major strengths of the REL for 1,4-dichlorochlorobenzene are the observation of a NOAEL and the demonstration of a dose-response relationship. The major uncertainties are the lack of human data and the lack of chronic, multiple-species health effects data.

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1,4-DICHLOROBENZENE

CAS No: 106-46-7

I.   PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C
Vapor pressure	10 mm Hg @ 25°C
Air concentration conversion	1 ppm = 6 mg/m^3

II.   HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 (µg/m^3)$^{-1}$
Slope Factor: 4.0 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III.   CARCINOGENIC EFFECTS

Human Studies

There are several case reports of human leukemia associated with occupational exposure to chlorinated benzenes, including 1,4 - dichlorobenzene (1,4-DCB) (Girard *et al*., 1969). One case of chronic lymphocytic leukemia involved exposure to a solvent mixture of 80% ortho-, 2% meta-, and 15% para-dichlorobenzene.   The association between leukemia and 1,4 - dichlorobenzene exposure was confounded by multiple chemical exposure.

Animal Studies

Loeser and Litchfield (1983) conducted a chronic inhalation carcinogenicity bioassay in male and female Alderly Park rats. In this study, groups of 76-79 rats were exposed to 0, 75, or 500 ppm p-DCB 5 hours/day, 5 days/week for 76 weeks. Control rats exhibited a high mortality rate and did not differ significantly from treated rats in overall tumor incidence (Table 1) or in the incidence of animals with multiple tumors and malignant tumors.

Table 1.   Tumor incidence in rats exposed to 1,4-dichlorobenzene (DCB) in air for 76 weeks (Loeser and Litchfield, 1983)

Concentration of 1,4-DCB	Combined Tumors (males)	Combined Tumors (females)
0 ppm	39/60	55/61
75 ppm	31/60	54/61
500 ppm	35/60	53/58

A parallel experiment was conducted using groups of 75 Swiss mice of either sex (Loeser and Litchfield, 1983). In this experiment, female mice were exposed to 0, 75, or 500 ppm 1,4 – DCB for 5 hours/day, 5 days/week, for 57 weeks. A similar experiment in male mice was terminated due to high mortality due to fighting and respiratory infections. As with the rats, no significant increase in any tumor type was detected.

The National Toxicology Program (NTP, 1987) studied the carcinogenicity of 1,4 - DCB in male and female F344 rats and B6C3F1 mice via chronic (103 week) oral intubation. Male rats were given 0, 150, or 300 mg/kg 1,4 - DCB for 5 days/week for 103 weeks. Male and female mice, and female rats were given 0, 300, or 600 mg/kg for the same duration. Sentinel animals were killed periodically to test for infectious pathogenic agents. The survival of male rats given 300 mg/kg was significantly lower than controls after 97 weeks, but the survival of treated female rats was unchanged from controls. The time-weighted average doses in the study were 0, 214, and 428 mg/kg/day for the mice, and 0, 107, and 214 mg/kg/day for the rats. Male rats treated with 1,4-DCB displayed nephropathy and mineralization and hyperplasia of renal tubules. The incidence of renal tubular adenocarcinomas was also dose-dependently increased in the male rats (1/50, 3/50, or 7/50 for the 0, 107, or 214 mg/kg groups, respectively). A significant dose-dependent increase in the incidence of mononuclear cell leukemia (5/50, 7/50, or 11/50 for the 0, 107, or 214 mg/kg groups, respectively) was observed in the male rats. Additionally, an increasing trend in the incidence of mesothelioma was observed in the male rats (1/50, 0/50, 4/50, for the 0, 107, or 214 mg/kg groups, respectively).

Mice of both sexes exposed to 1,4 - DCB had significantly increased incidence of hepatocellular adenomas and carcinomas (NTP, 1987). In addition, four male mice exposed to 428 mg/kg were found to have hepatoblastomas, a rare hepatocellular carcinoma. The incidence of follicular thyroid cell adenomas was increased in female mice exposed to 428 mg/kg ($p < 0.038$). As with the male rats, male mice showed evidence of kidney tubule damage when treated with 1,4 - DCB. Females were not similarly affected.

NTP concluded from these data that 1,4 - DCB was carcinogenic to male rats, but not female rats. In addition, NTP concluded that the increased incidence of hepatocellular adenomas and carcinomas was evidence of carcinogenicity in male and female mice.

IV.   DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by NTP (1987) was chosen by CDHS (1988) as the key study for the development of a cancer potency value for 1,4-DCB. In the NTP (1987) study, mice and rats exhibited significant increases in several types of tumors. The mice were exposed for 5 days/week, resulting in average daily doses of 0, 214, and 428 mg/kg/day 1,4-DCB. Mice of either sex exhibited a significant increase in hepatocellular carcinomas or adenomas. The incidence of hepatocarcinomas or adenomas was 17/50, 22/49, and 40/50 in the control, 214, and 428 mg/kg/day groups, respectively. In addition, male rats

showed a significant increase in kidney adenomas and mononuclear cell leukemia. The cancer potency for 1,4-DCB was calculated from the male mouse hepatocarcinoma and adenoma data.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of 1,4-DCB from the NTP (1987) data in male B6C3F1 mice (Crump *et al.*, 1982). The concentrations of 1,4-DCB given in the feed were 0, 214, or 428 mg/kg/day. The premature mortality of animals without tumors was subtracted from the sample groups. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 0.04 $[mg/kg\text{-}day]^{-1}$ was calculated (CDHS, 1988). An airborne unit risk factor of 1.1E-5 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

V.   REFERENCES

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ETHYLBENZENE

CAS No: 100-41-4

I.   PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 2003)

Molecular weight	106.2
Boiling point	136.2°C
Melting point	-94.9°C
Vapor pressure	9.6 mm Hg @ 25°C
Air concentration conversion	1 ppm = 4.35 mg/m^3 @ 25°C

II.   HEALTH ASSESSMENT VALUES

Unit Risk: 2.5×10^{-6} (µg/m^3)$^{-1}$
Inhalation Cancer Potency: 0.0087 (mg/kg-day)$^{-1}$
Oral Cancer Potency: 0.011 (mg/kg-day)$^{-1}$
[Calculated from male rat renal tumor data (NTP, 1999), using the linearized multistage (LMS) methodology with lifetime weighted average (LTWA) doses (OEHHA, 2007).

III.   METABOLISM and CARCINOGENIC EFFECTS

Metabolism

Ethylbenzene is rapidly and efficiently absorbed in humans via the inhalation route (ATSDR, 1999). Human volunteers exposed for 8 hours to 23-85 ppm retained 64% of inspired ethylbenzene vapor (Bardodej and Bardodejova, 1970). Gromiec and Piotrowski (1984) observed a lower mean uptake value of 49% with similar ethylbenzene exposures. There are no quantitative oral absorption data for ethylbenzene or benzene in humans but studies with [^{14}C]-benzene in rats and mice indicate gastrointestinal absorption in these species was greater than 97% over a wide range of doses (Sabourin *et al*., 1987).
Most of the metabolism of ethylbenzene is governed by the oxidation of the side chain (Fishbein, 1985). Engstrom (1984) studied the fate of ethylbenzene in rats exposed to 300 or 600 ppm (1305 or 2610 mg/m^3) ethylbenzene for six hours. Engstrom assumed 60 percent absorption of inhaled ethylbenzene and calculated that 83% of the 300 ppm dose was excreted in the urine within four hours of exposure. At the higher exposure of 600 ppm only 59 percent of the dose was recovered in the urine within 48 hr of exposure. Fourteen putative ethylbenzene metabolites were identified in the urine of exposed rats. The principal metabolites were 1-phenylethanol, mandelic acid, and benzoic acid. Metabolism proceeded mainly through oxidation of the ethyl moiety with ring oxidation appearing to play a minor role. Other metabolites included acetophenone, ω-hydroxyacetophenone, phenylglyoxal, and 1-phenyl-1, 2-ethandiol. Ring oxidation products include p-hydroxy- and m-hydroxyacetophenone, 2-ethyl- and 4-ethylphenol. With the exception of 4-hydroxyacetophenone all these other metabolites were seen only in trace amounts.

The metabolism of ethylbenzene was studied in humans (number unstated) exposed at 23 to 85 ppm (100 to 370 mg/m^3) in inhalation chambers for eight hours (Bardodej and Bardodejova, 1970). About 64 percent of the vapor was retained in the respiratory tract and only traces of ethylbenzene were found in expired air after termination of exposure. In 18 experiments with ethylbenzene, the principal metabolites observed in the urine were: mandelic acid, 64%; phenylglyoxylic acid, 25%; and 1-phenylethanol, 5%.

Engstrom *et al.* (1984) exposed four human male volunteers to 150 ppm ethylbenzene (653 mg/m^3) for four hours. Urine samples were obtained at two-hr intervals during exposure and periodically during the next day. For the 24-hr urine the metabolites were: mandelic acid, 71.5 ± 1.5%; phenylglyoxylic acid, 19.1 ± 2.0%; 1-phenylethanol, 4.0 ± 0.5%; 1-phenyl-1, 2-ethanediol, 0.53 ± 0.09%; acetophenone, 0.14 ± 0.04%; ω-hydroxyacetophenone, 0.15 ± 0.05%; m-hydroxyacetophenone, 1.6 ± 0.3%; and 4-ethylphenol, 0.28 ± 0.06%. A number of the hydroxy and keto metabolites were subject to conjugation. Differences were observed between the concentrations obtained with enzymatic and acid hydrolysis. For example, 50% of maximal yield of 4-ethylphenol was obtained with glucuronidase or acid hydrolysis and 100% with sulfatase indicating the presence of glucuronide and sulfate conjugates of this metabolite. Alternatively, acetophenone gave only 30-36% yield with enzymatic treatment but 100% with acid hydrolysis indicating the presence of other conjugates not susceptible to glucuronidase or sulfatase. The metabolic scheme proposed by Engstrom *et al.* (1984) is shown with modifications in Figure 1. The metabolism of ethylbenzene is similar in several respects to benzene in that benzene produces phenol, catechols and hydroquinone metabolites. As noted below these metabolites and their ethyl analogs participate in redox cycles generating the reactive oxygen species hydrogen peroxide, superoxide, and hydroxyl radical.

Gromiec and Piotrowski (1984) measured ethylbenzene uptake and excretion in six human volunteers exposed at concentrations of 18 to 200 mg/m^3 for eight hours. Average retention of ethylbenzene in the lungs was 49 ± 5% and total excreted mandelic acid accounted for 55 ± 2% of retained ethylbenzene.

Tardif *et al.* (1997) studied physiologically-based pharmacokinetic (PBPK) modeling of ternary mixtures of alkyl benzenes including ethylbenzene in rats and humans. As part of this investigation they determined Vmax and Km kinetic parameters for the rat by best fit of model simulations to the time-course data on the venous blood concentrations of ethylbenzene following single exposures. The maximal velocity (Vmax) was 7.3 mg/hr-kg body weight and the Michaelis-Menten affinity constant (Km) was 1.39 mg/L. For the human PBPK model the Vmax value from the rat was scaled on the basis of (body weight)$^{0.75}$. All other chemical and metabolic parameters were unchanged.
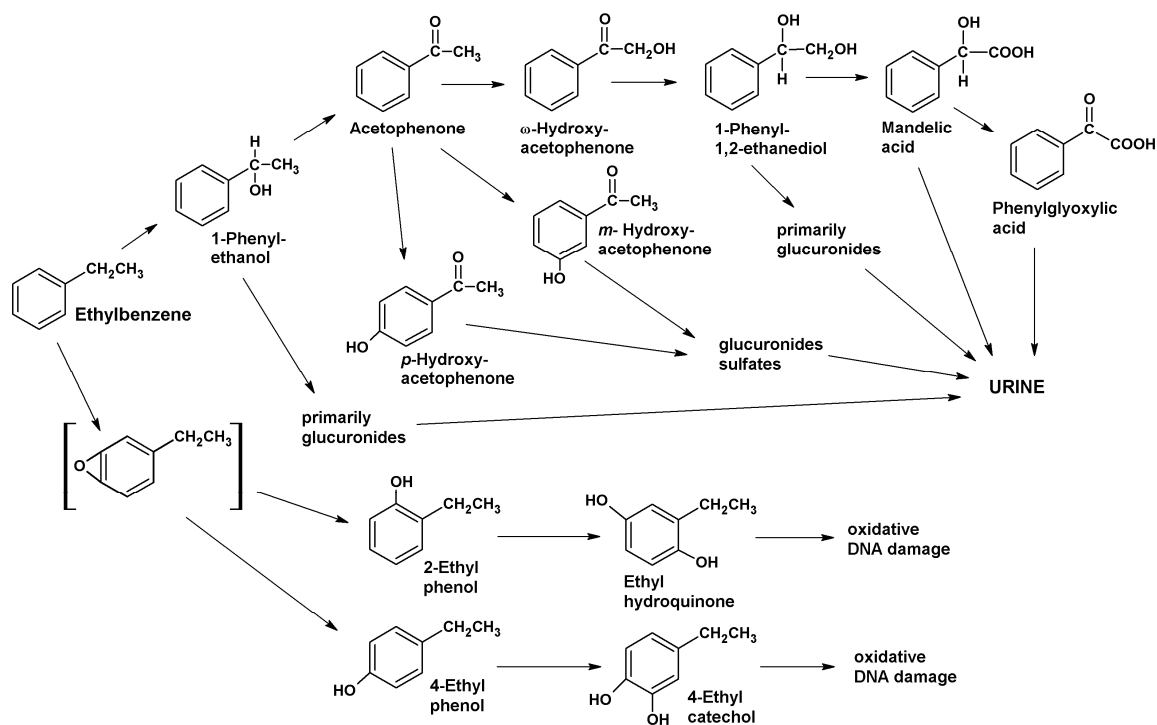
Figure 1. Ethylbenzene Metabolism (modified from Engstrom *et al.*, 1984).

The scaling of rodent metabolism of alkylbenzenes to humans was evaluated using kinetic data in an exposure study with human volunteers. Four adult male subjects (age, 22-47; body weight, 79-90 kg) were exposed to 33 ppm ethylbenzene for 7 hr/d in an exposure chamber. Urine samples were collected during (0-3 hr) and at the end (3-7 hr) of exposure and following exposure (7-24 hr). For the 0-24 hr collections mandelic acid amounted to 927 ± 281 μmol and phenylglyoxylic acid 472 ± 169 μmol. Venous blood (5.5 to 8 hr) and expired air (0.5 to 8 hr) were also measured in the subjects and exhibited good correspondence with PBPK model predictions. It is interesting that the metabolism of ethylbenzene in these human subjects was not significantly affected by simultaneous exposure to the other alkyl benzenes (toluene and xylene) studied. The metabolic parameters for ethylbenzene used by Haddad *et al.* (2001) and in the internal dosimetry modeling presented below were based on this study.

The oxidation of ethylbenzene to 1-phenylethanol by human liver microsomes and recombinant human cytochrome P450s was investigated by Sams *et al.* (2004). Human liver microsomes from seven subjects (four male, three female, age 37-74) and microsomes expressing recombinant human CYP1A2, 2A6, 2B6, 2C9*1(Arg144), 2C19, 2D6, 2E1, and 3A4 co-expressed with cytochrome P450 reductase/cytochrome b5 were both obtained from commercial sources. Kinetic experiments were conducted with microsomes and ethylbenzene over a 10-5000 μ*M* substrate concentration range. For chemical inhibition experiments, selective inhibitors of specific CYP isoforms were used to obtain maximum inhibition of the target CYP with minimum effect on other CYPs. Eadie-Hofstee plots (V vs. V/S) indicated that the reaction of ethylbenzene to 1-phenylethanol with human liver microsomes was biphasic with low and high affinity

components. The Michaelis-Menten equation was fit to the data and kinetic constants obtained by regression analysis. One microsome preparation was found to give a noticeably less curved Eadie-Hofstee plot and metabolized ethylbenzene at a much higher rate than the other preparations (Vmax = 2922 pmol/min/mg). It was excluded from the statistical analysis. For the high affinity reaction the mean Vmax was 689 ± 278 pmol/min/mg microsomal protein and the Km = 8.0 ± 2.9 μM (n = 6). For the low affinity reaction the Vmax was 3039 ± 825 pmol/min/mg and Km = 391 ± 117 μM (n = 6). The intrinsic clearance values of Vmax/Km were 85.4 ± 15.1 and 8.3 ± 3.0 for the high and low affinity reactions, respectively. The high affinity component of pooled human liver microsomes was inhibited 79%-95% by diethyldithiocarbamate, and recombinant CYP2E1 metabolized ethylbenzene with a low Km of 35 μM and low Vmax of 7 pmol/min/pmol P450 indicating that the CYP2E1 isoform catalyzed this component. Recombinant CYP1A2 and CYP2B6 exhibited high Vmaxs (88 and 71 pmol/min/pmol P450, respectively) and Km's (502 and 219 μM, respectively), indicating their role in the low affinity component. The mean Vmax and Km values above were used by OEHHA in addition to those from Haddad *et al.* (2001) in our human PBPK modeling of ethylbenzene.

Charest-Tardif *et al*. (2006) characterized the inhalation pharmacokinetics of ethylbenzene in male and female B6C3F1 mice. Initially groups of animals were exposed for four hr to 75, 200, 500 or 1000 ppm ethylbenzene. Subsequently groups of animals were exposed for six hr to 75 and 750 ppm for one or seven consecutive days. The maximum blood concentration (Cmax, mean (± SD), n = 4) observed after four hr exposure to 75, 200, 500 and 1000 ppm was 0.53 (0.18), 2.26 (0.38), 19.17 (2.74), and 82.36 (16.66) mg/L, respectively. The blood AUCs were 88.5, 414.0, 3612.2, and 19,104.1 (mg/L)-min, respectively, in female mice, and 116.7, 425.7, 3148.3, 16039.3 (mg/L)-min, respectively in male mice. The comparison of Cmax and kinetics of ethylbenzene in mice exposed to 75 ppm indicated similarity between 1 and 7-day exposures. However, at 750 ppm elimination of ethylbenzene appeared to be greater after repeated exposures. Overall, the single and repeated exposure PK data indicate that ethylbenzene kinetics is saturable at exposure concentrations above 500 ppm but is linear at lower concentrations.

Backes *et al*. (1993) demonstrated that alkylbenzenes with larger substituents (e.g., ethylbenzene, m-, p-xylene, n-propylbenzene) were effective inducers of microsomal enzymes compared to those with no or smaller substituents (benzene, toluene). Cytochrome P450 2B1 and 2B2 levels were induced with the magnitude of induction increasing with hydrocarbon size. P450 1A1 was also induced but less than 2B. A single intraperitoneal (i.p.) dose of 10 mmol/kg in rats was selected for optimum induction response with no overt toxic effects.

Bergeron *et al*. (1999) using the same daily dose of ethylbenzene for up to ten days observed changes in expression of CYP 2B1, 2B2, 2E1, and 2C11. While CYP 2C11 and 2E1 were attenuated by repeated dosing of ethylbenzene, CYP 2Bs were elevated after initial dosing despite the absence of detectable 2B1 or 2B2 mRNA. The authors interpreted this observation as the initial ethylbenzene dose leading to an increase in

ethylbenzene clearance and an overall decrease in tissue ethylbenzene levels with repeated dosing and decreased induction effectiveness.

Serron *et al*. (2000) observed that treatment of rats with ethylbenzene (i.p., 10 mmol/kg) led to increased free radical production by liver microsomes compared to corn oil controls. Oxygen free radical generation was measured *in vitro* by conversion of 2', 7'-dichlorofluorescein diacetate (DCFH-DA) to its fluorescent product 2', 7'-dichlorofluorescein (DCF). A significant elevation (40%) of DCF was seen despite lack of effect on overall P450 levels. The DCF product formation was inhibited by catalase but not by superoxide dismutase suggesting a H_2O_2 intermediate. Anti-CYP2B antibodies inhibited DCF production indicating involvement of CYP2B. As noted above ethylbenzene treatment induces increased production of CYP2B.

While the doses in these studies were quite high at over 1000 mg/kg-d by the intraperitoneal route, earlier studies by Elovaara *et al*. (1985) showed P450 induction in livers of rats exposed to 50, 300 and 600 ppm (218, 1305 and 2610 mg/m^3) for 6 hours/day, 5 days/week for up to 16 weeks. So it is possible that the types of effects discussed above, notably the production of reactive oxygen species via induced CYP 2B, may have occurred during the cancer bioassays.

Genotoxicity

In vitro and *in vivo* animal studies

Ethylbenzene has been tested for genotoxicity in a variety of *in vitro* and *in vivo* genotoxicity assays. Those studies have been reviewed by ATSDR (1999). Ethylbenzene has not demonstrated genotoxicity in *Salmonella* reverse mutation assays. Those studies are listed in Table 1. All studies were performed in the presence and absence of metabolic activation (rat liver S9), and were negative. It has not been tested in strains sensitive to oxidative DNA damage.

Table 1.   Ethylbenzene *Salmonella* reverse mutation studies

Test strains	Reference
TA98, TA100, TA1535, TA1537	Florin *et al*., 1980
TA98, TA100, TA1535, TA1537, TA1538	Nestmann *et al*., 1980
TA98, TA100, TA1535, TA1537, TA1538	Dean *et al*., 1985
TA97, TA98, TA100, TA1535	NTP, 1986
TA97, TA98, TA100, TA1535	NTP, 1999
TA98, TA100	Kubo *et al*., 2002

Ethylbenzene also did not induce mutations in the WP2 and WP2uvrA strains of *Escherichia coli* in the presence and absence of metabolic activation (Dean *et al*., 1985), or in *Saccharomyces cerevisiae* strains JDl (Dean *et al*., 1985), XVl85-14C, and D7 as measured by gene conversion assays (Nestmann and Lee, 1983).

Ethylbenzene has been observed to induce mutations in L5178Y mouse lymphoma cells at the highest nonlethal dose tested (80 μg/mL) (McGregor *et al.*, 1988; NTP, 1999). However, NTP noted significant cytotoxicity at this dose level (relative total growth was reduced to 34% and 13% of the control level in each of two trials).

Data on the ability of ethylbenzene to induce chromosomal damage in non-human mammalian cells are negative. Ethylbenzene did not cause chromosomal damage in rat liver epithelial-like (RL4) cells (Dean *et al.*, 1985). Additionally, ethylbenzene did not induce an increase in either sister chromatid exchanges (SCE) or chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence or absence of metabolic activation (NTP 1986, 1999).

The frequency of micronucleated erythrocytes in bone marrow from male NMRI mice exposed to ethylbenzene by intraperitoneal injection was not significantly increased compared to controls (Mohtashamipur *et al.*, 1985). Additionally, ethylbenzene did not increase the frequency of micronucleated erythrocytes in peripheral blood from male and female B6C3F$_1$ mice treated for 13 weeks with ethylbenzene (NTP, 1999).

Midorikawa *et al* (2004) reported oxidative DNA damage induced by the metabolites of ethylbenzene, namely ethylhydroquinone and 4-ethylcatechol. Ethylbenzene was metabolized to 1-phenylethanol, acetophenone, 2-ethylphenol, and 4-ethylphenol by rat liver microsomes *in vitro*. 2-Ethylphenol and 4-ethylphenol were ring-dihydroxylated to ethylhydroquinone (EHQ) and 4-ethylcatechol (EC). These dihydroxylated metabolites induced DNA damage in ^{32}P-labeled DNA fragments from the human p53 tumor suppressor gene and induced the formation of 8-oxo-7, 8-dihydro-2'-deoxyguanosine in calf thymus DNA in the presence of Cu2+. Addition of exogenous NADH enhanced EC-induced oxidative DNA damage but had little effect on EHQ action. The authors suggest that Cu+ and H$_2$O$_2$ produced via oxidation of EHQ and EC were involved in oxidative DNA damage. NADH enhancement was attributed to reactive species generated from the redox cycle of EC → 4-ethyl-1, 2-benzoquinone → EC. The NADH-mediated conversion of 4-Ethyl-1, 2-benzoquinone appears to be the result of a two electron reduction which accelerates the redox reaction, resulting in enhanced DNA damage (Figure 2).

Similar effects of NADH were observed with benzene metabolites benzoquinone (BQ) and catechol (Hirakawa *et al.* 2002). In the presence of Cu^{2+} and endogenous NADH, catechol (1,2-BQH$_2$) induced more DNA damage than 1,4-BQH$_2$. In the absence of NADH the DNA damaging activities were reversed. In both cases, DNA damage resulted from base modification at guanine and thymine residues in addition to DNA strand breaks by Cu$^+$ and H$_2$O$_2$ generated during the oxidation of 1,2-BQH$_2$ and 1,4-BQH$_2$ to 1,2_BQ and 1,4-BQ, respectively (Hirakawa *et al.*, 2002). The authors noted that NADH consumption in the presence of 1,2-BQH$_2$/1,2-BQ was faster than that in the 1,4-BQH$_2$/1,4-BQ system. The results suggest that the structure of 1,2-BQ may facilitate the two-electron reduction by NADH better than 1,4-BQ. Thus, the reduction of 1,2-BQ accelerates the turnover rate of the redox cycle in 1,2-BQH$_2$/1,2-BQ greater than in 1,4-BQH$_2$/1,4-BQ. The authors conclude that "…the NADH-dependent redox cycle may
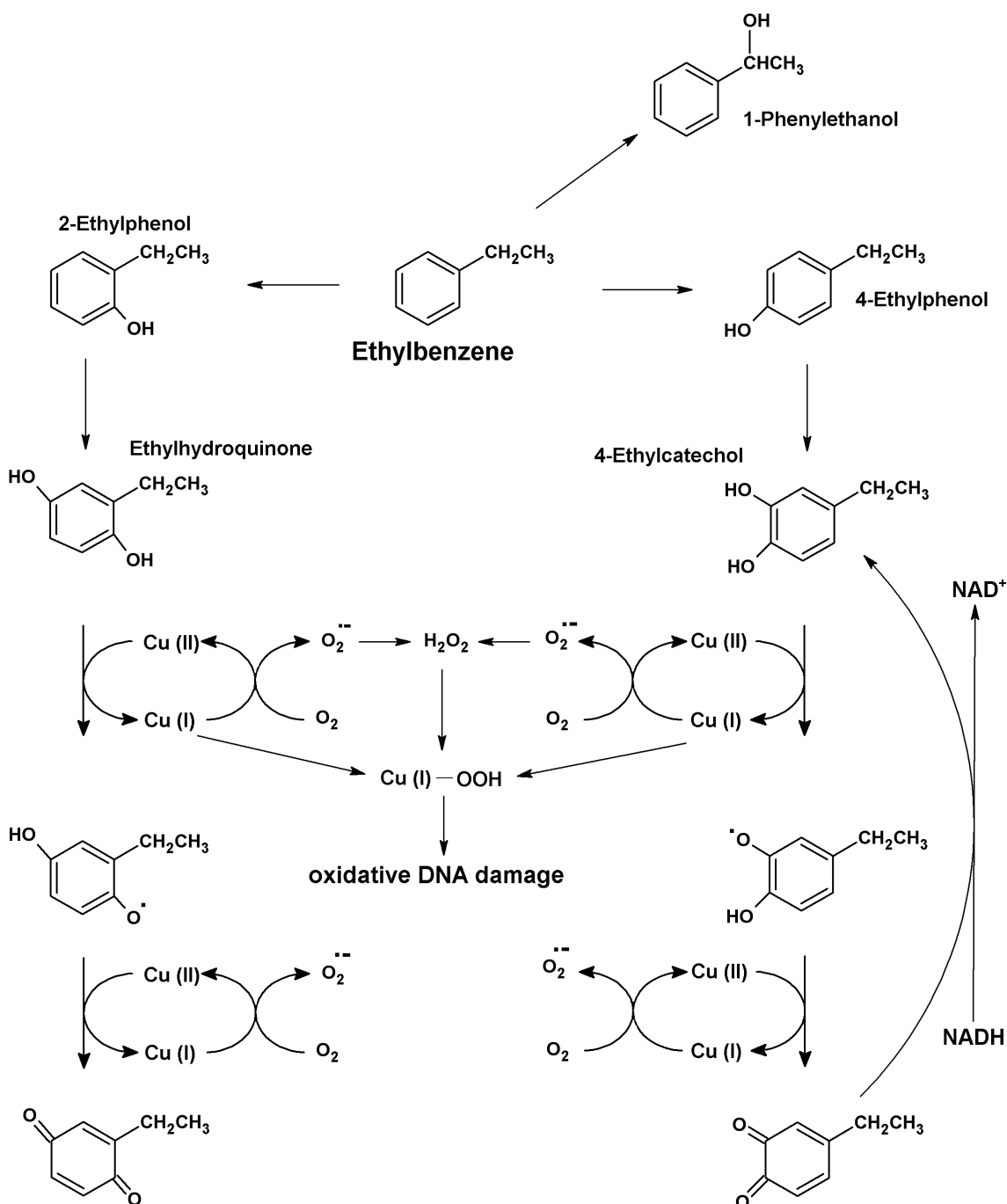
Figure 2. Possible mechanism of oxidative DNA damage induced by EHQ and EC. (Adapted from Midorikawa *et al.*, 2004)

continuously generate reactive oxygen species, resulting in the enhancement of oxidative DNA damage. NADH, a reductant existing at high concentrations (100- 200 µM) in certain tissues, could facilitate the NADH-mediated DNA damage observed in this study under physiological conditions."(Hirakawa *et al.*, 2002).

Similar reactions were also observed with methylcatechols, toluene metabolites that participated in Cu^{2+}-mediated DNA damage, which was enhanced by NADH compared with methylhydroquinone (Nakai *et al*., 2003; Murata *et al*., 1999).

In vitro and *in vivo* human studies

Norppa and Vainio (1983) exposed human peripheral blood lymphocytes to ethylbenzene in the absence of metabolic activation. The authors reported that ethylbenzene induced a marginal increase in SCEs at the highest dose tested, and that the increase demonstrated a dose-response.

Holz *et al*. (1995) studied genotoxic effects in workers exposed to volatile aromatic hydrocarbons (styrene, benzene, ethylbenzene, toluene and xylenes) in a styrene production plant. Peripheral blood monocytes were assayed for DNA adducts using a nuclease P1-enhanced ^{32}P-postlabeling assay, and DNA single strand breaks, SCEs and micronuclei frequencies in peripheral blood lymphocytes were determined in workers and controls. No significant increases in DNA adducts, DNA single strand breaks, SCEs or total micronuclei were noted in exposed workers. Significantly increased kinetochore-positive micronuclei (suggestive of aneuploidy-induction) were noted in total exposed workers, exposed smokers, and exposed non-smokers. However, the mixed exposures made it impossible to ascribe the kinetochore-positive micronuclei increase in exposed workers solely to ethylbenzene exposure.

The effects of benzene and ethylbenzene exposure on chromosomal damage in exposed workers were examined by Sram *et al*. (2004). Peripheral blood lymphocytes from exposed workers and controls were analyzed for chromosomal aberrations. Exposure to ethylbenzene resulted in a significant increase in chromosomal aberrations. A reduction in ethylbenzene concentration due to improved workplace emissions controls resulted in a reduction in chromosomal damage in exposed workers. However, these workers were also exposed to benzene, making it impossible to determine if the chromosomal damage was due to ethylbenzene alone.

Ethylbenzene sunlight-irradiation products

Toda *et al*. (2003) found that sunlight irradiation of ethylbenzene resulted in the formation of ethylbenzene hydroperoxide (EBH). EBH induced oxidative DNA damage in the presence of Cu^{2+} as measured by the formation of 8-hydroxy-deoxyguanosine (8-OH-dG) adducts in calf thymus DNA. The Cu^{2+}-specific chelator bathocuproine strongly inhibited EBH-induced oxidative DNA damage. Superoxide dismutase (catalyzes superoxide decomposition) partly inhibited 8-OH-dG adduct formation, and catalase (catalyzes hydrogen peroxide decomposition) slightly inhibited 8-OH-dG adduct formation.

Summary of ethylbenzene genotoxicity

The above data indicate that ethylbenzene generally has not been demonstrated to induce gene mutations or chromosomal damage in bacteria, yeast or non-human mammalian cells, with the exception of positive results in the L5178Y mouse lymphoma cell mutation assay at concentrations producing significant cytotoxicity (McGregor *et al.*, 1988; NTP, 1999). Data on the genotoxicity of ethylbenzene in humans is mixed (Norppa and Vainio, 1983; Holz *et al.*, 1995; Sram *et al.*, 2004), and interpretation of the epidemiological studies is made difficult because of confounding due to coexposures to other chemicals, including benzene. Ethylbenzene has been demonstrated to generate reactive oxygen species in liver microsomes from exposed rats (Serron *et al.*, 2000), and ethylbenzene hydroperoxide (a sunlight-irradiation product) has been demonstrated to induce oxidative DNA damage in calf thymus DNA *in vitro* (Toda *et al.*, 2003). The ethylbenzene metabolites EHQ and EC have demonstrated the ability to induce oxidative DNA damage in human DNA *in vitro* (Midorikawa *et al.*, 2004).

Animal Cancer Bioassays

Maltoni *et al.* (originally reported in 1985; additional information published in 1997) studied the carcinogenicity of ethylbenzene in male and female Sprague-Dawley rats exposed via gavage. The authors reported an increase in the percentage of animals with malignant tumors associated with exposure to ethylbenzene. In animals exposed to 800 mg/kg bw ethylbenzene, Maltoni *et al.* (1997) reported an increase in nasal cavity tumors, type not specified (2% in exposed females versus 0% in controls), neuroesthesioepitheliomas (2% in exposed females versus 0% in controls; 6% in exposed males versus 0% in controls), and oral cavity tumors (6% in exposed females versus 2% in controls; 2% in exposed males versus 0% in controls). These studies were limited by inadequate reporting and were considered inconclusive by NTP (1999) and IARC (2000).

The National Toxicology Program (NTP, 1999; Chan *et al.*, 1998) conducted inhalation cancer studies of ethylbenzene using male and female F344/N rats and B6C3F$_1$ mice. Groups of 50 animals were exposed via inhalation to 0, 75, 250 or 750 ppm ethylbenzene for 6.25 hours per day, 5 days per week for 104 (rats) or 103 (mice) weeks.

Survival probabilities were calculated by NTP (1999) using the Kaplan-Meier product-limit procedure. For male rats in the 75 ppm and 250 ppm exposure groups, survival probabilities at the end of the study were comparable to that of controls but significantly less for male rats in the 750 ppm exposure group (30% for controls and 28%, 26% and 4% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). NTP (1999) stated that the mean body weights of the two highest exposure groups (250 and 750 ppm) were "generally less than those of the chamber controls from week 20 until the end of the study." Expressed as percent of controls, the mean body weights for male rats ranged from 97 to 101% for the 75 ppm group, 90 to 98% for the 250 ppm group, and 81 to 98% for the 750 ppm group.

In female rats, survival probabilities were comparable in all groups (62% for controls and 62%, 68% and 72% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). NTP (1999) reported that the mean body weights of exposed female rats were "generally less than those of chamber controls during the second year of the study." Expressed as percent of controls, the mean body weights for female rats ranged from 92 to 99% for the 75 ppm group, 93 to 100% for the 250 ppm group, and 92 to 99% for the 750 ppm group.

The incidences of renal tumors (adenoma and carcinoma in males; adenoma only in females) were significantly increased among rats of both sexes in the high-dose group (males: 3/50, 5/50, 8/50, 21/50; females: 0/50, 0/50, 1/50, 8/49 in control, 75 ppm, 250 ppm and 750 ppm groups respectively [standard and extended evaluations of kidneys combined]). The incidence of testicular adenomas (interstitial and bilateral) was significantly elevated among high-dose male rats (36/50, 33/50, 40/50, 44/50 in control, 75 ppm, 250 ppm and 750 ppm groups respectively). NTP noted that this is a common neoplasm, which is likely to develop in all male F344/N rats that complete a natural life span; exposure to ethylbenzene "appeared to enhance its development." NTP concluded that there was clear evidence of carcinogenicity in male rats and some evidence in female rats, based on the renal tumorigenicity findings.

The survival probabilities at the end of the study for exposed male mice were comparable to that of controls (57% for controls and 72%, 64% and 61% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). The same was true for exposed female mice (survival probabilities at end of study: 71% for controls and 76%, 82% and 74% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). Mean body weights in exposed male mice were comparable to those of controls. NTP (1999) reported that the mean body weights in exposed female mice were greater in the 75 ppm group compared to controls after week 72, and generally lower in the 750 ppm group compared to controls from week 24 through week 68. Expressed as percent of controls, the ranges of mean body weights in exposed female mice were 96 to 110% in the 75 ppm group, 93 to 108% in the 250 ppm group, and 92 to 101% in the 750 ppm group.

Increased incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were observed in male mice in the high-dose group (7/50, 10/50, 15/50, 19/50 in control, 75 ppm, 250 ppm and 750 ppm groups respectively). Among female mice in the high-dose group, the incidences of combined hepatocellular adenoma or carcinoma and hepatocellular adenoma alone were significantly increased over control animals (for adenomas and carcinomas the tumor incidences were 13/50, 12/50, 15/50, 25/50 in control, 75 ppm, 250 ppm and 750 ppm groups, respectively). NTP (1999) concluded that these findings provided some evidence of carcinogenicity in male and female mice.

Human Studies of Carcinogenic Effects

Studies on the effects of workplace exposures to ethylbenzene have been complicated by concurrent exposures to other chemicals, such as xylenes and benzene. IARC (2000)

concluded that there was inadequate evidence in humans for the carcinogenicity of ethylbenzene.

Mode of Action for Ethylbenzene carcinogenesis

A mode of action (MOA) is a clear explanation of the critical events in an agent's influence on the development of tumors. An MOA analysis includes physical, chemical, and biological information and the entire range of information developed in the assessment contributes to a reasoned judgement concerning the plausibility of potential MOAs (U.S.EPA, 1996). An agent may work by more than one MOA at different sites and at the same tumor site. Inputs into an MOA analysis include tumor data in humans, animals, and in structural analogs, genetic toxicity and other key data e.g. on metabolites, DNA or protein adducts, oncogene activation and shape of the dose response. In any event conflicting data and data gaps often require careful evaluation before reaching any conclusions with respect to a prospective MOA (U.S.EPA, 1996).

OEHHA has not determined a convincing mode of action (MOA) for any of the tumor sites evaluated in this report. Various MOAs have been suggested for the tumors induced by ethylbenzene in rodent species. For instance it has been hypothesized that rat kidney tumor incidence increases are the result of ethylbenzene or its metabolites increasing the incidence and/or severity of chronic progressive nephropathy (CPN), a common process in aged control rats (Hard, 2002). However, OEHHA and others (Seely *et al*., 2002) have found no basis to support a conclusion that the sole or primary cause of the kidney tumors is exacerbation of CPN. Similarly, it has been suggested that an increase in eosinophilic foci in the liver, possibly associated with induction of cytochrome P450 enzymes, is involved in the mechanism of production of the liver tumors. In fact, the data from which a correlation between liver eosinophilic foci and liver tumors was inferred are not consistent or convincing in this respect. Moreover, such MOAs have not been adequately elucidated with respect to their quantitative dose-response relations, or how significant they are with respect to other MOAs, possibly involving genotoxicity, which may also be operating.

A proposed MOA for ethylbenzene-induced tumors, especially those in the mouse lung, involves the generation of quinone metabolites. This is analogous to the actions of styrene and naphthalene, which are also carcinogenic. OEHHA recognizes the plausibility of quinone metabolites participating in a potential MOA for ethylbenzene-induced lung cancer in mice (see *Genotoxicity* above). However, a suggestion that the role of these metabolites is confined to cytotoxicity (resulting in promotion of spontaneous tumors) is not convincing. The observation of oxidative DNA damage *in vitro* (Midorikawa *et al*., 2004) supports a role for quinone metabolites in carcinogenic initiation, following the analogy with benzene (a well-known genotoxic carcinogen targeting multiple sites in various species including humans). The observation of chromosomal damage in peripheral blood lymphocytes of workers exposed to ethylbenzene and benzene (Sram *et al*., 2004) may be indicative of quinone metabolite induced DNA damage. Thus, the involvement of quinone metabolites is plausible and supported by at least some data. Although this does not of itself establish the quantitative

nature of the dose-response relationship, a mechanism involving oxidative DNA damage might display low-dose linearity. Since ring oxidation may produce a genotoxic epoxide metabolite it is possible that more than one metabolic process which generates genotoxic intermediates may be operating. In our view the genotoxicity of ethylbenzene, particularly with respect to oxidative DNA effects, merits further investigation.

OEHHA therefore concludes that the limited data do not conclusively establish any particular MOA for ethylbenzene carcinogenesis. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction. Because of this, the default linear approach has been used for extrapolating the dose-response curve to low doses.

IV.   DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Unit risk values for ethylbenzene were calculated based on data in male and female rats and mice from the studies of NTP (1999) utilizing both linearized multistage and benchmark dose methods. The incidence data used to calculate unit risk values are listed below in Tables 2 thru 6. The methodologies for calculating average concentration, lifetime weighted average (LTWA) dose and PBPK adjusted internal dose are discussed below. An internal dose metric representing the amount of ethylbenzene metabolized per kg body weight per day (metabolized dose) was used in the dose response analysis with published PBPK modeling parameters. In addition, for the mouse, recent pharmacokinetic data simulating mouse bioassay conditions were used to improve PBPK model predictions (Tables 5 and 6).

The metabolized dose metric is considered the most appropriate metric for assessment of carcinogenic risks when the parent compound undergoes systemic metabolism to a variety of oxidative metabolites which may participate in one or more mechanisms of carcinogenic action, and the parent compound is considered unlikely to be active. In this case the dose response relation is likely to be more closely related to the internal dose of metabolites than of the parent compound. Other metrics commonly investigated using PBPK methods are the area under the concentration-time curve (AUC), and the maximum concentration (Cmax) for parent or metabolites in blood and target tissues. The PBPK metabolized dose metric was used in the ethylbenzene dose-response analysis.

Table 2.   Incidence of renal tubule adenoma or carcinoma in male rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance[e]	
				Quantal Response	%	Fisher Exact Test	TrendTest
0	0	0	0	3/42	7.1		
75	60.7	35.6	19.09	5/42	11.9	$p = 0.356$	$p < 0.001$
250	202	119	58.78	8/42	19.0	$p = 0.0972$	
750	607	356	124.26	21/36	58.3	$p < 0.001$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses determined by multiplying the lifetime average concentrations during the dosing period by the male rat breathing rate (0.264 m^3/day) divided by the male rat body weight (0.450 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. Effective rate. Animals that died before the first occurrence of tumor (day 572) were removed from the denominator. Total number of tumors/number of survivors.
e. The p-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The p-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 3.   Incidence of testicular adenoma in male rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance	
				Quantal Response	%	Fisher Exact Test[e]	Trend Test
0	0	0	0	36/48	75.0		
75	60.7	35.6	19.09	33/46	71.7	$p = 0.450$N	$p < 0.001$[f]
250	202	119	58.78	40/49	81.6	$p = 0.293$	$p = 0.010$[g]
750	607	356	124.26	44/47	93.6	$p < 0.05$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.

b. Lifetime weighted average doses determined by multiplying the lifetime average concentrations during the dosing period by the male rat breathing rate (0.264 m^3/day) divided by the male rat body weight (0.450 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.

c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.

d. Effective rate. Animals that died before the first occurrence of tumor (day 420) were removed from the denominator. Total number of tumors/number of survivors

e. The p-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. An "N" after the p-value signifies that the incidence in the dose group is lower than that in the control group.

f. Results of trend tests conducted by NTP (1999) using the life table and logistic regression tests.

g. Result of Cochran-Armitage trend test conducted by NTP (1999).

Table 4.   Incidence of renal tubule adenoma in female rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m³)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance[e]	
				Quantal Response	%	Fisher Exact Test	Trend Test
0	0	0	0	0/32	0		
75	60.7	41.6	21.60	0/35	0	--	$p < 0.001$
250	202	139	67.04	1/34	2.9	$p = 0.515$	
750	607	416	144.62	8/37	21.6	$p < 0.01$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m3/ppm.

b. Lifetime weighted average doses were determined by multiplying the lifetime average concentrations during the dosing period by the female rat-breathing rate (0.193 m3/day) divided by the female rat body weight (0.282 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.

c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.

d. Effective rate. Animals that died before the first occurrence of tumor (day 722) were removed from the denominator. Total number of tumors/number of survivors

e. The p-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The *p*-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 5.   Incidence of lung alveolar/bronchiolar carcinoma or adenoma in male mice exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	PBPK metabolized dose: Charest-Tardif[d] (mg/kg-d)	Tumor incidence[e]		Statistical significance[f]	
					Quantal Response	%	Fisher Exact Test	Trend Test
0	0	0	0	0	7/46	15.2		
75	60.7	69.3	40.40	46.60	10/48	20.8	$p = 0.331$	
250	202	231	89.38	152.8	15/50	30.0	$p = 0.0688$	$p = 0.004$
750	607	693	134.77	340.2	19/48	40.0	$p < 0.01$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses were determined by multiplying the average concentrations during the dosing period by the male mouse breathing rate (0.0494 m^3/day) divided by the male mouse body weight (0.0429 kg) and by 103 weeks/104 weeks to correct for less than lifetime exposure.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. PBPK metabolized dose based on published parameters from Charest-Tardif *et al.* (2006).
e. Effective rate. Animals that died before the first occurrence of tumor (day 418) were removed from the denominator. Total number of tumors/number of survivors.
f. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The *p*-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 6.   Incidence of liver hepatocellular carcinoma or adenoma in female mice exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	PBPK metabolized dose: Charest-Tardif[d] (mg/kg-d)	Tumor incidence[e] Quantal Response	%	Fisher Exact Test[f]	Trend Test
0	0	0	0	0	13/47	27.7		
75	60.7	71.6	41.53	47.98	12/48	25.0	$p = 0.479$N	$p = 0$[g]
250	202	239	91.22	157.3	15/47	31.9	$p = 0.411$	$p = 0.002$[h]
750	607	716	136.68	348.1	25/48	52.1	$p < 0.05$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses were determined by multiplying the average concentrations during the dosing period by the female mouse breathing rate (0.0463 m^3/day) divided by the female mouse body weight (0.0389 kg) and by 103 weeks/104 weeks to correct for less than lifetime exposure.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. PBPK metabolized dose based on published parameters from Charest-Tardif *et al*. (2006).
e. Effective rate. Animals that died before the first occurrence of tumor (day 562) were removed from the denominator. Total number of tumors/number of survivors.
f. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. An "N" after the *p*-value signifies that the incidence in the dose group is lower than that in the control group.
g. Result of trend test conducted by NTP (1999) using the life table method.
h. Results of trend tests conducted by NTP (1999) using the logistic regression and Cochran-Armitage trend tests.

Methodology

Linearized Multistage Approach

The default approach, as originally delineated by CDHS (1985), is based on a linearized form of the multistage model of carcinogenesis (Armitage and Doll, 1954). Cancer potency is estimated from the upper 95% confidence limit, q_1^*, on the linear coefficient q_1 in a model relating lifetime probability of cancer (*p*) to dose (d):

$$p = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)] \qquad (1)$$

with constraints, $q_i \geq 0$ for all i. The default number of parameters used in the model is n, where n is the number of dose groups in the experiment, with a corresponding polynomial degree of n-1.

The parameter q_1^* is estimated by fitting the above model to dose response data using MSTAGE (Crouch, 1992). For a given chemical, the model is fit to one or more data sets. The default approach is to select the data for the most sensitive species and sex.

To estimate animal potency, q_{animal}, when the experimental exposure is less than lifetime the parameter q_1^* is adjusted by assuming that the lifetime incidence of cancer increases with the third power of age. The durations of the NTP experiments were at least as long as the standard assumed lifetime for rodents of 104 weeks, so no correction for short duration was required.

Benchmark Dose Methodology

U.S. EPA (2005) and others (*e.g.* Gaylor *et al.*, 1994) have more recently advocated a benchmark dose method for estimating cancer risk. This involves fitting a mathematical model to the dose-response data. A linear or multistage procedure is often used, although others may be chosen in particular cases, especially where mechanistic information is available which indicates that some other type of dose-response relationship is expected, or where another mathematical model form provides a better fit to the data. A point of departure on the fitted curve is defined: for animal carcinogenesis bioassays this is usually chosen as the lower 95% confidence limit on the dose predicted to cause a 10% increase in tumor incidence (LED_{10}). Linear extrapolation from the point of departure to zero dose is used to estimate risk at low doses either when mutagenicity or other data imply that this is appropriate, or in the default case where no data on mechanism are available. The slope factor thus determined from the experimental data is corrected for experimental duration in the same way as the q_1^* adjustments described for the linearized multistage procedure. In the exceptional cases where data suggesting that some other form of low-dose extrapolation is appropriate, a reference dose method with uncertainty factors as required may be used instead.

The quantal tumor incidence data sets were analyzed using the BMDS software (version 1.3.2) of U.S.EPA (2000). In general the program models were fit to the data with the X^2 fit criterion $\geq$ 0.1. In those cases when more than one model gave adequate fit the model that gave the best fit in the low dose region (visually and by X^2 residual) was chosen for the LED_{10} estimation.

Implementation of LMS and BMD Methodology

The linearized multistage approach and the benchmark dose methodology were both applied to the tumor incidence data for ethylbenzene in the NTP (1999) studies. No nonlinear mode of carcinogenic action has been established for ethylbenzene. Hard (2002) suggested that "chemically induced exacerbation of CPN [chronic progressive nephropathy] was the mode of action underlying the development of renal neoplasia" in the NTP ethylbenzene studies. In a retrospective evaluation of NTP chronic studies, Seely *et al.* (2002) found that renal tubule cell neoplasms (RTCNs) "tend to occur in animals with a slightly higher severity of CPN than animals without RTCNs. However, the differential is minimal and clearly there are many male F344 rats with severe CPN without RTCNs." Seely *et al.* (2002) go on to say that "the data from these retrospective reviews suggest that an increased severity of CPN may contribute to the overall tumor response. However, any contribution appears to be marginal, and additional factors are likely involved."

Stott *et al.* (2003) reported accumulation of the male rat specific protein α2u-globulin in 1-week and 4-week inhalation studies of ethylbenzene in groups of six (1-week study) or eight (4-week study) male rats; the accumulation measured as an increase in hyaline droplets in proximal convoluted tubules was statistically significant only in the 1-week study. In the 13-week and 2-year inhalation studies of ethylbenzene, NTP (1992; 1999) found no evidence of an increase in hyaline droplets in treated rats. NTP (1999) therefore dismissed any involvement of α2u-globulin accumulation in renal tumor development in rats. The fact that the lesion appears in both male and female rats further argues against the involvement of α2u-globulin in the development of kidney toxicity. This mechanism was discounted by Hard (2002) as well. Stott *et al.* (2003) also postulated mechanisms of tumorigenic action involving cell proliferation and/or altered cell population dynamics in female mouse liver and male mouse lung. Stott et al. (2003) propose various hypothetical mechanisms which might involve nonlinear dose responses but the metabolism data clearly show the formation of epoxides and related oxidative metabolites, which could potentially be involved in a genotoxic mechanism of carcinogenic action possibly similar to benzene. Midorikawa *et al*. (2004) reported that the oxidative metabolism of ethylbenzene metabolites ethylhydroquinone and 4-ethylcatechol resulted in oxidative DNA damage *in vitro*. In view of the variety of metabolites and possible modes of action a low-dose linearity assumption is considered appropriate when extrapolating from the point of departure to obtain an estimate of the cancer risk at low doses with the BMD methodology as is use of the LMS approach.

Calculation of Lifetime Weighted Average Dose

Male and female rats (NTP, 1999) were exposed to ethylbenzene for 6.25 hours/day, five days/week for 104 weeks. Male and female mice (NTP, 1999) were exposed to ethylbenzene for 6.25 hours/day, five days/week for 103 weeks. Average concentrations, expressed in mg/m^3, during the exposure period were calculated by multiplying the reported chamber concentrations by 6.25 hours/24 hours, five days/seven days and 4.35 mg/m^3/ppm.

The average body weights of male and female rats were calculated to be 0.450 kg and 0.282 kg, respectively, based on data for controls reported by NTP (1999). The average body weights of male and female mice were estimated to be approximately 0.0429 kg and 0.0389 kg, respectively, based on data for controls reported by NTP (1999). Inhalation rates (I) in m^3/day for rats and mice were calculated based on Anderson *et al.* (1983):

$$I_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3} \tag{3}$$

$$I_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3} \tag{4}$$

Breathing rates were calculated to be 0.264 m^3/day for male rats, 0.193 m^3/day for female rats, 0.0494 m^3/day for male mice, and 0.0463 m^3/day for female mice. Lifetime weighted average (LTWA) doses were determined by multiplying the average concentrations during the dosing period by the appropriate animal breathing rate divided by the corresponding animal body weight. For mice, the exposure period (103 weeks) was less than the standard rodent lifespan (104 weeks), so an additional factor of 103 weeks/104 weeks was applied to determine lifetime average doses.

Physiologically Based Pharmacokinetic (PBPK) Modeling

The carcinogenic potency of ethylbenzene was calculated using rodent PBPK models to estimate internal doses under bioassay conditions. Extrapolations to human potencies were done using interspecies scaling. For comparison, a human PBPK model was used to estimate risk-specific doses for occupational and ambient environmental exposure scenarios. The PBPK models were comprised of compartments for liver, fat, vessel poor tissues (e.g., muscle), vessel rich tissues, and lung. Typical model parameters are given in Table 7 for flow-limited PBPK models and a model diagram is shown in Figure 2. Chemical and metabolic parameters for mouse and human models were taken from Haddad *et al.* (2001) and additionally from Sams *et al.* (2004) for human metabolism. The rat PBPK model was based on Dennison *et al.* (2003). Simulations were conducted using Berkeley Madonna (v.8.3.9) software (e.g., 6.25 hr exposure/day x 5 days/wk for one week simulations of bioassay exposure levels, see sample model equations in Appendix A). The chemical partition coefficients used in the Haddad et al. model were: blood:air, 28.0; fat:blood, 55.57; liver:blood, 2.99; muscle:blood, 0.93; and vessel rich:blood, 2.15 (Haddad *et al.*, 2001). For the Dennison et al. rat model the chemical partition coefficients were: blood:air, 42.7; fat:blood, 36.4; liver:blood, 1.96; muscle:blood, 0.609; and vessel rich:blood, 1.96. The metabolic parameters from Haddad *et al.* (2001) were: VmaxC = 6.39 mg/hr/kg body weight scaled to the ¾ power of body weight; Km = 1.04 mg/L. For the rat model the metabolic parameters were: VmaxC = 7.60 mg/kg-d scaled to the 0.74 power of body weight and Km = 0.1 mg/L. A second set of human metabolic parameters from Sams *et al.* (2004) was also used. In this case constants for low and high affinity saturable pathways were incorporated into the models: high affinity Vmax = 689 pmol/min/mg microsomal protein, Km = 8.0 μM; low affinity Vmax = 3039 pmol/min/mg protein, Km = 391 μM. A value of 28 mg/mL liver for microsomal protein concentration was assumed. Published values we reviewed ranged from 11 to 35 mg/g tissue. The value we used was similar to that of Kohn and Melnick (2000) (30 mg/g liver) and Medinsky *et al.* (1994) (35 mg/g liver). All model units were converted to moles, liters, or hours for simulation. A molecular weight of 106.16 g/mol for ethylbenzene was

used throughout. In addition to PBPK modeling based on published parameters the recent pharmacokinetic data of Charest-Tardif *et al*. (2006) was used in the mouse PBPK modeling for comparison purposes. During the final revisions of this document we obtained the recently published paper of Nong *et al*. (2007), which describes a mouse PBPK model for ethylbenzene inhalation based on the pharmacokinetic data of Charest-Tardif *et al*. (2006) and other parameter measurements. This model differs from that of Haddad *et al*. (2001) in having gender- and dose-specific chemical and metabolic parameters. The model also includes metabolism by lung and vessel-rich tissues in addition to liver. We employed the Nong *et al*. model in simulations of bioassay conditions identical to the Haddad *et al*. (2001) and Charest-Tardif *et al*. (2006) based models run previously, except that only the BMD dose response analysis was performed with the resulting total metabolized dose.

Although no systematic evaluation of PBPK model parameter uncertainty was conducted, the fact that we essentially used two rat models (Haddad *et al*., 2001 in the first draft and Dennison *et al*., 2004 in the revised draft) and two mouse models (Haddad *et al*. 2001, and Nong *et al*. 2007) and three key metabolic parameters (Charest-Tardif *et al*., 2006) for the mouse addresses this concern to some extent. The potency estimates in all cases were similar indicating a relative insensitivity to the PBPK parameters varied.

Johansen and Filser (1992) studied a series of volatile organic chemicals including ethylbenzene and developed theoretical values for clearance of uptake (CLupt) defined as the product of the rate constant for transfer of chemical from air to body and the volume of air in a closed chamber. The CLupt values were based on alveolar ventilation (Qalv), cardiac output (Qtot), and blood:air partition coefficients (Pbi). For most chemicals the experimentally determined values for inhalation uptake in rats and mice were about 60% of the theoretical values. The values determined for ethylbenzene in the rat of 70 mL/min for CLupt and 73 mL/min for alveolar ventilation are about 50% the value given in Table 7 (i.e., 4.38 L/hr vs. 8.58 L/hr). In the work described below selected simulations were run with lower alveolar ventilation rates for comparison with the main analysis.

The primary model prediction was the amount of ethylbenzene metabolized over the course of the simulation. The AUCs, the areas under the concentration x time curves for mixed venous concentration and liver concentration of ethylbenzene, were also recorded. The values for one week simulations of the amount metabolized (mmoles) were divided by 7d/week and body weight in kg to give daily values and multiplied by the molecular weight to give the PBPK metabolized dose in mg/kg-d. These values were then used in the dose response assessment of individual tumor site incidences using the benchmark dose software of U.S. EPA (BMDS v. 1.3.2) to obtain ED_{10}s, LED_{10}s and curve fit statistics.

Table 7. Parameters for Ethylbenzene PBPK Models.

Parameter	Mouse	Rat	Human
Alveolar ventilation rate Qalv, L/hr	$15*BW^{0.7}$	$12*BW^{0.74}$	$36*BW^{0.7}$ occ $15*BW^{0.7}$ env
Cardiac output Qtot, L/hr	$15*BW^{0.7}$	$15*BW^{0.74}$	$18*BW^{0.7}$ occ $15*BW^{0.7}$ env
Blood flows (fraction of cardiac output)			
Fat, Qf	0.09	0.07	0.05
Liver, Ql	0.25	0.183	0.26
Muscle, Qm	0.15	0.237	0.25
Vessel Rich Group, Qvrg	0.51	0.51	0.44
Tissue volumes, L (fraction of body weight unless otherwise indicated)			
Fat, Vf	0.06	0.035*BW + 0.0209	0.20, 0.40
Liver, Vl	0.04	0.037	0.026
Muscle, Vm	0.76	0.91*BW - (Vf + Vl + Vvrg + Vlu)	0.61, 0.41
Vessel Rich Group, Vvrg	0.05	0.054	0.036
Lung, Vlu	0.014	0.002	0.014
Body weight, BW kg	0.043 male 0.039 female	0.45 male 0.28 female	70
Metabolism VmaxC	6.39[a] 25.56[b]*	7.60[c]	6.39[a]
Km mg/L	1.04[a]	0.10[c]	1.04[a]
Metabolism High/Low Affinity Vmax mg/hr/L_{liver} High/Low Affinity Km mg/L			122.8/542.0[d] 0.85/41.5[d]

Note: occ = occupational scenario values; env = environmental exposure scenario; [a]Haddad et al. (2001) mg/hr-kg$^{3/4}$; [b]this value provided better fit to the kinetic data of Charest-Tardif et al. (2006); [c]Dennison et al. (2003) mg/hr-kg$^{0.74}$; [d]Sams et al. (2004).
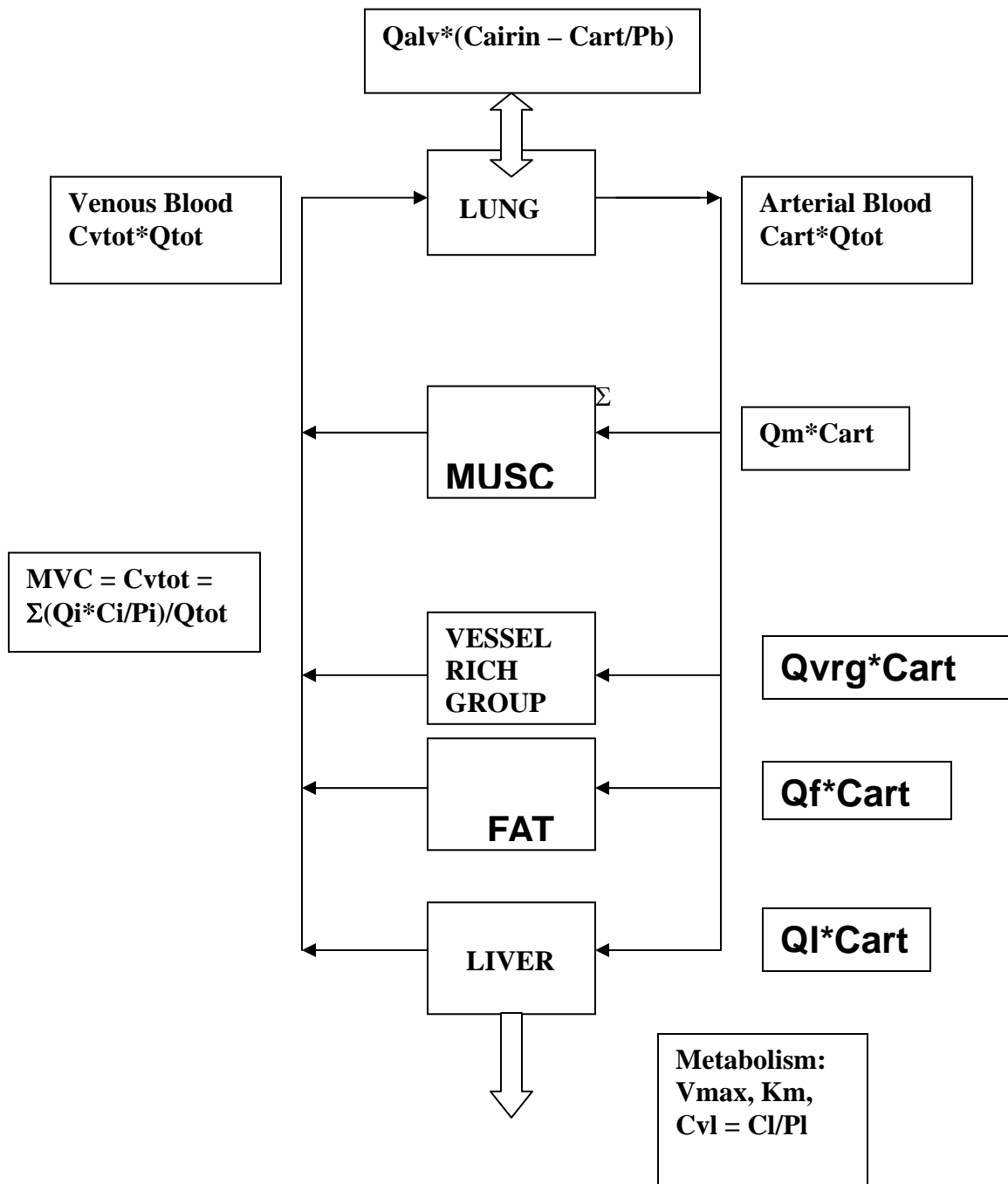
Figure 2. General Scheme for Ethylbenzene PBPK Model:

Qtot = Cardiac Output; Qalv = Alveolar Ventilation Rate ; Pb = Blood/Air Partition Coefficient; Pi = Tissue/Blood Partition Coefficients; Qi = Tissue Fractional Blood Flows ;Cart = Arterial Blood Concentration; Cvtot = Mixed Venous Blood Concentration; Cairin = Inhaled Concentration (e.g. ppm Ethylbenzene); Cexhaled = Cart/Pb(Concentration of Ethylbenzene Exhaled); Ci = Ai/Vi = Mass/Volume.

Internal to External Dose Conversion

In order to estimate external equivalent air concentrations associated with internal doses, the PBPK models were used. Simulation of 10 ppb ethylbenzene for 8 hours in the human PBPK model with the Haddad *et al*. (2001) parameters resulted in the predicted uptake of 3.04 μmoles in tissues and blood compared to 3.96 μmoles inhaled, or an uptake of 77%. Practically all of the 3.04 μmoles represents metabolized ethylbenzene. Based on these results, OEHHA assumed that all absorbed ethylbenzene is metabolized at low dose. Thus, for the inhalation route, the internal metabolized dose is converted to an external dose by applying an uptake factor of 77%. As noted above, uptake values of 49 to 65% have been observed in studies with human subjects exposed via inhalation to ethylbenzene. OEHHA has occasionally used a default value of 50% for inhalation uptake of similar volatile organic compounds.

For the oral route at low dose, OEHHA assumed that ethylbenzene is 100% metabolized and that uptake of ethylbenzene is also 100%. Thus, at low dose, the internal metabolized dose of ethylbenzene would be equivalent to an external applied dose by the oral route. No conversion factor for internal to external dose is necessary in this case.

Interspecies Extrapolation

Interspecies extrapolation from experimental animals to humans is normally based on the following relationship, where bw_h and bw_a are human and animal body weights, respectively, and potency (*e.g.*, q_{animal}) is expressed on a per dose per body weight basis (e.g., (mg/kg-d)$^{-1}$ see Watanabe *et al*. (1992):

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{1/4} \qquad (2)$$

This is equivalent to an adjustment based on (human body weight)$^{3/4}$ relative to the animal body weight or $BWh^{3/4}/BWa^{4/4} = (BWh/BWa)^{4/4-3/4} = (BWh/BWa)^{1/4}$. This is the default relationship currently recommended by OEHHA and by U.S. EPA (2005)

Alternatively, when performing calculations based on applied dose in terms of air concentrations, the assumption has sometimes been made that air concentration values are equivalent between species (CDHS, 1985). However, using the interspecies scaling factor shown above is preferred because it is assumed to account not only for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), but also for pharmacodynamic considerations i.e. tissue responses to chemical exposure.

When extrapolating from an animal potency in terms of PBPK adjusted internal dose, only a pharmacodynamic scaling factor is required. Since an equal contribution of pharmacokinetic and pharmacodynamic considerations is assumed, animal potency values already adjusted for pharmacokinetic considerations require a scaling factor of only $(bw_h/bw_a)^{1/8}$:

$$q_{\text{human}} = q_{\text{animal}} \times \left(\frac{bw_h}{bw_a} \right)^{1/8} \tag{3}$$

Derivation of the Human Inhalation Unit Risk Value

To derive the human inhalation unit risk value, the human internal potency value based on PBPK metabolized dose is multiplied by the human breathing rate (assumed to be 20 m^3/day), divided by the human body weight (assumed to be 70 kg) and multiplied by the estimated inhalation uptake factor in humans (0.77 for ethylbenzene). This yields a human inhalation unit risk value in terms of external air concentration.

For the case of LTWA doses, the human inhalation unit risk value is derived by multiplying the human inhalation cancer potency value by the human breathing rate (assumed to be 20 m^3/day), divided by the human body weight (assumed to be 70 kg). Because the LTWA doses represent external applied dose from an inhalation study, no uptake factor is necessary in deriving the unit risk value.

Inhalation and Oral Cancer Potency Values

The cancer potency derived based on internal doses (i.e., PBPK metabolized dose) is equivalent to the oral cancer potency, because of the assumption of 100% oral uptake and 100% metabolism of ethylbenzene at low doses. To derive the inhalation cancer potency, the human inhalation unit risk value is multiplied by the human body weight (assumed to be 70 kg) and divided by the human breathing rate (assumed to be 20 m^3/day).

For the case of LTWA doses, the human cancer potency derived based on these external applied doses from the inhalation study is equivalent to the inhalation cancer potency. To determine the oral cancer potency, the inhalation cancer potency is multiplied by the ratio of the oral to inhalation uptake factors (i.e., 1/0.77).

Example Calculations – BMD Approach

In this section, example calculations of the human cancer potency values (oral and inhalation) and the human unit risk value based on the LED_{10} for the male rat kidney tumor data and either the PBPK metabolized doses or the LTWA doses are provided. The same logic would apply to the derivation using the LMS methodology, with the only difference being that the animal potency is taken directly from the MSTAGE program under the LMS approach instead of being calculated from the LED_{10} in the BMD approach. To distinguish the results obtained under the two approaches, the terms P_{animal}, P_{human}, and U_{human} were used for the values derived using the BMD methodology.

Calculations based on BMD methodology and PBPK metabolized doses

Under the BMD methodology, the ED_{10}s and LED_{10}s are obtained from the BMDS program, with the animal potency value being simply $0.1/LED_{10}$ (i.e., 10% risk (0.1) divided by the 95% lower confidence limit on the dose that induced 10% risk or LED_{10}; this is the definition of a

slope). To obtain the animal potency based on internal dose ($P_{animal\_internal}$), 0.1 is divided by the LED_{10} derived for the male rat kidney tumor data and the PBPK metabolized doses:

$$P_{animal\_internal} = 0.1/LED_{10} = 0.1/25.38 = 0.00394 \text{ (mg/kg-d)}^{-1}$$

The human potency value based on internal dose ($P_{human\_internal}$) is calculated from the animal potency as follows:

$$P_{human\_internal} = 0.00394 \text{ (mg/kg-day)}^{-1} \text{ x } (70 \text{ kg}/0.450 \text{ kg})^{1/8}$$
$$= 0.0074 \text{ (mg/kg-day)}^{-1}$$

$P_{human\_internal}$ is equivalent to the oral human potency, because of the assumptions of 100% oral uptake and 100% metabolism of ethylbenzene at low dose.

The human unit risk value (U_{human}) is derived from the internal human cancer potency as follows:

$$U_{human} = 0.0074 \text{ (mg/kg-day)}^{-1} \text{ x } (20 \text{ m}^3/\text{day}/70 \text{ kg}) \text{ x } 0.77$$
$$= 1.64 \text{ x } 10^{-3} \text{ (mg/m}^3)^{-1}$$
$$= 1.64 \text{ x } 10^{-6} \text{ (µg/m}^3)^{-1}$$

As noted above the value of 0.77 was based on the prediction of the human ethylbenzene PBPK model, assuming exposure to low levels of ethylbenzene, and is similar to values obtained in studies with human subjects. By applying this uptake factor and assuming that the metabolism of ethylbenzene is 100% at low dose, the resulting unit risk value is expressed in terms of external concentration.

The inhalation cancer potency is derived from the unit risk value as follows:

$$P_{human\_inhalation} = 1.64 \text{ x } 10^{-3} \text{ (mg/m}^3)^{-1} \text{ x } (70 \text{ kg}/20 \text{ m}^3/\text{day})$$
$$= 0.0057 \text{ (mg/kg-day)}^{-1}$$

Calculations based on BMD methodology and LTWA doses

The LED_{10} based on the male rat kidney data and the LTWA doses is determined using the BMDS software. The animal potency, which in this case is the inhalation animal potency (P_{animal_inh}), is determined by dividing the LED_{10} into 0.1:

$$P_{animal\_inh} = 0.1/LED_{10} = 0.1/42.62 = 0.002346 \text{ (mg/kg-d)}^{-1}$$

The human inhalation cancer potency (P_{human_inh}) is derived from the animal potency using the interspecies scaling factor:

$$P_{human\_inh} = 0.002346 \text{ (mg/kg-day)}^{-1} \text{ x } (70 \text{ kg}/0.450 \text{ kg})^{1/4}$$
$$= 0.0083 \text{ (mg/kg-day)}^{-1}$$

The unit risk factor is derived from the human inhalation cancer potency as follows:

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$$U_{human} = 0.0083 \text{ (mg/kg-day)}^{-1} \times (20 \text{ m}^3\text{/day/70 kg})$$
$$= 2.4 \times 10^{-3} \text{ (mg/m}^3)^{-1}$$
$$= 2.4 \times 10^{-6} \text{ (}\mu\text{g/m}^3)^{-1}$$

For the calculation based on LTWA doses, the oral cancer potency is derived from the inhalation cancer potency by multiplying by the ratio of uptake factors (1/0.77):

$$P_{human\_oral} = 0.0083 \text{ (mg/kg-day)}^{-1} \times (1/0.77)$$
$$= 0.011 \text{ (mg/kg-day)}^{-1}$$

Results and Discussion

Linearized multistage approach

Tables 8a and 8c list the q_{animal}, q_{human} and unit risk values based on the linearized multistage approach. The cancer potencies and unit risk values were derived using the applied LTWA doses and PBPK adjusted internal doses, as described above. The most sensitive tumor sites are the male rat testicular interstitial cell adenoma and the male rat kidney adenoma and carcinoma, when the LTWA doses are used. If PBPK doses are used, the most sensitive sites are the male rat testicular interstitial cell adenoma and the male mouse lung. Regardless of whether LTWA or PBPK doses are used, the results based on the male mouse lung tumor data, the female mouse liver tumor data, and the male rat renal tumor data are comparable, producing unit risk values of approximately 0.002 $(\text{mg/m}^3)^{-1}$. Further, the results using either the LTWA doses or the PBPK metabolized doses are quite similar indicating that the PBPK modeling does not markedly improve the estimates. Some of the inherent uncertainty associated with PBPK modeling is demonstrated by the fact that the results based on the PBPK modeling using the Charest-Tardif parameters differ by roughly a factor of two for the mice compared to the results derived based on the other equally valid PBPK modeling approach.

The testicular interstitial cell adenoma site gives the highest values. However, the very high background incidences of this tumor make it less reliable and suitable for dose-response analysis than the male rat kidney site.

Thus, the unit risk value of 0.0025 $(\text{mg/m}^3)^{-1}$ derived based on the LMS approach from the male rat kidney tumor data using the LTWA doses is selected as the representative value for ethylbenzene. It is very similar to the estimate derived using the PBPK approach (0.0026 $(\text{mg/m}^3)^{-1}$), and does not require the many assumptions made in applying the more complex PBPK approach.

Table 8a. Cancer potency and unit risk values for ethylbenzene derived using the linearized multistage procedure (LMS) with applied LTWA doses based on data from NTP (1999).

Sex, species	Site, tumor type	q_{animal_inh} $(mg/kg\text{-}day)^{-1}$	q_{human_inh}[a] $(mg/kg\text{-}day)^{-1}$	Human unit risk value[b] $(mg/m^3)^{-1}$	Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.002472	0.0087	**0.0025**	$p = 0.81$
	Testicular interstitial cell adenoma	0.006547	0.023	0.0066	$p = 0.52$
Female rats	Renal tubule adenoma	0.0005528	0.0022	0.00063	$p = 0.95$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.0008494	0.0054	0.0015	$p = 0.75$
Female mice	Liver hepatocellular carcinoma or adenoma	0.0009421	0.0061	0.0017	$p = 0.68$

a.   The interspecies extrapolation was applied to q_{animal_inh} in $(mg/kg\text{-}d)^{-1}$ to determine q_{human_inh} $(mg/kg\text{-}day)^{-1}$, as described above.

b   Unit risk was determined by multiplying the human cancer potency in $(mg/kg\text{-}day)^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg), as described above.

c.   A p-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit with the LMS procedure.

Table 8b. Cancer potency and unit risk values for ethylbenzene derived using the BMD procedure with applied LTWA doses based on data from NTP (1999).

Sex, species	Site, tumor type	P_{animal_inh} (mg/kg-day)$^{-1}$	P_{human_inh}[a] (mg/kg-day)$^{-1}$	Human unit risk value[b] (mg/m^3)$^{-1}$	Model Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.002589	0.0091	0.0026	Quantal Linear $p = 0.49$
	Testicular interstitial cell adenoma	0.006333	0.022	0.0063	Quantal Linear $p = 0.73$
Female rats	Renal tubule adenoma	0.0004704	0.0019	0.00054	Quantal Quadratic $p = 0.99$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.0008062	0.0051	0.0015	Quantal Linear $p = 0.75$
Female mice	Liver hepatocellular carcinoma or adenoma	0.0009256	0.0060	0.0017	Quantal Linear $p = 0.74$

a.   The interspecies extrapolation of $(BW_h/BW_a)^{1/4}$ was applied to P_{animal_inh} in (mg/kg-d)$^{-1}$ to determine P_{human_inh} (mg/kg-day)$^{-1}$, as described above.
b   Unit risk was determined by multiplying the human cancer potency in (mg/kg-day)$^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg).
c.   A p-value ≥ 0.1 for the chi-square goodness-of-fit test indicates an adequate fit with the BMD procedure.

Table 8c. Cancer potency and unit risk values for ethylbenzene derived using the linearized multistage procedure with PBPK metabolized doses and bioassay data from NTP (1999).

Sex, species	Site, tumor type	$q_{animal\_internal}$ (mg/kg-day)$^{-1}$	$q_{human\_internal}$[a] (mg/kg-day)$^{-1}$	Human unit risk value[b] (mg/m^3)$^{-1}$	Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.00473	0.0089	0.0020	$p = 0.68$
	Testicular interstitial cell adenoma	0.0154	0.029	0.0064	$p = 0.89$
Female rats	Renal tubule adenoma	0.00101	0.0020	0.00044	$p = 0.97$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.003747 0.001680[d]	0.0094 0.0042[d]	0.0021 0.00092[d]	$p = 0.99$ $p = 0.93$[d]
Female mice	Liver hepatocellular carcinoma or adenoma	0.002702 0.001705[d]	0.0069 0.0044[d]	0.0015 0.00097[d]	$p = 0.86$ $p = 0.73$[d]

a. The interspecies extrapolation of $(bw_h/bw_a)^{1/8}$ was applied to $q_{animal\_internal}$ in (mg/kg-d)$^{-1}$ to determine $q_{human\_internal}$ in (mg/kg-day)$^{-1}$, as described above.
b. Unit risk was determined by multiplying the human internal cancer potency in (mg/kg-day)$^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg) and by an uptake factor of 0.77, as described above.
c. A p-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit with the LMS procedure.
d. These values obtained with PBPK model adjusted to approximate the PK data of Charest-Tardif *et al.* (2006).

Table 8d. Cancer potency and unit risk values for ethylbenzene derived using the BMD procedure with PBPK metabolized doses and bioassay data from NTP (1999).

Sex, species	Site, tumor type	$P_{animal\_internal}$ (mg/kg-day)$^{-1}$	$P_{human\_internal}$[a] (mg/kg-day)$^{-1}$	Human unit risk value[b] (mg/m^3)$^{-1}$	Model Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.00394	0.0089	0.00164	Multistage (order = 3) $p = 0.57$
	Testicular interstitial cell adenoma	0.01460	0.027	0.00594	Quantal Quadratic $p = 0.87$
Female rats	Renal tubule adenoma	0.00126	0.0025	0.00055	Multistage (order = 3) $p = 0.98$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.003557	0.0090	0.0020	Multistage (order = 3) $p = 0.99$
		0.001595[d]	0.0040[d]	0.00088[d]	Quantal Linear $p = 0.93$
		0.000908[e]	0.00229[e]	0.00050[e]	$p = 0.74$
Female mice	Liver hepatocellular carcinoma or adenoma	0.002604	0.0066	0.0015	Multistage (order = 3) $p = 0.86$
		0.0007523[d]	0.0019[d]	0.00042[d]	Quantal Quadratic $p = 0.94$[d]
		0.00104[e]	0.00265[e]	0.00058[e]	Multistage (order = 3) $p = 0.67$

a. The interspecies extrapolation of $(BWh/BWa)^{1/8}$ was applied to $P_{animal\_intneral}$ in (mg/kg-d)$^{-1}$ to determine $P_{human\_internal}$ (mg/kg-day)$^{-1}$, as described above.

b. Unit risk was determined by multiplying the human internal cancer potency in (mg/kg-day)$^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg) and by an uptake factor of 0.77, as described above.

c. A p-value of 0.1 or greater for the chi-square goodness-of-fit test indicates an adequate fit with the BMD procedure.

d. These values obtained with PBPK model adjusted to approximate the mouse pharmacokinetic data of Charest-Tardif *et al.* (2006).

e. These values obtained with the PBPK model of Nong *et al.* (2007). Cardiac output = 24BW^0.75; Alveolar ventilation = 0.68*Cardiac output.

Benchmark Dose Approach

Tables 8b and 8d list the P_{animal}, P_{human}, and human unit risk values based on the BMD approach. The cancer potencies and unit risk values were derived using the applied LTWA doses and PBPK adjusted internal doses, as described above. As expected the results from the BMD approach are quite similar to those just described using the LMS approach. Unit risk values ranged from 0.00054 to 0.0063 $(mg/m^3)^{-1}$. When LTWA doses are used, the most sensitive sites are the male rat testicular interstitial cell adenoma and the male rat kidney adenoma and carcinoma. When PBPK doses are used, the most sensitive sites are the male rat testicular interstitial cell adenomas and the male mice lung tumors. Regardless of whether LTWA or PBPK doses are used, the unit risk values based on male rat kidney, male mouse lung, and female mouse liver are comparable at approximately 0.002 $(mg/m^3)^{-1}$. The results based on the Charest-Tardif PBPK parameters are about a factor of two to four less than those based on the PBPK parameters from Haddad. The results obtained with the Nong *et al.* (2007) PBPK model were similar to the Charest-Tardif *et al.* (2006) adjusted mouse model. This is not surprising since they are largely based on the same kinetic data (Table 8d). The various estimates indicate some of the uncertainty in the PBPK approach.

As discussed above, the male rat testicular tumors are not considered appropriate for unit risk and potency estimation because of the high background rate. The preferred unit risk value of 0.0025 $(mg/m^3)^{-1}$, is derived from the male rat kidney data based on LTWA doses with the LMS method. The value derived using the BMD approach based on LTWA doses is not significantly different (0.0026 $(mg/m^3)^{-1}$).

Human PBPK Models

Initial predictions of risk-specific exposure concentrations from a human PBPK model used metabolic parameters from Haddad *et al.* (2001), two exposure scenarios, and two methods of risk estimation. The exposure scenarios utilized were an occupational-like time of exposure (8.0 hr exposure/day x 5 d/week; 7 days simulation) and a continuous environmental time of exposure (24 hr/d x 7d/week; 10 days simulation). Two methods of risk estimation were used. In method I a human potency value, P_{human}, was used to estimate an internal dose equivalent to 1 x 10^{-6} lifetime theoretical risk (e.g., 10^{-6} risk/0.0087 $(mg/kg`-d)^{-1}$ = 1.15 x 10^{-4} mg/kg-d.) The human PBPK model with differing exposure scenarios was then used to estimate the external ethylbenzene concentrations resulting in that internal dose. In method II the animal LED_{10} was divided by 10^5 to obtain the 10^{-6} risk specific dose and the equivalent external concentration was adjusted for possible pharmacodynamic (PD) differences between rats and humans (i.e., $(70/0.45)^{1/8}$). For the tumor site of male rat kidney the 1 x 10^{-6} values from the human models vary by 2-fold (0.48 to 0.79 ppb; Table 9). The same analysis was repeated with the human metabolic parameters from Sams *et al.* (2004) and the range was similar (0.33 to 0.74 ppb). PBPK models with higher body weight of 90 kg and 40% body fat gave only slightly higher ppb predictions. According to the discussion above, the preferred value for the unit risk of ethylbenzene is 2.5 x 10^{-6} $(\mu g/m^3)^{-1}$, based on the data for male rat kidney tumors. With the human model unit risk estimates ranged from 1.27 x 10^{-6} to 3.06 x 10^{-6} ppb^{-1} (2.9 x 10^{-7} to 7.0 x 10^{-7} $[\mu g/m^3]^{-1}$ at 4.35 $\mu g/m^3$/ppb) or somewhat lower than the animal PBPK based values. These unit risk estimates from the human PBPK models were not used as final values due to issues of

tumor site concordance and human variability and parameter uncertainty. The information is provided here for comparative purposes and methodology development.

Table 9. Estimates of Virtually Safe Exposure Levels (ppb) based on Human PBPK Modeling[a]

Method/Model	Occupational Scenario	Environmental Scenario
I . Human Potency based		
70 kg human 20% fat Haddad	0.70	0.50
20% fat Sams	0.66	0.33
90 kg human 40% fat Haddad	0.79	0.56
40% fat Sams	0.74	0.34
II. Animal LED$_{10}$ based		
70 kg human 20% fat Haddad	0.68	0.48
20% fat Sams	0.64	0.32
90 kg human 40% fat Haddad	0.74	0.53
40% fat Sams	0.69	0.34

[a] Note: Values are calculated for 1×10^{-6} theoretical lifetime cancer risk. Occupational scenario was 8.0 hr/d x 5 days/week, for one-week simulations; environmental scenario was continuous exposure for one week. Method I used the human potency (Ph) in $(mg/kg-d)^{-1}$ to calculate a 10^{-6} risk internal dose in metrics of ethylbenzene metabolized by the liver (AMET, μmol/d). Method II uses the animal LED$_{10}$ to calculate a 10^{-6} risk dose. The human models were the 70 kg default with 20% fat and a 90 kg variant with 40% fat (and comparatively less muscle). The Ph was based on the male rat kidney tumors of 0.0087 $(mg/kg-d)^{-1}$. Inhalation was 20 m^3/d. The models were run with metabolic parameters from Haddad *et al*. (2001) and Sams *et al*. (2004).

Conclusion

The male rat was the most sensitive sex and species tested by NTP (1999) in the inhalation carcinogenesis studies of ethylbenzene. While the highest potency and unit risk values were obtained for rat testicular adenomas, the high background rate of this common tumor made interpretation difficult. NTP considered the increased incidences of renal tubule carcinoma or adenoma to provide clear evidence of the carcinogenic activity of ethylbenzene, and this site was considered to be the more reliable basis for estimating human cancer potency.

OEHHA has examined various proposals for the mode of action of ethylbenzene in causing the observed increases in tumor incidence in rodent lung, kidney and liver. Some of these involve cytotoxicity or exacerbation of existing degenerative processes, which might be considered capable of increasing tumor incidence by a non-genotoxic mechanism, although the precise implications of these proposals for dose-response relationships have not been fully explored.

Moreover, it appears likely that metabolism of ethylbenzene involves generation of reactive metabolites. These metabolites include quinone/hydroquinone species capable of causing oxidative DNA damage and carcinogenesis, analogous to the processes established for benzene and some similar carcinogens. OEHHA concludes that overall, the limited data do not conclusively establish any particular mode of action for ethylbenzene carcinogenesis, and indeed several of the proposed processes may be influential. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction. Because of this, the default linear approach has been used for extrapolating the dose-response curve to low doses.

Using either the LMS or BMD methodology with different dose metrics, the 95% upper confidence bound on the unit risk value for purposes of calculating cancer risks associated with exposure to ethylbenzene is in the range 5.5×10^{-4} to 6.6×10^{-3} $(mg/m^3)^{-1}$, based on the incidence data from the NTP (1999) studies (Table 10). <u>The unit risk value of 2.5×10^{-3} $(mg/m^3)^{-1}$, or 2.5×10^{-6} $(\mu g/m^3)^{-1}$, based on the renal tubule carcinoma or adenoma incidence data in male rats and using the LMS methodology applied to LTWA doses, is considered the most appropriate for purposes of calculating cancer risks associated with exposure to low levels of ethylbenzene</u>. As noted above and summarized in Table 10 below, unit risks based on the PBPK internal doses were not markedly different than those based on the LTWA doses, and involved a number of assumptions. Because the PBPK modeling is uncertain and the results were relatively insensitive to the approach used, the LMS results based on the LTWA doses were selected as most appropriate. The inhalation cancer potency, from which the unit risk value was derived, is 0.0087 $(mg/kg-d)^{-1}$. The oral cancer potency value of 0.011 $(mg/kg-d)^{-1}$ is derived from the inhalation potency value by multiplying by the ratio of the uptake values (i.e., 1/0.77). The inhalation and oral cancer potency values are considered applicable to low dose ethylbenzene exposures.

Table 10. Comparison of unit risk values for ethylbenzene

Species/sex/tumor site	Unit Risk value $(mg/m^3)^{-1}$			
	LTWA doses, LMS approach	LTWA doses, BMD approach	PBPK doses, LMS approach	PBPK doses, BMD approach
Male rat kidney	0.0025	0.0026	0.0020	0.0016
Male rat testicular	0.0066	0.0063	0.0064	0.0059
Female rat kidney	0.00063	0.00054	0.00044	0.00055
Male mouse lung	0.0015	0.0015	0.0021	0.0020
Female mouse liver	0.0017	0.0017	0.0015	0.0015

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Appendix A

Berkeley Madonna Model Code Example (Male Rat 75 ppm x 6.25 hr/d x 5days/week, 1 week simulation.
If cut and pasted into BM demo program available online this model will run)

```
METHOD Stiff

STARTTIME = 0
STOPTIME= 168
DT = 0.001

{ethylbenzene moles}
init Af = 0
Limit Af >= 0
init Al = 0
Limit Al >= 0
init Am = 0
Limit Am >= 0
init Avrg = 0
Limit Avrg >= 0
init Alu = 0
Limit Alu >= 0

{moles, metabolized}
init Ametl = 0
init Ametlg = 0

{tissue flows L/hr}
Qtot = 15*BW^0.74
Qalv = 12*BW^0.74
Qf = 0.07*Qtot
Qvrg = 0.51*Qtot
Ql = 0.183*Qtot
Qm = Qtot - (Ql + Qf + Qvrg)
Qlu = Qtot

{tissue volumes L}
Vf = 0.035*BW + 0.0205
Vl = 0.037*BW
Vm = 0.91*BW - (Vf + Vl + Vvrg + Vlu)
Vvrg = 0.054*BW
Vlu = 0.014*BW
BW = 0.45

{blood/air and tissue/blood partition coefficients}
Pb = 42.7
Pl = 1.96
Pf = 36.4
Pm = 0.609
Pvrg = 1.96
Plu = 1.96

{ethylbenzene metabolic parameters, CLh, Vmax mol/hr, Km, M}
VmaxC = 7.6
Vmax = VmaxC*BW^0.74/(1000*106.16)
```

```
Km = 0.1/(1000*106.16)
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 6.25 THEN 75*(1E-6/25.45) ELSE IF (24<TIME) AND (TIME <=
30.25) THEN 75*(1E-6/25.45) ELSE IF (48<TIME) AND (TIME <= 54.25) THEN
75*(1E-6/25.45) ELSE IF (72<TIME) AND (TIME <= 78.25) THEN 75*(1E-6/25.45)
ELSE IF (96<TIME) AND (TIME <= 102.25) THEN 75*(1E-6/25.45) ELSE 0

{calculated concentrations of ethylbenzene}
Cart = Pb*(Qalv*Cair + Qtot*Cvtot)/(Pb*Qtot + Qalv)
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvm = Am/(Vm*Pm)
Cvlu = Alu/(Vlu*Plu)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cexh = Cart/Pb

{differential equations for ethylbenzene uptake and metabolism}
d/dt(Alu) = Qtot*(Cvtot - Cvlu)
d/dt(Al) = Ql*(Cart - Cvl)  - Vmax*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(Am) = Qm*(Cart - Cvm)

{amount of ethylbenzene metabolized}
d/dt(Ametl)  = Vmax*Cvl/(Km + Cvl)
d/dt(Ametlg) = (Vmax*Cvl/(Km + Cvl))/BW
init AUCvtot = 0
init AUCvl = 0
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) =  Cvl
```

CHRONIC TOXICITY SUMMARY

ETHYLBENZENE

(Phenylethane; NCI-C56393)

CAS Registry Number: 100-41-4

I.   Chronic Toxicity Summary

Inhalation reference exposure level   **2000 μg/m³ (400 ppb)**
Critical effect(s)   Liver, kidney, pituitary gland in mice and rats
Hazard index target(s)   Alimentary system (liver); kidney; endocrine
                                                                system

II.   Physical and Chemical Properties (HSDB, 1994)

Description   colorless liquid
Molecular formula C_8H_{10}
Molecular weight   106.16 g/mol
Boiling point   136.2°C
Melting point   -95°C
Vapor pressure   10 torr @ 25.9°C
Density   0.867 g/cm³ @ 20°C
Solubility   Soluble in ethanol and ether, low solubility in
                                      water (0.014 g/100 ml at 15°C)
Conversion factor   1 ppm = 4.35 mg/m³

III.   Major Uses or Sources

Ethylbenzene is used as a precursor in the manufacture of styrene (HSDB, 1994). It is also used in the production of synthetic rubber, and is present in automobile and aviation fuels. It is found in commercial xylene (Reprotext, 1994). In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of ethylbenzene was approximately 0.4 ppb (CARB, 1999a). The latest annual statewide emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 161,846 pounds of ethylbenzene (CARB, 1999b).

IV.   Effects of Human Exposure

Studies on the effects of workplace exposures to ethylbenzene have been complicated by concurrent exposures to other chemicals, such as xylenes (Angerer and Wulf, 1985). Bardodej

and Cirek (1988) reported no significant hematological or liver function changes in 200 ethylbenzene production workers over a 20-year period.

V.   Effects of Animal Exposure

Rats and mice (10/sex/group) were exposed to 0, 100, 250, 500, 750, and 1000 ppm (0, 434, 1086, 2171, 3257, and 4343 mg/m^3) ethylbenzene 6 hours/day, 5 days/week for 90 days (NTP, 1988; 1989; 1990). Rats displayed significantly lower serum alkaline phosphatase in groups exposed to 500 ppm or higher. Dose-dependent increases in liver weights were observed in male rats beginning at 250 ppm, while this effect was not seen until 500 ppm in the females. An increase in relative kidney weights was seen in the 3 highest concentrations in both sexes. Minimal lung inflammation was observed in several of the treatment groups, but this phenomenon was attributed to the presence of an infectious agent rather than to ethylbenzene exposure. The mice in this study did not show any treatment-related effects except for elevated liver and kidney weights at 750 and 1000 ppm, respectively.

Rats and mice were exposed to ethylbenzene (greater than 99% pure) by inhalation for 2 years (NTP, 1999; Chan *et al*., 1998). Groups of 50 male and 50 female F344/N rats were exposed to 0, 75, 250, or 750 ppm, 6 hours per day, 5 days per week, for 104 weeks. Survival of male rats in the 750 ppm group was significantly less than that of the chamber controls. Mean body weights of 250 and 750 ppm males were generally less than those of the chamber controls beginning at week 20. Mean body weights of exposed groups of females were generally less than those of chamber controls during the second year of the study. In addition to renal tumors, the incidence of renal tubule hyperplasia in 750 ppm males was significantly greater than that in the chamber controls. The severity of nephropathy in 750 ppm male rats was significantly increased relative to the chamber controls. Some increases in incidence and severity of nephropathy were noted in all exposed female rats, but these were statistically significant only at 750 ppm.

Groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation, 6 hours per day, 5 days per week, for 103 weeks. Survival of exposed mice was similar to controls. Mean body weights of females exposed to 75 ppm were greater than those of the chamber controls from week 72 until the end of the study. In addition to lung and liver tumors, the incidence of eosinophilic liver foci in 750 ppm females was significantly increased compared to that in the chamber controls. There was a spectrum of nonneoplastic liver changes related to ethylbenzene exposure in male mice, including syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis. The incidences of hyperplasia of the pituitary gland pars distalis in 250 and 750 ppm females and the incidences of thyroid gland follicular cell hyperplasia in 750 ppm males and females were significantly increased compared to those in the chamber control groups. Based on an evaluation of all the non-cancer data in mice and rats OEHHA staff selected 75 ppm as the NOAEL for the NTP (1999) study.

Rats (17-20 per group) were exposed to 0, 600, 1200, or 2400 mg/m^3 for 24 hours/day on days 7 to 15 of gestation (Ungvary and Tatrai, 1985). Developmental malformations in the form of "anomalies of the uropoietic apparatus" were observed at the 2400 mg/m^3 concentration.

Skeletal retardation was observed in all exposed groups compared with controls. The incidence of skeletal abnormalities increased with higher concentrations of ethylbenzene.

Rabbits exposed by these investigators to the same concentrations as the rats on days 7 to 15 of gestation, exhibited maternal weight loss with exposure to 1000 mg/m^3 ethylbenzene. There were no live fetuses in this group for which abnormalities could be evaluated. No developmental defects were observed in the lower exposure groups.

Rats (78-107 per group) and rabbits (29-30 per group) were exposed for 6 or 7 hours/day, 7 days/week, during days 1-l9 and 1-24 of gestation, respectively, to 0, 100, or 1000 ppm (0, 434, or 4342 mg/m^3) ethylbenzene (Andrew *et al.*, 1981; Hardin *et al.,* 1981). No effects were observed in the rabbits for maternal toxicity during exposure or at time of necropsy. Similarly, no effects were seen in the fetuses of the rabbits. The only significant effect of ethylbenzene exposure in the rabbits was a reduced number of live kits in the 1000 ppm group. A greater number and severity of effects were seen in rats exposed to 1000 ppm ethylbenzene. Maternal rats exposed to 1000 ppm exhibited significantly increased liver, kidney, and spleen weights compared with controls. Fetal rats showed an increase in skeletal variations at the 1000 ppm concentration, but the results of the 100 ppm exposure were not conclusive.

Clark (1983) found no significant effects on body weight, food intake, hematology, urinalysis, organ weights or histopathology in rats (18 per group) exposed to 100 ppm (434 mg/m^3) ethylbenzene for 6 hours/day, 5 days/week, for 12 weeks.

Degeneration of the testicular epithelium was noted in guinea pigs and a rhesus monkey exposed to 600 ppm (2604 mg/m^3) for 6 months (Wolf *et al.*, 1956). No effects were reported for female monkeys exposed to the same conditions.

Cragg *et al.* (1989) exposed mice and rats (5/sex/group) to 0, 99, 382, and 782 ppm (0, 430, 1659, and 3396 mg/m^3) 6 hours/day, 5 days/week for 4 weeks. Some evidence of increased salivation and lacrimation was seen in the rats exposed to 382 ppm. No other gross signs of toxicity were observed. Both male and female rats had significantly enlarged livers following exposure to 782 ppm. Female mice also showed a significant increase in liver weight at this concentration. No histopathological lesions were seen in the livers of these mice.

Dose-dependent induction of liver cytochrome P450 enzymes in rats by ethylbenzene was observed by Elovaara *et al.* (1985). Rats (5 per group) were exposed to 0, 50, 300, or 600 ppm (0, 217, 1302, or 2604 mg/m^3) ethylbenzene for 6 hours/day, 5 days/week for 2, 5, 9, or 16 weeks. Cytochrome P450 enzyme induction, and microscopic changes in endoplasmic reticulum and cellular ultrastructure were evident at all ethylbenzene concentrations by week 2, and persisted throughout the exposure. Liver weights were not elevated in these studies.

VI.   Derivation of the Chronic Reference Exposure Level

Study	NTP, 1999; Chan *et al.*, 1998
Study population	Male and female rats and mice (50 per group)
Exposure method	Discontinuous inhalation
Critical effects	Nephrotoxicity, body weight reduction (rats) hyperplasia of the pituitary gland; liver cellular alterations and necrosis (mice)
LOAEL	250 ppm
NOAEL	75 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	103 weeks.
Average experimental exposure	13 ppm for NOAEL group
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.4 ppm (400 ppb; 2 mg/m^3; 2,000 µg/m^3)

The REL is based on a lifetime toxicity/carcinogenesis study. The NOAEL for non-neoplastic effects in the study was 75 ppm, and the LOAEL was 250 ppm. Some shorter duration studies discussed above (e.g. NTP, 1988, 1989, 1990) identify higher concentrations as NOAELs, but the study used (NTP 1999) is the most recent available and is considered the most reliable for assessing chronic effects.

U.S. EPA based its RfC on developmental toxicity studies in rats and rabbits (Andrew *et al.*, 1981; Hardin *et al.*, 1981; U.S. EPA, 1994). The NOAEL in the studies was 100 ppm, and the LOAEL was 1000 ppm. In accordance with its methodology, U.S. EPA did not use a time-weighted average concentration for the discontinuous exposure experiment since the key effect was developmental toxicity.   If OEHHA methodology is followed (which includes the time-weighted averaging of the exposure concentrations, and uncertainty factors of 3 (interspecies, with RGDR = 1) and 10 (intraspecies), this study would indicate a REL of 0.6 ppm (3 mg/m^3). The study by Ungvary and Tatrai (1985) reported a NOAEL of 600 mg/m^3 for developmental and maternal effects in several species. However, the reporting and general quality of this paper create less confidence in its results.

For comparison to the proposed REL of 0.4 ppm, Clark (1983) found no significant effects in rats exposed to 100 ppm ethylbenzene 6 h/day, 5 d/week, for 12 weeks. This NOAEL can be time-adjusted to 18 ppm, then divided by a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10 which results in a REL of 0.2 ppm. (The default value of 1 for RGDR was used). It appears that the proposed REL provides a sufficient margin of safety to provide

protection against the reported developmental effects (Andrew *et al.,* 1981; Hardin *et al.,* 1981; Ungvary and Tatrai, 1985)

VII.   Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylbenzene include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis, and the observation of a NOAEL in lifetime chronic inhalation exposure studies. The major area of uncertainty is the lack of adequate human exposure data.

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ACUTE TOXICITY SUMMARY

HYDROGEN SULFIDE

(sulfur hydride; sulfuretted hydrogen)

CAS Registry Number: 7783-06-4

I.   Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**42 μg/m³**
Critical effect(s)	Headache, nausea, physiological responses to odor
Hazard Index target(s)	CNS

II.   Physical and Chemical Properties (AIHA, 1991 except as noted)

Description	colorless gas
Molecular formula	H_2S
Molecular weight	34.08
Density	1.39 g/L @ 25°C
Boiling point	-60.7°C
Melting point	unknown
Vapor pressure	1 atm @ -60.4°C
Flash point	26°C
Explosive limits	upper = 4.3% by volume in air
	lower = 46% by volume in air
Solubility	soluble in water, hydrocarbon solvents, ether, and ethanol
Odor threshold	0.0081 ppm (Amoore and Hautala, 1983)
Odor description	resembles rotten eggs
Metabolites	bisulfite (HSO_3), thiosulfate ($S_2O_3^{2-}$) (Baxter and Van Reen, 1958)
Conversion factor	1 ppm = 1.4 mg/m³ @ 25°C

II.   Major Uses or Sources

Hydrogen sulfide (H_2S) is used as a reagent and an intermediate in the preparation of other reduced sulfur compounds. It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986).

IV.   Acute Toxicity to Humans

Hydrogen sulfide is an extremely hazardous gas (ACGIH, 1992). Hydrogen sulfide exposure is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977). The mortality in acute hydrogen sulfide intoxications has been reported to be 2.8% (Arnold *et al.*, 1985) to 6% (WHO, 1981). While severe intoxication is especially of concern when exposure

occurs in confined spaces, an accidental release of hydrogen sulfide into the air surrounding industrial facilities can cause very serious effects. For example, at Poza Rica, Mexico 320 people were hospitalized and 22 died (WHO, 1981). An inhalation LC_{Lo} of 600 and 800 ppm (840 and 1,120 mg/m³) for 30 and 5 minutes, respectively, is reported (Hazardtext, 1994). A lethal exposure was documented for a worker exposed to approximately 600 ppm H_2S for 5-15 minutes (Simson and Simpson, 1971). Inhalation of 1,000 ppm (1,400 mg/m³) is reported to cause immediate respiratory arrest (ACGIH, 1992). Concentrations greater than 200 ppm (280 mg/m³) H_2S are reported to cause direct irritant effects on exposed surfaces and can cause pulmonary edema following longer exposures (Spiers and Finnegan, 1986). The mechanism of H_2S toxicity, cellular hypoxia caused by inhibition of cytochrome oxidase, is similar to that for cyanide and can be treated by induction of methemoglobin or with hyperbaric oxygen (Elovaara *et al*., 1978; Hsu *et al*., 1987).

At concentrations exceeding 50 ppm (70 mg/m³), olfactory fatigue prevents detection of H_2S odor. Exposure to 100-150 ppm (140-210 mg/m³) for several hours causes local irritation (Haggard, 1925). Exposure to 50 ppm for 1 hour causes conjunctivitis with ocular pain, lacrimation, and photophobia; this can progress to keratoconjunctivitis and vesiculation of the corneal epithelium (ACGIH, 1992). Bhambhani and Singh (1991) showed that 16 healthy subjects exposed to 5 ppm (7 mg/m³) H_2S under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood. Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m³) H_2S caused coughing and throat irritation after 15 minutes.

In another study, ten asthmatic volunteers were exposed to 2 ppm H_2S for 30 minutes and pulmonary function was tested (Jappinen *et al*., 1990). All subjects reported detecting "very unpleasant" odor but "rapidly became accustomed to it." Three subjects reported headache following exposure. No significant changes in mean FVC or FEV_1 were reported. Although individual values for specific airway resistance (SR_{aw}) were not reported, the difference following exposure ranged from -5.95% to +137.78%. The decrease in specific airway conductance, SG_{aw}, ranged from -57.7% to +28.9%. The increase in mean SR_{aw} and the decrease in mean SG_{aw} were not statistically significant. However, significantly increased airway resistance and decreased airway conductance were noted in two of ten asthmatic subjects which may be biologically significant.

Hydrogen sulfide is noted for its strong and offensive odor. Based on a review of 26 studies, the average odor detection threshold ranged from 0.00007 to 1.4 ppm (Amoore, 1985). The geometric mean of these studies is 0.008 ppm. In general, olfactory sensitivities decrease by a factor of 2 for each 22 years of age above 20 (Venstrom and Amoore, 1968); the above geometric mean is based on the average age of 40.

For hydrogen sulfide, concentrations that substantially exceed the odor threshold result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1985). The perceived intensity of the odor of hydrogen sulfide depends on the longevity of the concentration, and the intensity increases 20% for each doubling concentration (Amoore, 1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winneke, 1975;

Winneke and Kastka, 1977; Hellman and Small, 1974; Adams *et al.,* 1968; and NCASI, 1971). The geometric mean for these studies is 5, indicating that when an unpleasant odor reaches an average concentration of 5 times its detection threshold, the odor will result in annoying discomfort. Applying the 5-fold multiplier to the mean detectable level, 0.008 ppm, results in a mean annoyance threshold of 0.04 ppm. At the current California Ambient Air Quality Standard (CAAQS) of 0.03 ppm, the level would be detectable by 83% of the population and would be discomforting to 40% of the population. These estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper 1985) at 0.03 ppm H2S exposures from geyser emissions. The World Health Organization (WHO) reports that in order to avoid substantial complaints about odor annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970).

Predisposing Conditions for Hydrogen Sulfide Toxicity

Medical: Unknown

Chemical: Ethanol has been shown to potentiate the effects of H_2S by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m³) H_2S (Beck *et al*., 1979).

V.   Acute Toxicity to Laboratory Animals

A median lethal concentration (LC_{50}) in rats exposed to H_2S for 4 hours was estimated as 440 ppm (616 mg/m³) (Tansy *et al*., 1981). An inhalation LC_{Lo} of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m³) for 1 hour is reported in mice (RTECS, 1994). In another study, mortality was significantly higher for male rats (30%), compared to females (20%), over a range of exposure times and concentrations (Prior *et al*., 1988). A concentration of 1,000 ppm (1,400 mg/m³) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m³) for 2 hours resulted in altered leucine incorporation into brain proteins in mice (Elovaara *et al*., 1978). Kosmider *et al*. (1967) reported abnormal electrocardiograms in rabbits exposed to 100 mg/m³ (71 ppm) H_2S for 1.5 hours.

Khan *et al*. (1990) exposed groups of 12 male Fischer 344 rats to 0, 10, 50, 200, 400, or 500-700 ppm hydrogen sulfide for 4 hours. Four rats from each group were sacrificed at 1, 24, or 48 hours post-exposure. Cytochrome c oxidase activity in lung mitochondria was significantly (p<0.05) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1-hour post-exposure compared to controls. A NOAEL of 10 ppm was identified in this study for effects on lung mitochondrial cytochrome c oxidase activity.

VI.   Reproductive or Developmental Toxicity

Xu *et al*. (1998) conducted a retrospective epidemiological study in a large petrochemical complex in Beijing, China in order to assess the possible association between petrochemical exposure and spontaneous abortion. The facility consisted of 17 major production plants which

are divided into separate workshops, allowing for the assessment of exposure to specific chemicals. Married women (n = 2853), who were 20-44 years of age, had never smoked, and who reported at least one pregnancy during employment at the plant, participated in the study. According to their employment record, about 57% of these workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy. There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals compared with those working in nonchemical plants. Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to petrochemicals was consistently associated with an increased risk of spontaneous abortion (overall odds ratio (OR) = 2.7 (95% confidence interval (95% CI) = 1.8 to 3.9) after adjusting for potential confounders). When the analysis was performed with the exposure information obtained from the women' interview responses for (self reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI = 2.0 to 4.0). The analysis was repeated by excluding those 452 women who provided inconsistent reports between recalled exposure and work history, and a comparable risk of spontaneous abortion (OR 2.9; 95% CI 2.0 to 4.4) was found. In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals. There were 106 women (3.7% of the study population) exposed only to hydrogen sulfide, and the results for hydrogen sulphide (OR 2.3; 95% CI = 1.2 to 4.4) were significant. No hydrogen sulfide exposure concentration was reported.

VII.   Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 42 µg/m³
(California Ambient Air Quality Standard)

Study	California State Department of Public Health, 1969; CARB, 1984; Reynolds and Kamper, 1985; Amoore, 1985
Study population	panel of 16 people; general population
Exposure method	inhalation of increasing concentrations of H_2S
Critical effects	headache, nausea
LOAEL	0.012-0.069 ppm (range of odor threshold)
NOAEL	≤ 0.01 ppm
Exposure duration	not stated (tested until odor detected)
Extrapolated 1 hour concentration	0.012-0.069 ppm (geometric mean = 0.03 ppm) (1 hour = minimum duration for an air standard)
LOAEL uncertainty factor	not used
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	0.03 ppm (0.042 mg/m³; 42 µg/m³)

The 1-hour California Ambient Air Quality Standard (AAQS) for hydrogen sulfide was originally based on an olfactory perception study by the California State Department of Public Health (1969). Sixteen individuals were each exposed to increasing concentrations of H_2S until his or her odor threshold was reached. The range of the odor thresholds was 0.012-0.069 ppm, and the geometric mean was 0.029 ppm (geometric standard deviation = 0.005 ppm). The mean odor threshold (rounded to 0.03 ppm) was selected as the AAQS for H_2S. However, others have reported that the odor threshold is as low as 0.0081 ppm (Amoore and Hautala, 1983). In 1984 CARB reviewed the AAQS for H_2S and found that the standard was necessary not only to reduce odors, but also to reduce the physiological symptoms of headache and nausea. (CARB, 1984). Furthermore, Amoore (1985) conducted a study that estimated 40% of the population would find 0.03 ppm (0.042 mg/m³) to be an objectionable concentration. In public testimony before the ARB it was stated that some people reported headaches and other symptoms at the standard (Reynolds and Kamper, 1985). Thus this recommended level protective against mild adverse effects may be need to be reexamined as more data become available.

Level Protective Against Severe Adverse Effects

No recommendation can be made due to the limitations of the database.

An ERPG-2 of 30 ppm (AIHA, 1991) was based on experimental data showing that exposure of rats to 45 ppm (63 mg/m³) H_2S for 4 hours resulted in no deaths (Rogers and Ferin, 1981). In addition, rabbits exposed to 71 ppm (100 mg/m³) H_2S for 1.5 hours developed cardiac irregularities, measured by electrocardiogram, and decreased myocardial ATP phosphorylase (Kosmider *et al.*, 1967). The rationale for the margin of safety used for the ERPG-2 is not presented.

Level Protective Against Life-threatening Effects

No recommendation can be made due to the limitations of the database.

The AIHA ERPG-3 for hydrogen sulfide of 100 ppm (AIHA, 1991) was based on case reports of conjunctivitis, respiratory irritation, and unconsciousness in humans exposed to estimated concentrations of 200-300 ppm (280-420 mg/m³) H_2S for 20 minutes to 1 hour (Ahlborg, 1951; Yant, 1930). In addition, a 1-hour LC_{50} of 712 ppm (997 mg/m³) in rats is cited (CIIT, 1983). The case reports cited in the ERPG document are inadequate to establish acute exposure levels in humans because the concentrations and durations of exposure are only estimates. In addition, there are no LC_{50} data in the CIIT (1983) report. Rats (5 female and 5 male) exposed to H_2S concentrations ranging from 400-600 ppm (560-840 mg/m³) for 4 hours showed dose-dependent lethality rates ranging from 30% - 100% (Tansy *et al.*, 1981). On the other hand, two of three rhesus monkeys exposed to a concentration of 500 ppm (700 mg/m³) for only 35 minutes or less died, which suggests that primates are more sensitive to the lethal effect of H_2S than rats (Lund and Wieland, 1966). The rationale for the margin of safety used for the ERPG-3 was not presented.

NIOSH (1995) reports a (revised) IDLH for hydrogen sulfide of 100 ppm based on acute inhalation toxicity data in humans and animals, but the values from animals appear to be more heavily weighted than the human data in the selection of the IDLH.

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CHRONIC TOXICITY SUMMARY

HYDROGEN SULFIDE

(hydrogen sulphide; dihydrogen sulfide; dihydrogen monosulfide;
sulfur hydride; sulfureted hydrogen; hydrosulfuric acid)
CAS registry number: 7783-06-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**10 μg/m^3 (8 ppb)**
Critical effect(s)	Nasal histological changes in B6C3F1 mice
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1999)

Description	Colorless gas
Molecular formula	H_2S
Molecular weight	34.08
Density	1.4 g/L @ 25° C (air = 1) (AIHA, 1991)
Boiling point	−60.7° C (CRC, 1994)
Melting point	−85.5ºC (CRC, 1994)
Vapor pressure	15,600 Torr @ 25ºC
Solubility	Soluble in water, hydrocarbon solvents, ether, and ethanol
Odor threshold	8.1 ppb (11 μg/m^3) (Amoore and Hautala, 1983)
Odor description	Resembles rotten eggs
Conversion factor	1 ppm = 1.4 mg/m^3 @ 25° C

III. Major Uses or Sources

Hydrogen sulfide (H_2S) is used as a reagent and an intermediate in the preparation of other reduced sulfur compounds (HSDB, 1999). It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986). The annual statewide industrial emissions from point sources at facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 5,688,172 pounds of hydrogen sulfide (CARB, 1999).

IV.   Effects of Human Exposure

Although numerous case studies of acutely toxic effects of H_2S exist, there is inadequate occupational or epidemiological information for specific chronic effects in humans exposed to H_2S.

Bhambhani and Singh (1991) showed that 16 healthy subjects exposed for short durations to 5 ppm (7 mg/m^3) H_2S under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood. Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m^3) H_2S caused coughing and throat irritation after 15 minutes.

In another study, ten asthmatic volunteer subjects were exposed to 2 ppm H_2S for 30 minutes and pulmonary function was tested (Jappinen *et al.*, 1990). All subjects reported detecting "very unpleasant" odor but "rapidly became accustomed to it." Three subjects reported headache following exposure. No significant changes in mean FVC or FEV_1 were reported. Although individual values for specific airway resistance (SR_{aw}) were not reported, the difference following exposure ranged from -5.95% to $+137.78\%$. The decrease in specific airway conductance, SG_{aw}, ranged from -57.7% to +28.9%. The increase in mean SR_{aw} and decrease in mean SG_{aw} were not statistically significant.

Kilburn and Warshaw (1995) investigated whether people exposed to sulfide gases, including H_2S, as a result of working at or living downwind from the processing of "sour" crude oil demonstrated persistent neurobehavioral dysfunction. They studied thirteen former workers and 22 neighbors (of a California coastal oil refinery) who complained of headaches, nausea, vomiting, depression, personality changes, nosebleeds, and breathing difficulties. Their neurobehavioral functions and a profile of mood states were compared to 32 controls (matched for age and educational level). The exposed subjects' mean values were statistically significantly different (abnormal) compared to controls for several tests (two-choice reaction time; balance (as speed of sway); color discrimination; digit symbol; trail-making A and B; immediate recall of a story). Their profile of mood states scores were much higher than those of controls. Visual recall was significantly impaired in neighbors, but not in the former workers. The authors concluded that neurophysiological abnormalities were associated with exposure to reduced sulfur gases, including H_2S from crude oil desulfurization.

Xu *et al*. (1998) conducted a retrospective epidemiological study in a large petrochemical complex in Beijing, China in order to assess the possible association between petrochemical exposure and spontaneous abortion. The facility consisted of 17 major production plants divided into separate workshops, which allow for the assessment of exposure to specific chemicals. Married women (n = 2853), who were 20-44 years of age, had never smoked, and who reported at least one pregnancy during employment at the plant, participated in the study. According to their employment record, about 57% of these workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy. There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals compared with those working in nonchemical plants. Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to

petrochemicals was consistently associated with an increased risk of spontaneous abortion (overall odds ratio (OR) = 2.7 (95% confidence interval (CI) = 1.8 to 3.9) after adjusting for potential confounders). When the analysis was performed with the exposure information obtained from interview responses for (self reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI = 2.0 to 4.0). When the analysis was repeated by excluding those 452 women who provided inconsistent reports between recalled exposure and work history, a comparable risk of spontaneous abortion (OR 2.9; 95% CI = 2.0 to 4.4) was found. In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals. There were 106 women (3.7% of the study population) exposed only to hydrogen sulfide, and the results for hydrogen sulphide (OR 2.3; 95% CI = 1.2 to 4.4) were significant. No hydrogen sulfide exposure concentration was reported.

Four workers were exposed for several minutes to concentrations of hydrogen sulfide sufficient to cause unconciousness. Four other workers were exposed chronically to H_2S and developed lacrimation, eye irritation, nausea, vomiting, headache, sore throat, and skin irritation but retained conciousness as the result of a 150-minute release. Both groups were subjected to olfactory testing 2 to 3 years later (Hirsch and Zavala, 1999). Six of eight workers showed deficits in odor detection and identification, with the workers who had experienced unconciousness most severely affected in the followup tests.

Three patients exposed acutely to unknown concentrations of hydrogen sulfide developed persistent cognitive impairment (Wasch *et al*,. 1989). While standard neurological and physical examinations were unremarkable, all three subjects had prolonged P-300 latencies and persistent neurological and neurobehavioral deficits.

V.   Effects of Animal Exposure

Rats (Fischer and Sprague-Dawley, 15 per group) were exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week for 90 days (CIIT, 1983a,b). Measurements of neurological and hematological function revealed no abnormalities due to H_2S exposure. A histological examination of the nasal turbinates also revealed no significant exposure-related changes. A significant decrease in body weight was observed in both strains of rats exposed to 80 ppm (112 mg/m^3).

In a companion study, the Chemical Industry Institute of Toxicology conducted a 90-day inhalation study in mice (10 or 12 mice per group) exposed to 0, 10.1, 30.5, or 80 ppm (0, 14.1, 42.7, or 112 mg/m^3, respectively) H_2S for 6 hours/day, 5 days/week (CIIT, 1983c). Neurological function was measured by tests for posture, gait, facial muscle tone, and reflexes. Ophthalmological and hematological examinations were also performed, and a detailed necropsy was included at the end of the experiment. The only exposure-related histological lesion was inflammation of the nasal mucosa of the anterior segment of the noses of mice exposed to 80 ppm (112 mg/m^3) H_2S. Weight loss was also observed in the mice exposed to 80 ppm. Neurological and hematological tests revealed no abnormalities. The 30.5 ppm (42.5 mg/m^3) level was considered the NOAEL for histological changes in the nasal mucosa. (Adjustments were made by U. S. EPA to this value to calculate an RfC of 0.9 μg/m^3.)

Fischer F344 rats inhaled 0, 1, 10, or 100 ppm hydrogen sulfide for 8 hours/day for 5 weeks (Hulbert *et al*, 1989). No effects were noted on baseline measurements of airway resistance, dynamic compliance, tidal volume, minute volume, or heart rate. Two findings were noted more frequently in exposed rats: (1) proliferation of ciliated cells in the tracheal and bronchiolar epithelium, and (2) lymphocyte infiltration of the bronchial submucosa. Some exposed animals responded similarly to controls to aerosol methacholine challenge, whereas a subgroup of exposed rats were hyperreactive to concentrations as low as 1 ppm.

Male rats were exposed to 0, 10, 200, or 400 ppm H_2S for 4 hours (Lopez *et al.*, 1987). Samples of bronchoalveolar and nasal lavage fluid contained increased inflammatory cells, protein, and lactate dehydrogenase in rats treated with 400 ppm. Lopez and associates later showed that exposure to 83 ppm (116 mg/m^3) for 4 hours resulted in mild perivascular edema (Lopez *et al.*, 1988).

A study by Saillenfait *et al.* (1989) investigated the developmental toxicity of H_2S in rats. Rats were exposed 6 hours/day on days 6 through 20 of gestation to 100 ppm hydrogen sulfide. No maternal toxicity or developmental defects were observed..

Hayden *et al.* (1990) exposed gravid Sprague-Dawley rat dams continuously to 0, 20, 50, and 75 ppm H_2S from day 6 of gestation until day 21 postpartum. The animals demonstrated normal reproductive parameters until parturition when delivery time was extended in a dose dependent manner (with a maximum increase of 42% at 75 ppm). Pups which were exposed in utero and neonatally to day 21 postpartum developed with a subtle decrease in time of ear detachment and hair development and with no other observed change in growth and development through day 21 postpartum.

VI.   Derivation of Chronic REL

Study	CIIT, 1983c
Study population	B6C3F1 mice (10-12 per group)
Exposure method	Discontinuous inhalation
Critical effects	Histopathological inflammatory changes in the nasal mucosa
LOAEL	80 ppm (112 mg/m^3)
NOAEL	30.5 ppm (42.5 mg/m^3)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	90 days
Average experimental exposure	5.4 ppm for NOAEL group (30.5 x 6/24 x 5/7)
Human equivalent concentration	0.85 ppm (gas with extrathoracic respiratory effects, RGDR = 0.16, based on mouse MV_a = 0.033 L/min; MV_h = 13.8 L/min; SA_a(ET) = 3.0 cm^2; Sa_h(ET) = 200 cm^3) (U.S. EPA, 1994)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	8 ppb (10 µg/m^3)

The adverse effects reported in chronic animal studies occur at higher concentrations than effects seen in acute human exposures. For example, human irritation was reported at concentrations of 2.5-5 ppm for 15 minutes (Bhambhani and Singh, 1985), yet no effects on laboratory animals were observed at concentrations up to 80 ppm for 90 days. This suggests either that humans are more sensitive to H$_2$S, or that the measurements in laboratory animals are too crude to detect subtle measures of irritation. However, the uncertainty factor and HEC attempt to account for these interspecies differences.

VII.   Data Strengths and Limitations for Development of the REL

Hydrogen sulfide is the leading chemical agent causing human fatalities following inhalation exposures. Although lower concentration acute exposures have been quantitatively studied with human volunteers, the dose-response relationship for human toxicity due to hydrogen sulfide exposure is not known. Thus, a major area of uncertainty is the lack of adequate long-term human exposure data. Subchronic (but not chronic) studies have been conducted with several animal species and strains, and these studies offer an adequate basis for quantitative risk assessment.

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations, adequate histopathogical analysis, and the observation of a NOAEL.

Hydrogen sulfide has a strong unpleasant odor. The threshold for detection of this odor is low, but shows wide variation among individuals. A level of 7 $\mu g/m^3$, based on a 30 minute averaging time, was estimated by a Task Force of the International Programme on Chemical Safety (IPCS) (1981) to not produce odor nuisance in most situations. On the other hand, the current California Ambient Air Quality standard for hydrogen sulfide, based on a 1 hour averaging time, is 42 $\mu g/m^3$ (30 ppb).

Amoore (1985) analyzed a large number of reports from the scientific literature and found that reported thresholds for detection were log-normally distributed, with a geometric mean of 10 $\mu g/m^3$ (8 ppb). Detection thresholds for individuals were reported to be log-normally distributed in the general population, with a geometric standard deviation of 4.0, *i.e.* 68% of the general population would be expected to have a detection threshold for hydrogen sulfide between 2.5 and 40 $\mu g/m^3$ (2 and 32 ppb). Sources of variation included age, sex, medical conditions, and smoking. Training and alertness of the subject in performing the test also affected the results.

Amoore (1985) drew attention to the difference between a detection threshold under laboratory conditions, and the levels at which an odor could be recognized, or at which it was perceived as annoying. Analysis of various laboratory and sociological studies suggested that a level at which an odor could be recognized was typically a factor of three greater than the threshold for detection, while the level at which it was perceived as annoying was typically a factor of five greater than the threshold. Annoyance was characterized both in terms of esthetic or behavioral responses, and by physiological responses such as nausea and headache. He therefore predicted that, although at 10 $\mu g/m^3$ (the proposed REL) 50% of the general population would be able to detect the odor of hydrogen sulfide under controlled conditions, only 5% would find it annoying at this level. At 50 $\mu g/m^3$, 50% would find the odor annoying.

On this basis, the proposed REL of 10 $\mu g/m^3$ (8 ppb) is likely to be detectable by many people under ideal laboratory conditions, but it is unlikely to be recognized or found annoying by more than a few. It is therefore expected to provide reasonable protection from odor annoyance in practice. However, this consideration cannot be entirely dismissed due to the wide inter-individual variation in sensitivity to odors. Amoore (1985) also points out that many industrial operations generating hydrogen sulfide also generate organic thiol compounds with similar, but even more potent odors (e.g., methyl mercaptan, butyl mercaptan). Such compounds may in fact have detection thresholds as much as a hundred-fold lower than hydrogen sulfide, so even minute quantities have a powerful impact on odor perception. Because of the concurrent emission of these contaminants, the incidence of odor complaints near hydrogen sulfide emitting sites correlated poorly with the levels of hydrogen sulfide measured in the affected areas.

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LEAD AND LEAD COMPOUNDS (INORGANIC)

CAS No.: 7439-92-1

I. PHYSICAL AND CHEMICAL PROPERTIES

Molecular weight	207.2 (Budavari, 1989)
Boiling point	1740° C (Budavari, 1989)
Melting point	327.4° C (Budavari, 1989)
Vapor pressure	1.77 mm Hg at 1000° C (Budavari, 1989)
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.2 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: (inhalation) 4.2 E-2 $(mg/kg\text{-}day)^{-1}$
(oral) 8.5 E-3 $(mg/kg\text{-}day)^{-1}$
[Calculated by OEHHA (1997) from rat kidney tumor incidence data (Azar *et al.*, 1973) using a linearized multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies and case reports of people occupationally exposed to lead provide some evidence of carcinogenicity but are not convincing due to lack of controlling for confounders such as smoking and to the simultaneous exposure of some workers to known human carcinogens including arsenic and cadmium. These studies have been reviewed by several agencies (IARC, 1980; U.S. EPA, 1986; 1989a; 1989b; ATSDR, 1990).

The epidemiologic study by Selevan *et al.* (1985) suggested that human cancer may be induced in the same organ in which cancer is induced in animals. A cohort of 1,987 lead smelter workers was studied. The study confirmed previous reports of occupationally-induced, chronic, fatal renal disease after long term exposure to lead and yielded a Standardized Mortality Ratio (SMR) of 204 for kidney cancer, but the numbers were small (6 cases observed) and the SMR for kidney cancer was not statistically significant.

Recently the study has been updated to include 11 years of follow-up and 363 additional deaths (Steenland *et al.*, 1992). No additional deaths from nonmalignant kidney disease had occurred but 3 additional deaths from kidney cancer had occurred. The updated SMR from kidney cancer was 193 (9 total kidney cancer deaths, 95% confidence interval (CI = 0.88, 3.67), i.e., not statistically significant at the 5% level). The SMR for kidney cancer for those with the highest lead exposure was statistically significant (SMR = 239 based on 8 cancers, 95% CI = 1.03, 4.71). The study suffers from lack of detailed data on lead exposure levels and from potential confounding exposures to cadmium, arsenic, and tobacco smoke.

In an epidemiologic study of 7,121 deceased California plumbers and pipefitters, Cantor *et al.* (1986) found increased cancer incidence for all neoplasms and for cancers of several sites including the respiratory system, kidney, and stomach. In addition to lead, these workers were exposed to carcinogens such as asbestos and chromium. Since excess mesotheliomas were observed (16 observed, 2 expected), asbestos exposure likely contributed to the observed increase in stomach and respiratory system cancer. Asbestos, chromium, and cigarette smoking are likely contributors to lung cancer but are not generally considered causes of kidney cancer.

There are 2 case reports of renal cancer in men occupationally exposed to toxic levels of lead (Baker *et al.*, 1980; Lilis, 1981). Baker *et al.* (1980) thought that the histology in the renal tumor in their case report was similar to that of kidney tumors in lead-exposed animals. Despite the long history of human lead exposure and the chronic nephropathy induced by lead, the data on lead-induced, human renal cancer is not definitive.

In regard to induction of cancer in organs other than the kidney, the largest occupational cohort studied for lead-induced cancer included approximately 6,800 employees of 6 lead smelters and recycling plants and 10 battery manufacturing plants in the United States (Cooper and Gaffey, 1975; Cooper, 1976; Kang *et al.*, 1980; Cooper, 1981; Cooper *et al.*, 1985; Cooper, 1988). Statistically significant increases in cancer have been reported for total malignant neoplasms in lead production workers (Cooper and Gaffey, 1975), total malignant neoplasms and cancers of both the digestive tract and the respiratory tract in lead production workers and in battery workers (Kang *et al.*, 1980), no sites (Cooper, 1981; 1988), and total malignancies in the battery workers (Cooper at al., 1985) principally due to cancers of the respiratory and digestive tracts. In these studies several factors including cigarette smoking could not be ruled out as confounders.

Ades and Kazantzis (1988) studied 4,293 men at a zinc-lead-cadmium smelter in Great Britain. An effect of lead exposure on lung cancer was noted but lead exposure was highly correlated with exposure to arsenic, a known respiratory carcinogen, and no data on cigarette smoking were reported.

Fu and Boffetta (1995) have conducted a meta-analysis of the published studies on cancer and workplace exposures to inorganic lead compounds. The studies include the 2 case reports, 16 papers dealing with cohort studies, and 7 papers dealing with case-control studies. The meta-analysis showed a statistically significant, excess relative risk of cancer overall (RR = 1.11, 95% CI = 1.05-1.17), of stomach cancer (RR = 1.33, CI = 1.18-1.49), of lung cancer (RR = 1.29, CI = 1.10-1.50), and of bladder cancer (RR = 1.41, CI = 1.16=1.71). The relative risk for kidney cancer did not reach statistical significance (RR = 1.19, CI = 0.96-1.48). A separate analysis of studies involving workers heavily exposed to lead found higher relative risks for stomach cancer (RR = 1.50, CI = 1.23-1.43, based on 4 studies) and lung cancer (RR = 1.42, CI = 1.29-1.62, based on 4 studies). The meta-analysis is further indication of a relationship between lead exposure and cancer, but it is limited by the paucity of information in the various studies on confounders such as cigarette smoking, dietary habits, and other occupational carcinogens at many of the workplaces studied (Fu and Boffetta, 1995).

There are corroborative findings relevant to the potential of lead to be both an initiator and a promoter of carcinogenicity (Goyer, 1992). Results of these studies will not be discussed here.

Animal Studies

There are a large number of carcinogenicity studies in rodents in which lead compounds were administered by the oral route, either in feed or in drinking water. Although other types of tumors are occasionally seen, the principal finding has been kidney tumors, both benign and malignant, in rats. Important studies are summarized in Table 1.

No long-term studies in animals to investigate carcinogenicity due to lead inhalation have been conducted. Intratracheal instillation of lead oxide was employed in one study of cancer (Kobayashi and Okamoto, 1974). No tumors were seen in 20 hamsters after 10 intratracheal instillations of 1 mg of lead oxide, which gave a comparatively low total dose of 10 mg. In that study, however, simultaneous administration of lead with benzo[a]pyrene (10 instillations of 1 mg), which by itself also did not cause tumors, did act to produce lung tumors. Lead might be acting as a promoter or co-carcinogen for benzo[a]pyrene-initiated carcinogenicity.

Table 1: Kidney tumors induced by lead compounds

Author(s)	Pb Compound	Species	Sex	Route	Time[a]	Concentration	Total Lead Dose (g)	Tumor Incidence
van Esch and Kroes (1969)	subacetate	mouse	M	diet	24 mo	0.1%	2	6/26
			F			0.1%	2	2/25
van Esch and Kroes (1969)	subacetate	hamster	M, F	diet	24 mo	0.1%	7	M 0/22, F 0/24
						0.5%	35	M 0/22, F 0/24
Schroeder et al. (1970)	nitrate	rat	M	water	life	25 ppm	0.5	0/52
Zawirska and Medras (1968)	acetate	rat	M	po / feed	18 mo	3 mg/day, then 4 mg/day	1	58/94
			F				1	14/32
Nogueira (1987)	acetate	rat	M	feed	6 mo	0.5%	9	0/12
						1.0%	17	9/10
Azar et al. (1973)	acetate	rat	F	diet	24 mo	0-2000 ppm	0-26	up to 13/20
Boyland et al. (1962)	acetate	rat	M	diet	12 mo	1.0%	34	15/16
Kasprzak et al. (1985)	subacetate	rat	M	feed	18 mo	1.0%	38	13/29
Koller et al. (1985)	acetate	rat	M	water	18 mo	2600 ppm	38	13/16
van Esch et al. (1962)	subacetate	rat	M, F	diet	24 mo	0.1%	10	M 5/12, F 6/13
			M, F		24 mo	1.0%	97	M 6/7, F 7/9
Mao and Molnar (1967)	subacetate	rat	M	diet	life	1.0%	97	31/40

[a] Time is in months unless otherwise noted.

IV.   DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The U.S. EPA, IARC, and the State of California have all determined that, based on animal studies, lead is a carcinogen. The relevant animal studies have been reviewed by U.S. EPA and IARC (IARC, 1980; 1987; U.S. EPA, 1986; 1989a; 1989b). U.S. EPA has classified lead and lead compounds in class B2, probable human carcinogens. This conclusion is based on sufficient animal evidence and inadequate human evidence. IARC has concluded: "There is sufficient evidence that lead subacetate is carcinogenic to mice and rats and that lead acetate and lead phosphate are carcinogenic to rats." There are inadequate human data. IARC classifies lead in Group 2B, possibly carcinogenic to humans.

The quantitative cancer risk assessment is based on the best available animal data set for risk assessment, male rat kidney tumors. The U.S. EPA Air Quality Criteria for Lead document (U.S. EPA, 1986; 1989a) examined lead's carcinogenicity but it also did not contain a formal quantitative risk assessment. OEHHA relied extensively on these U.S. EPA documents in the preparation of its quantitative cancer risk assessment.

Methodology

A large number of animal studies have shown kidney tumors following oral exposure to lead compounds (Tables 1), but there are no studies of carcinogenicity due to lead inhalation. The best tumor dose-response data for use in quantitative cancer risk assessment are those of Azar *et al.* (1973). In the Azar *et al.* study, lead as lead acetate was given to groups of male and female rats in the feed at concentrations of 0, 10, 50, 100, 500, 1000, and 2000 ppm (nominal concentrations) for 2 years. Kidney tumors, mainly adenomas, were seen in a dose-dependent relationship in the 3 highest dose groups in males. Tumors were also seen in the 2000 ppm dose group in females (7/20 or 35%). Cancer risk at ambient levels was estimated by extrapolating at least 5 orders of magnitude from these data by means of the best fitting linearized multistage model.

The data used to calculate cancer risk from the rat kidney tumors (Azar *et al.*, 1973) are given in Table 2. Doses were first converted to human equivalent doses (HED) (Anderson *et al.*, 1983). Using the computer software GLOBAL86 (Howe *et al.*, 1986), a linearized multistage model was fit to the male kidney tumor dose-response data. The male rat kidney tumor data yielded a maximum likelihood estimate (MLE) for q_1 (the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered in the equation for the multistage model) of 0 $(mg/kg/day)^{-1}$, an MLE for q_2 of $2.5 \times 10^{-3}(mg/kg/day)^{-2}$, and an Upper 95% Confidence Limit (UCL) on q_1 (also known as q_1^* and as the cancer potency) of 8.5×10^{-3} $(mg/kg/day)^{-1}$.

Available human data indicate that approximately 50% of inhaled lead is absorbed compared to approximately 10% of ingested lead (summarized by Owen, 1990). If the percentage of lead absorbed by inhalation is similar for rats and humans and if the standard assumption that an

average adult human has a body weight of 70 kg and an average air intake of 20 m^3 per day is used, an oral intake of 1 mg/kg/day lead is equivalent to an inhalation exposure of 3,500 μg/m^3 for 24 hr. Using the latter units, the 95% UCL for q$_1$ equals 2.4×10^{-6} (μg/m^3)$^{-1}$, which assumes equivalent absorption by the 2 routes. If there is approximately 5 times higher absorption by the respiratory tract compared to the gastrointestinal tract (Owen, 1990), the inhalation risk can be multiplied by 5 and the corrected inhalation unit risk is 1.2×10^{-5} (μg/m^3)$^{-1}$.

To derive a range of risks, the study by Koller *et al.* (1985), which showed the greatest sensitivity to lead's carcinogenicity, was selected. In that study, 13 out of 16 male rats drinking water containing 2600 ppm lead acetate developed renal tumors, compared to 0 of 10 in controls. The resulting human equivalent dose (HED) was calculated as 60.1 mg/kg-day. Using the GLOBAL86 program, an MLE for q$_1$ of 0.0279 (mg/kg-day)$^{-1}$ and a 95% UCL, q$_1$* of 0.0455 (mg/kg-day)$^{-1}$ were obtained. The latter potency was divided by 3500 to obtain a preliminary inhalation unit risk of 1.3×10^{-5} (μg/m^3)$^{-1}$, which, when corrected for the 5-fold greater absorption by inhalation compared to ingestion in humans (Owen 1990), yielded a final inhalation unit risk of 6.5×10^{-5} (μg/m^3)$^{-1}$.

Therefore, the 95% UCL obtained for the range of inhalation unit risks is 1.2×10^{-5} (μg/m^3)$^{-1}$ to 6.5×10^{-5} (μg/m^3)$^{-1}$. The best value of the cancer unit risk for air was selected as 1.2×10^{-5} per μg/m^3.

Table 2:   Kidney tumors in rats fed lead[a]

Lead in food (ppm)		Animal dose (mg/kg-day)	HED[b] (mg/kg-day)	Number of rats[c]		%	% died
Added	Measured			exp[d]	tumors		
0	3	0.225	0.038	20[f]	0	0	50
0	5	0.39	0.067	100	0	0	37
10	18	1.40	0.238	50	0	0	36
50	62	4.78	0.818	50	0	0	36
100	141	10.88	1.86	50	0	0	36
500	548	42.27	7.22	50	5	10	52
1000[e]	1130	79.65	13.6	20[f]	10	50	50
2000[e]	2102	162	27.2	20[f]	16	80	80

[a] Data from Azar *et al.* (1973).
[b] Human Equivalent Dose = daily dose $\times (70/0.35)^{1/3}$.
[c] Among similar size groups of female rats, kidney tumors were seen only in 7 of 20 animals in the 2000 ppm group.
[d] Number of animals exposed to indicated level of lead in food.
[e] The rate of body weight gain was depressed in both groups. Since mortality was not increased in the 1000 ppm group, it can be considered a Maximally Tolerated Dose (MTD).
[f] The groups with only 20 rats per dose level were also studied for 2 years but were begun several months after the other dose groups.

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OCCUPATIONAL SAFETY AND HEALTH GUIDELINE FOR

METHYL MERCAPTAN

INTRODUCTION

This guideline summarizes pertinent information about methyl mercaptan for workers, employers, and occupational safety and health professionals who may need such information to conduct effective occupational safety and health programs. Recommendations may be superseded by new developments in these fields; therefore, readers are advised to regard these recommendations as general guidelines.

SUBSTANCE IDENTIFICATION

• **Formula:** CH_4S

• **Structure:** CH_3—SH

• **Synonyms:** Mercaptomethane, methanethiol, methyl sulfhydrate, thiomethyl alcohol

• **Identifiers:** CAS 74-93-1; RTECS PB4375000; DOT 1064, label required: "Flammable Gas"

• **Appearance and odor:** Colorless gas with an odor like decaying cabbage

CHEMICAL AND PHYSICAL PROPERTIES

• **Physical data**
1. Molecular weight: 48.11
2. Boiling point (at 760 mmHg): 5.96°C (40.4°F)
3. Specific gravity (water = 1): 0.8665
4. Vapor density (air = 1 at boiling point of methyl mercaptan): 1.66
5. Melting point: -123°C (-190°F)
6. Vapor pressure at 20°C (68°F): 1,276 mmHg
7. Solubility in water, g/100 g water at 20°C (68°F): 2.4
8. Ionization potential: 9.44 eV

• **Reactivity**
1. Incompatibilities: Strong oxidizing agents. Elevated temperature may generate high internal pressure and cause containers to burst.
2. Hazardous decomposition products: Toxic vapors and gases (e.g., sulfur dioxide and carbon monoxide) may be released in a fire involving methyl mercaptan.

3. Caution: Liquid methyl mercaptan will attack some forms of plastics, coatings, and rubber.

• **Flammability**
1. Flash point: -18°C (0°F) (open cup)
2. Flammable limits in air, % by volume: Lower, 3.9; upper, 21.8
3. Extinguishant: Carbon dioxide, dry chemicals, or alcohol foam
4. Class IA Flammable Liquid (29 CFR 1910.106), Flammability Rating 4 (NFPA)

• **Warning properties**
1. Odor threshold: 1 ppb
2. Evaluation of warning properties for respirator selection: Because of its odor, methyl mercaptan can be detected below the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL); thus it is treated as a chemical with adequate warning properties.

EXPOSURE LIMITS

The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for methyl mercaptan is 10 parts of methyl mercaptan per million parts of air (ppm) [20 milligrams of methyl mercaptan per cubic meter of air (mg/m^3)] as a ceiling concentration which shall at no time be exceeded. The NIOSH REL is 0.5 ppm $(1.0 mg/m^3)$ as a ceiling concentration determined in any 15-minute sampling period. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) is 0.5 ppm $(1 mg/m^3)$ as a time-weighted average (TWA) concentration for a normal 8-hour workday and a 40-hour workweek (Table 1).

Table 1.—Occupational exposure limits for methyl mercaptan

	Exposure limits	
	ppm	mg/m³
OSHA PEL ceiling	10	20
NIOSH REL ceiling (15 min)	0.5	1.0
ACGIH TLV® TWA	0.5	1.0

HEALTH HAZARD INFORMATION

• **Routes of exposure**
Methyl mercaptan may cause adverse health effects following exposure via inhalation or dermal or eye contact.

• **Summary of toxicology**
1. *Effects on animals:* Acute inhalation of methyl mercaptan by rats and mice caused restlessness, increased respiration, muscular weakness progressing to paralysis, convulsions, respiratory depression, deficient oxygenation of the blood (cyanosis), and death due to respiratory paralysis. Subchronic inhalation of methyl mercaptan by monkeys, rats, and mice caused altered blood chemistries in all three species, pulmonary edema in monkeys, and persistent hepatitis and cellular changes of the liver, lungs, and kidneys in mice.
2. *Effects on humans:* An accidental industrial exposure of a worker to methyl mercaptan caused elevated blood pressure, severe hemolytic anemia, methemoglobinemia, deep coma, and death due to pulmonary embolus 28 days following exposure.

• **Signs and symptoms of exposure**
1. *Short-term (acute):* Exposure to methyl mercaptan can cause headache, dizziness, staggered gait, nausea, vomiting, pulmonary irritation, expiratory wheezing, rapid heart beat (tachycardia), rigidity of the arms and legs, bluish discoloration of the skin and mucous membranes (cyanosis), and irritation of the eyes and mucous membranes.
2. *Long-term (chronic):* Low-level exposure to methyl mercaptan can cause dermatitis.

RECOMMENDED MEDICAL PRACTICES

• **Medical surveillance program**
Workers with potential exposures to chemical hazards should be monitored in a systematic program of medical surveillance intended to prevent or control occupational injury and disease. The program should include education of employers and workers about work-related hazards, placement of workers in jobs that do not jeopardize their safety and health, earliest possible detection of adverse health effects, and referral of workers for diagnostic confirmation and treatment. The occurrence of disease (a "sentinel health event," SHE) or other work-related adverse health effects should prompt immediate evaluation of primary preventive measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). A medical surveillance program is intended to supplement, not replace, such measures.

A medical surveillance program should include systematic collection and epidemiologic analysis of relevant environmental and biologic monitoring, medical screening, morbidity, and mortality data. This analysis may provide information about the relatedness of adverse health effects and occupational exposure that cannot be discerned from results in individual workers. Sensitivity, specificity, and predictive values of biologic monitoring and medical screening tests should be evaluated on an industry-wide basis prior to application in any given worker group. Intrinsic to a surveillance program is the dissemination of summary data to those who need to know, including employers, occupational health professionals, potentially exposed workers, and regulatory and public health agencies.

• **Preplacement medical evaluation**
Prior to placing a worker in a job with a potential for exposure to methyl mercaptan, the physician should evaluate and document the worker's baseline health status with thorough medical, environmental, and occupational histories, a physical examination, and physiologic and laboratory tests appropriate for the anticipated occupational risks. These should concentrate on the function and integrity of the skin and nervous and respiratory systems. Medical surveillance for respiratory disease should be conducted by using the principles and methods recommended by NIOSH and the American Thoracic Society (ATS).

A preplacement medical evaluation is recommended in order to detect and assess preexisting or concurrent conditions which may be aggravated or result in increased risk when a worker is exposed to methyl mercaptan at or below the NIOSH REL. The examining physician should consider the probable frequency, intensity, and duration of exposure, as well as the nature and degree of the condition, in placing such a worker. Such conditions, which should not be regarded as absolute contraindications to job placement, include chronic diseases of the skin and respiratory system.

• **Periodic medical screening and/or biologic monitoring**
Occupational health interviews and physical examinations should be performed at regular intervals. Additional examinations may be necessary should a worker develop symptoms that may be attributed to exposure to methyl mercaptan. The interviews, examinations, and appropriate medical screening and/or biologic monitoring tests should be directed at identifying an excessive decrease or adverse trend in the physiologic function of the skin and nervous and respiratory systems as compared to the baseline status of the individual worker or to expected values for a suitable reference population. The following tests should be used and interpreted according to standardized procedures and evaluation criteria recommended by NIOSH and the ATS: standardized questionnaires and tests of lung function.

• **Medical practices recommended at the time of job transfer or termination**
The medical, environmental, and occupational history interviews, the physical examination, and selected physiologic and laboratory tests which were conducted at the time of placement should be repeated at the time of job transfer or termination. Any changes in the worker's health status should be compared to those expected for a suitable reference population.

MONITORING AND MEASUREMENT PROCEDURES

• **Ceiling concentration evaluation**
Measurements to determine worker exposure should be taken during periods of maximum expected airborne concentrations of methyl mercaptan. Each measurement to determine the NIOSH REL (ceiling exposure) in the worker's breathing zone (air that most nearly represents that inhaled by the worker)

should consist of a 15-minute sample or a series of consecutive samples that total 15 minutes. A minimum of three measurements should be taken during one workshift, and the highest of all measurements taken is an estimate of the worker's exposure. If the periods of maximum exposure are not clearly defined, a statistical procedure which can be used as a peak exposure detection strategy is given in the *Occupational Exposure Sampling Strategy Manual*.

• **Method**
There are no NIOSH-validated sampling and analytical methods for methyl mercaptan. Direct reading devices calibrated to measure methyl mercaptan may be used if available.

PERSONAL PROTECTIVE EQUIPMENT

Chemical protective clothing (CPC) should be selected after utilizing available performance data, consulting with the manufacturer, and then evaluating the clothing under actual use conditions.

Workers should be provided with and required to use CPC, gloves, face shields (8-inch minimum), and other appropriate protective clothing necessary to prevent skin contact with methyl mercaptan.

Workers should be provided with and required to use splash-proof safety goggles where liquid methyl mercaptan may come in contact with the eyes.

SANITATION

Clothing which is contaminated with liquid methyl mercaptan should be removed immediately and placed in closed containers for storage until it can be discarded or until provision is made for the removal of methyl mercaptan from the clothing. If the clothing is to be laundered or cleaned, the person performing the operation should be informed of methyl mercaptan's hazardous properties.

Change and shower rooms should be provided with separate locker facilities for street and work clothes.

Skin that becomes contaminated with methyl mercaptan should be promptly washed with soap and water.

The storage, preparation, dispensing, or consumption of food or beverages, the storage or application of cosmetics, the storage or smoking of tobacco or other smoking materials, or the storage or use of products for chewing should be prohibited in work areas.

Workers who handle methyl mercaptan should wash their faces, hands, and forearms thoroughly with soap and water before eating, smoking, or using toilet facilities.

COMMON OPERATIONS AND CONTROLS

Common operations in which exposure to methyl mercaptan may occur and control methods which may be effective in each case are listed in Table 2.

Table 2.—Operations and methods of control for methyl mercaptan

Operations	Controls
During use in the manufacture and processing of methyl mercaptan and methionine; during use as a catalyst or activator; during use in wood processing	Process enclosure, local exhaust ventilation, general dilution ventilation, personal protective equipment
During use in the synthesis of chemical intermediates for the manufacture of resins, plastics, insecticides, and pressure-sensitive and oil-resistant adhesives	Process enclosure, local exhaust ventilation, general dilution ventilation, personal protective equipment
During use as an odorant and warning agent in natural gas; during use in jet fuels; during the cleaning and maintenance of storage containers	Local exhaust ventilation, general dilution ventilation, personal protective equipment

EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, remove the victim from further exposure, send for medical assistance, and initiate emergency procedures.

• **Eye exposure**
Where there is any possibility of a worker's eyes being exposed to methyl mercaptan, an eye-wash fountain should be provided within the immediate work area for emergency use.

If methyl mercaptan gets into the eyes, flush them immediately with large amounts of water for 15 minutes, lifting the lower and upper lids occasionally. Get medical attention as soon as possible. Contact lenses should not be worn when working with this chemical.

• **Skin exposure**
Where there is any possibility of a worker's body being exposed to methyl mercaptan, facilities for quick drenching of the body should be provided within the immediate work area for emergency use.

If methyl mercaptan gets on the skin, wash it immediately with soap and water. If methyl mercaptan penetrates the clothing, remove the clothing immediately and wash the skin with soap and water. Get medical attention promptly.

• **Rescue**
If a worker has been incapacitated, move the affected worker from the hazardous exposure. Put into effect the established emergency rescue procedures. Do not become a casualty. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises.

SPILLS AND LEAKS

Workers not wearing protective equipment and clothing should be restricted from areas of spills or leaks until cleanup has been completed.

If methyl mercaptan is spilled or leaked, the following steps should be taken:

1. If methyl mercaptan is in the gaseous form, stop the flow of gas. If the source of the leak is a cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place in the open air and repair the leak or allow the cylinder to empty.
2. Remove all ignition sources.
3. Ventilate area of spill or leak.
4. For small quantities of liquids containing methyl mercaptan, absorb on paper towels and place in an appropriate container. Place towels in a safe place such as a fume hood for evaporation. Allow sufficient time for evaporation of the vapors so that the hood duct work is free from methyl mercaptan vapors. Burn the paper in a suitable location away from combustible material.
5. Large quantities of liquids containing methyl mercaptan may be absorbed in vermiculite, dry sand, earth, or a similar material and placed in an appropriate container. Methyl mercaptan should not be allowed to enter a confined space such as a sewer because of the possibility of an explosion.
6. Liquids containing methyl mercaptan may be collected by vacuuming with an appropriate system. If a vacuum system is used, there should be no sources of ignition in the vicinity of the spill, and flashback prevention devices should be provided.

WASTE REMOVAL AND DISPOSAL

U.S. Environmental Protection Agency, Department of Transportation, and/or state and local regulations shall be followed to assure that removal, transport, and disposal are in accordance with existing regulations.

RESPIRATORY PROTECTION

It must be stressed that the use of respirators is the least preferred method of controlling worker exposure and should not normally be used as the only means of preventing or minimizing exposure during routine operations. However, there are some exceptions for which respirators may be used to control exposure: when engineering and work practice controls are not technically feasible, when engineering controls are in the process of being installed, or during emergencies and certain maintenance operations including those requiring confined-space entry (Table 3).

In addition to respirator selection, a complete respiratory protection program should be instituted which as a minimum complies with the requirements found in the OSHA Safety and Health Standards 29 CFR 1910.134. A respiratory protection program should include as a minimum an evaluation of the worker's ability to perform the work while wearing a respirator, the regular training of personnel, fit testing, periodic en-

vironmental monitoring, maintenance, inspection, and cleaning. The implementation of an adequate respiratory protection program, including selection of the correct respirators, requires that a knowledgeable person be in charge of the program and that the program be evaluated regularly.

Only respirators that have been approved by the Mine Safety and Health Administration (MSHA, formerly Mining Enforcement and Safety Administration) and by NIOSH should be used. **Remember! Air-purifying respirators will not protect from oxygen-deficient atmospheres.**

For each level of respiratory protection, only those respirators that have the minimum required protection factor and meet other use restrictions are listed. All respirators that have higher protection factors may also be used.

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Table 3.—Respiratory protection for methyl mercaptan

Condition	Minimum respiratory protection*†
Concentration:	
Less than or equal to 5 ppm	Any supplied-air respirator
	Any self-contained breathing apparatus
	Any chemical cartridge respirator with organic vapor cartridge(s)
Less than or equal to 12.5 ppm	Any supplied-air respirator operated in a continuous flow mode
	Any powered air-purifying respirator with organic vapor cartridge(s)
Less than or equal to 25 ppm	Any self-contained breathing apparatus with a full facepiece
	Any supplied-air respirator with a full facepiece
	Any chemical cartridge respirator with a full facepiece and organic vapor cartridge(s)
	Any air-purifying full facepiece respirator (gas mask) with a chin-style or front- or back-mounted organic vapor canister
	Any powered air-purifying respirator with a tight-fitting facepiece and organic vapor cartridge(s)
	Any supplied-air respirator with a tight-fitting facepiece and operated in a continuous flow mode
Less than or equal to 400 ppm	Any supplied-air respirator with a half-mask and operated in a pressure-demand or other positive pressure mode
Planned or emergency entry into environments containing unknown concentrations or levels above 400 ppm	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive pressure mode
Firefighting	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
Escape only	Any air-purifying full facepiece respirator (gas mask) with a chin-style or front- or back-mounted organic vapor canister
	Any appropriate escape-type self-contained breathing apparatus

* Only NIOSH/MSHA-approved equipment should be used.
† The respiratory protection listed for any given condition is the minimum required to meet the NIOSH REL of 0.5 ppm (1.0 mg/m³) (ceiling).

NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE TO

- ## n-ALKANE MONO THIOLS
- ## CYCLOHEXANETHIOL
- ## BENZENETHIOL

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO

n-ALKANE MONO THIOLS, CYCLOHEXANETHIOL, and BENZENETHIOL

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1954, the American Conference of Governmental Industrial Hygenists (ACGIH) proposed tentative threshold limit values (TLV's) of 50 ppm for methyl mercaptan (methanethiol), 250 ppm for ethyl mercaptan (ethanethiol), and 10 ppm for butyl mercaptan (butanethiol) [128], expressed as time-weighted average (TWA) concentrations for an 8-hour day. All three of these values were adopted in 1962. In 1963, the TLV's, defined as TWA concentrations except when designated as ceiling concentrations, for both ethyl mercaptan and methyl mercaptan were changed to ceiling concentrations of 20 ppm.

In 1964, the ACGIH proposed a reduced TLV of 10 ppm for methyl mercaptan, which was adopted in 1966. In 1965, the ACGIH proposed a ceiling value of 10 ppm for ethyl mercaptan. This was adopted in 1967. The ACGIH established the TLV's by analogy with the toxicity of hydrogen sulfide [131]. Methyl mercaptan was regarded as having an acute toxicity similar to, but less than, that of hydrogen sulfide, according to studies by de Rekowski [132] and Frankel [133]. This analogy was supported by citing the Ljunggren and Norberg report [53], and a TLV of 10 ppm was recommended. By a similar analogy, ethyl mercaptan was regarded as being only one-tenth as toxic as hydrogen sulfide. The inhalation studies by Fairchild and Stokinger [59] on mice and rats were cited, with 4-hour LC_{50}'s for ethyl mercaptan of 2,770 and 4,420 ppm, respectively. These values were considered to be similar to values obtained for butyl mercaptan. Reports of headache, nausea, and irritation experienced by humans at levels approaching 10 ppm led the ACGIH to propose and adopt a ceiling concentration of 10 ppm for ethyl mercaptan. In contrast, butyl mercaptan at 10 ppm was considered to be odorous, but not sufficiently so to be seriously objectionable. In addition, the odor of butyl mercaptan was considered to be similar to that of hydrogen sulfide, and a TLV of 10 ppm was recommended. In the notice of intended changes for the 1968 TLV list, the ACGIH stated values of 0.5 ppm as the proposed TLV's for butyl, ethyl, and methyl mercaptans. These TLV's were adopted as TWA limits in 1970, and no further changes have been made in the recommended values for these thiols through the 1977 TLV listing. In 1977, the ACGIH [134] proposed a TLV for phenyl mercaptan (benzenethiol) of 0.5 ppm (2 mg/cu m), expressed as a TWA concentration.

The justification for the change respecting methanethiol was presented in the 1976 edition of Documentation of the Threshold Limit Values for Substances in Workroom Air [131]. Methanethiol was cited as being similar to hydrogen sulfide in toxicity but with a stronger, more disagreeable odor; the latter statement was not supported. The 0.5 ppm TLV is the

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equivalent (approximately) of 0.98 mg methanethiol/cu m. For ethanethiol, the TLV of 0.5 ppm (approximately 1.3 mg/cu m) was based on the effects in humans--headache, nausea, and irritation--of exposure to the chemical at 4 ppm for 3 hours/day [48]. For butanethiol, the TLV of 0.5 ppm (approximately 2 mg/cu m) just noted and from its readily noticeable odor at 0.1-1.0 ppm (approximately 0.4-4.0 mg/cu m of air).

In 1968, Mississippi had TWA limits of 50 ppm for methyl mercaptan and 10 ppm for butyl mercaptan [135], and Massachusetts listed a TWA limit of 250 ppm for ethyl mercaptan. Pennsylvania listed a TWA limit of 5 ppm for methyl mercaptan in 1968; earlier TWA limits were 20 ppm for ethyl mercaptan and 10 ppm for butyl mercaptan.

The current Occupational Safety and Health Administration limits, stated in 29 CFR 1910.1000, based on the ACGIH-adopted values for 1968, are 10 ppm for butyl mercaptan, expressed as a TWA concentration, and a ceiling value of 10 ppm for methyl and ethyl mercaptans.

Austria, Belgium, Finland, Switzerland, and Yugoslavia have established limits for methyl, ethyl, and butyl mercaptans at 0.5 ppm. The Netherlands has limits for only methyl and butyl mercaptans at 0.5 ppm, and the Federal Republic of Germany lists a limit for ethyl mercaptan at 0.5 ppm. The USSR limit is 0.8 ppm for ethyl mercaptan. Rumania has limits of 30, 50, and 30 ppm for methyl, ethyl, and butyl mercaptans, respectively [135].

Basis for the Recommended Standard

(a) Environmental Concentration Limits

There is no definitive study that allows derivation of a dose-effect relationship for thiols in humans or in animals. Human studies are available for methane-, ethane-, and butanethiol, but these are essentially acute exposures designed to measure odor thresholds. The human exposure data presented in Chapter III indicated that exposure to thiols can produce CNS depression [12-14], and one death has been reported [12] following overwhelming exposure. In an experimental study [15], human exposure to ethanethiol at 4 ppm (1 mg/cu m) for 3 hours/day for 5 days caused olfactory fatigue and mucosal irritation. These effects returned to normal after cessation of exposure. Furthermore, exposure at 0.4 ppm under the same conditions did not cause the effects mentioned above. In another controlled experiment with volunteers [45], no significant adverse effects were noted after exposure to ethanethiol at 50 ppm (120 mg/cu m) or 112 ppm (270 mg/cu m) for 20 minutes, except for increases in breathing rate, which returned to normal after cessation of exposure. Signs and symptoms of CNS toxicity occurred in workers exposed for 1 hour to butanethiol at concentrations guessed to lie within the range of 50-500 ppm (180-1,800 mg/cu m) [15]. The workers exhibited asthenia, muscular weakness, and malaise.

Based on the animal toxicity data presented in Chapter III, the thiols can be categorized into two classes according to the degree of toxicity: (1) C_1-C_{12}, C_{16}, and C_{18} alkane thiols and cyclohexanethiol; and (2) benzenethiol. The inhalation toxicity data presented suggest that ethanethiol and butanethiol were equitoxic in rats and mice. Propanethiol was slightly less toxic than ethanethiol when inhaled or when administered orally and ip. Hexanethiol was four to five times as toxic as ethanethiol by inhalation but was only slightly more toxic than ethanethiol to rats and mice when given orally or ip [59]. Other acute inhalation studies in animals [54,60] indicated that methanethiol and pentanethiol are of approximately the same order of toxicity as ethanethiol. Therefore, the C_1-C_6 thiols can be grouped together as approximately equitoxic.

Several studies demonstrate subchronic toxicity of thiols in animal species [54,62]. Twenty-five exposures to methanethiol at 300 ppm (591 mg/cu m) killed all the mice [54]. Inhalation exposures of monkeys, rats, and mice to methanethiol at 50 ppm (98.5 mg/cu m) continuously for 90 days caused morbidity and mortality [62] in all three species.

Although the LD_{50} values for a mixture of C_7-C_{11} thiols and for dodecanethiol suggest a lower order of acute toxicity [61], subchronic inhalation exposure to these thiols does produce some organ changes suggestive of those seen in animals intoxicated with the lower molecular weight thiols. Therefore, these thiols are grouped with the C_1-C_6 thiols on the basis of their subchronic effects. Single exposure of mice by iv route for thiols C_3, C_4, C_6-C_{12}, C_{16}, C_{18}, and cyclohexanethiol resulted in similar LD_{50}'s (WW Wannamaker III, written communication, December 1977). Thus, available toxicity data presented in Chapter III for cyclohexanethiol as well as the information available on skin sensitization in guinea pigs and rats for higher molecular weight thiols indicate that this compound and the C_{16} and C_{18} thiols should all be grouped with the C_1-C_{12} thiols [59,61,66,67].

Both the human and animal toxicity data show adverse effects resulting from relatively short-term inhalation exposure to thiols at 50 ppm. These findings indicate that workplace concentrations of thiols should be kept well below this concentration. The minimal effects of olfactory fatigue and mucosal irritation [15] observed when individuals were exposed to 4 ppm ethanethiol ceased when the inhalation exposure was stopped, and no effects were observed at 0.4 ppm exposure. Because there is no evidence that adherence to the TLV of 0.5 ppm has resulted in any cases of toxicity, NIOSH recommends that the concentration of C_1-C_{12}, C_{16}, C_{18} alkane thiols, or cyclohexanethiol, or any combination of these thiols, in the workplace air should not exceed 0.5 ppm as a ceiling concentration for any 15-minute period. Since the toxic action of thiols, on short term-exposure, is expressed largely by reversible mucosal irritation [12,13,15,16], a ceiling

concentration limit is deemed more appropriate than a TWA concentration limit. The use of a ceiling concentration instead of a TWA has the effect of increasing the protection provided to the worker about twofold. NIOSH believes that adherence to the proposed ceiling concentration would prevent both irritative and systemic effects arising from occupational exposure to the aliphatic thiols.

Because C_1-C_{12}, C_{16}, C_{18} alkane thiols, or cyclohexanethiol can cause respiratory changes leading to respiratory failure, muscular weakness leading to paralysis, mild to severe cyanosis, and coma leading to death [12,15,53], exposure to several of them, even at or below the recommended workplace environmental concentration, may produce additive effects. These possibly additive effects should be considered when simultaneous exposure to several thiols occurs. The formula stated in 29 CFR 1910.1000(d)(2)(i) can be used to calculate the equivalent exposure limit (E_m) for the mixture when such plural exposures may occur:

$$E_m = \frac{C_1}{L_1} + \frac{C_2}{L_2} + \ldots \ldots \frac{C_n}{L_n}$$

where:

C = the concentration of a thiol
L = the permissible exposure limit of the thiol

Table VI-1 gives the mg/cu m equivalent to 0.5 ppm for each of these thiols.

Because benzenethiol is not only more toxic than the other thiols [59] but also has a comparatively marked potential for causing eye and organ damage, eg, at 0.72 ppm, at one-third the concentration of ethanethiol (2.1 ppm), as indicated by Katz and Talbert [16] (Table VI-2), NIOSH recommends that the concentration of benzenethiol in the workplace air should not exceed 0.1 ppm (0.45 mg/cu m) as a ceiling concentration for any 15-minute period.

(b) Sampling and Analysis

The technology is currently available to sample and analyze thiols at the recommended environmental limits and to allow institution of the required engineering controls. As discussed in Chapter IV and presented in greater detail in Appendix I, use of a sampling kit containing freeze-out traps and ethyl benzene at -78 C is recommended for collection of lower molecular weight thiols (C_1-C_3), and adsorption on Chromosorb 104 is recommended for personal breathing zone air sampling of higher molecular weight thiols (C_4-C_{18}). A possible solution to the problem would be the application of thermal desorption techniques. With the use of such methods, the entire sample adsorbed on a solid sorbent can be delivered to

TABLE VI-1

NIOSH RECOMMENDED EXPOSURE LIMITS FOR THIOLS

| Thiol | Ceiling Concentration Limits* | |
	mg/cu m	Approximate ppm Equivalents
Methanethiol	1.0	0.5
Ethanethiol	1.3	0.5
1-Propanethiol	1.6	0.5
1-Butanethiol	1.8	0.5
1-Pentanethiol	2.1	0.5
1-Hexanethiol	2.4	0.5
1-Heptanethiol	2.7	0.5
1-Octanethiol	3.0	0.5
1-Nonanethiol	3.3	0.5
1-Decanethiol	3.6	0.5
1-Undecanethiol	3.9	0.5
1-Dodecanethiol	4.1	0.5
1-Hexadecanethiol	5.3	0.5
1-Octadecanethiol	5.9	0.5
Cyclohexanethiol	2.4	0.5
Benzenethiol	0.5	0.1

*Limit not to exceed 0.5 ppm when more than one thiol is present
except for benzenethiol

N-NITROSODI-N-PROPYLAMINE

CAS No: 621-64-7

I.   PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	130.12
Boiling point	not available
Melting point	not available
Vapor pressure	0.086 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.3 mg/m^3

II.   HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-3 (μg/m^3)$^{-1}$
Slope Factor: 7.0 E+0 (mg/kg-day)$^{-1}$
[calculated from a cancer slope factor derived by US EPA (1986)]

III.   CARCINOGENIC EFFECTS

Human Studies

No studies addressing the carcinogenicity of N-nitrosodi-n-propylamine to humans have been conducted.

Animal Studies

Druckrey *et al.* (1967) treated a total of 48 BD rats (sex unspecified) orally with N-nitrosodi-n-propylamine at concentrations of 4, 8, 15, or 30 mg/kg body weight 7 days per week for life (16, 16, 15, and 1 animal, respectively). An untreated control group was not included in the study, although background tumor incidence was reported to be negligible. Liver carcinoma incidence was 14/16, 15/16, 15/15, and 1/1 in the four dose groups, respectively.   Tumor induction time was dose-related.   The authors also note tumors of the esophagus (8/48) and tongue (6/48).

Lijinsky and Taylor (1978, 1979) exposed 15 male Sprague-Dawley rats to N-nitrosodi-n-propylamine in drinking water 5 days/week for 30 weeks at 1.8 mg/day resulting in a daily dose of 5.1 mg/kg-day. No control group was included. Liver carcinomas (9/15), esophageal papillomas (6/15) and carcinomas (8/15), and nasal adenocarcinomas (8/15) were observed among exposed rats.

Lijinsky and Reuber (1981) exposed 20 Fischer 344 rats (sex unspecified) to N-nitrosodi-n-propylamine in drinking water at 0.9 mg/day for 5 days/week for 30 weeks resulting in a daily dose of 2.6 mg/kg-day. No control group was included. Esophageal carcinomas (20/20) and forestomach tumors (12/20) developed in exposed animals.

IV.   DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

US EPA (1986) based its selection of a cancer potency on a study which demonstrates induction of liver tumors by N-nitrosodi-n-propylamine. US EPA (1986) used the data from Druckrey *et al.*(1967) in the induction of hepatocellular carcinoma in BD rats exposed to N-nitrosodi-n-propylamine in drinking water to calculate a cancer potency value.

Methodology

The high tumor incidence in all the N-nitrosodi-n-propylamine treated animals suggests time-dependent analysis is more appropriate than multistage analysis in the derivation of a cancer potency value. A dosage estimate for use in deriving the cancer potency value was based on the following relationship, where d is the daily dose, C is the mmol to mg conversion factor (130.2 mg/mmol), k is an empirically derived constant estimated from a plot of k versus the number of carbon atoms for lower di-N-alkylnitrosamines ($k=1.7 \times 10^4$ mmol/kg-day), t_{50} is the median time of tumor induction, and n is a representative value for dialkylnitrosamines (n=2.3; Druckrey *et al.*, 1967):

$$d = \frac{C \times k}{t_{50}{}^{n}}$$

The resulting daily dose estimate was 0.578 mg/kg-day. Applying this estimate to a rearrangement of the one-hit model gave an animal cancer potency value (q_{animal}) of 1.2 (mg/kg-day)$^{-1}$.

$$q_{animal} = -\ln(0.5/\text{day}) / d$$

Conversion of the q_{animal} to a human cancer potency estimate (q_{human}) was made based on the following relationship, where bw_h is the assumed human body weight (70 kg) and bw_a is the assumed experimental animal body weight (0.35 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimate of q_{human} was 7.0 (mg/kg-day)$^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-3 (μg/m^3)$^{-1}$.

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ACUTE TOXICITY SUMMARY

TOLUENE

(methyl benzene, methyl benzol, phenyl methane, toluol)

CAS Registry Number: 108-88-3

I.   Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**37,000 μg/m³**
Critical effect(s)	headache, dizziness, slight eye and nose irritation
Hazard Index target(s)	Nervous System; Eyes; Respiratory System; Reproductive/developmental

II.   Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless liquid
Molecular formula	C_7H_8
Molecular weight	92.13
Density	0.861 g/cm^3 @ 25ºC (Low *et al*, 1988)
Boiling point	111ºC
Melting point	-95ºC
Vapor pressure	28.1 mm Hg @ 25ºC (USEPA, 1984)
Flashpoint	4º C, closed cup
Explosive limits	upper = 7%: lower = 1.27%
Solubility	miscible in organic solvents
Odor threshold	1.6 ppm (geometric mean) (AIHA, 1989)
Odor description	sour, burnt (AIHA, 1989)
Metabolites	hippuric acid
Conversion factor	1 ppm = 3.75 mg/m³ @ 25ºC

III.   Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations. It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitors, adhesives, and solvent based cleaning agents. Toluene is also used in printing operations, leather tanning, and chemical processes. Benzene and other polycyclic aromatic hydrocarbons (PAHs) are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene exposure.

IV.   Acute Toxicity to Humans

Dysfunction of the central nervous system and narcosis are the major effects of acute exposure to toluene (ATSDR, 1989). Irritation of the skin, eye, and respiratory tract can also result. Inhalational abuse of toluene with high level exposure for long periods of time has produced

progressive and irreversible changes in brain structure and function (Spencer and Schaumberg, 1985).

Two separate workplace incidents involving acute inhalation exposure to toluene in several workers resulted in effects of euphoria, drunkenness, dizziness, nausea, confusion, incoordination, drowsiness, and loss of consciousness (Longley *et al*., 1967). The toluene concentrations were estimated at 10,000 to 30,000 ppm (40,000 to 110,000 mg/m³) although no actual measurements were made. No long-term follow-up of the exposed workers was conducted.

Reaction time and perceptual speed were studied in 12 young male subjects exposed by inhalation to toluene concentrations ranging from 100 to 700 ppm (400 to 3,000 mg/m³), each for a 20-minute interval (Gamberale and Hultengren, 1972). Statistically significant impaired reaction time was apparent following exposure to 300 ppm (1,000 mg/m³) toluene. A statistically significant impairment in perceptual speed was observed at 700 ppm toluene. No effects were observed at 100 ppm.

Two groups of middle aged workers, one with previous occupational exposure to solvents and one without, were exposed once to 100 ppm (400 mg/m³) of toluene for 6.5 hours (Baelum *et al*., 1985). Fatigue, sleepiness, a feeling of intoxication, and eye, nose and throat irritation were reported. Decrements in manual dexterity, color discrimination, and accuracy in visual perception were also observed. Greater sensitivity to toluene was noted for those subjects with previous solvent exposure.

Nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 10 to 100 ppm (40 mg/m³ to 400 mg/m³) for 6 hours (Andersen *et al*, 1983). Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 100 ppm. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 100 ppm. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 10 and 40 ppm.

A battery of neurobehavioral and performance tests was conducted among 42 young men and women exposed by inhalation for 7 hours to 0, 75, and 150 ppm (0, 280, and 560 mg/m³) toluene (Echeverria *et al*., 1989). Statistically significant decrements in visual short term memory, visual perception, and psychomotor skills were observed at 150 ppm compared to control exposures. A dose-dependent increase in subjective symptoms of headache and eye irritation was also observed.

Wilson (1943) reported that workers exposed to concentrations of commercial toluene ranging from 50 to 200 ppm (200 to 750 mg/m³) for periods of 1 to 3 weeks experienced headaches, lassitude, and loss of appetite. At 200 to 500 ppm (750 to 2,000 mg/m³), symptoms of nausea, bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss were also observed. Exposure to 500 to 1,500 ppm (2,000 to 5,600 mg/m³) resulted in palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time.

Red blood cell counts were decreased and there were 2 cases of aplastic anemia. The hematologic effects were most likely caused by benzene impurities (ACGIH, 1986).

Three volunteer subjects exposed by inhalation to toluene concentrations ranging from 50 to 100 ppm (200 to 400 mg/m³), 8 hours per day, 2 times per week over 8 weeks experienced fatigue, drowsiness, and headaches (von Oettingen *et al*., 1942). At 200 to 800 ppm (750 to 3,000 mg/m³), symptoms of muscular weakness, confusion, impaired coordination, paresthesia, and nausea were also reported. After exposure to 800 ppm, all 3 subjects reported considerable after-effects (severe nervousness, muscular fatigue, and insomnia) lasting several days.

Predisposing Conditions for Toluene Toxicity

Medical: Since toluene is metabolized by the liver, persons with liver disease may be sensitive to its acute effects (ATSDR, 1993). Persons with preexisting neurologic or heart disease may also be at increased risk for adverse effects resulting from exposure to toluene (Reprotext, 1999).

Chemical: Because salicylates and alcohol competitively inhibit toluene metabolism, concurrent use of these substances may increase susceptibility to toluene toxicity (ATSDR, 1993). Persons using over-the-counter bronchial dilators containing epinephrine might be more sensitive to arrhythmogenic effects (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

The 1-hour LC_{50} for toluene in the rat is 26,700 ppm (100,000 mg/m³) (Pryor *et al*, 1978). The 6-hour LC_{50}s in rats and mice are 4,618 ppm (17,320 mg/m³) and 6,949 ppm (26,060 mg/m³), respectively (Bonnet *et al*., 1982). The 8-hour LC_{50} is 5,300 ppm (19,900 mg/m³) in the mouse (Svirbely *et al*, 1943).

Attention deficits and impairment of visual-motor abilities were observed in 6 macaque monkeys exposed by inhalation for 50 minutes to 2,000-4,500 ppm (7,500-17,000 mg/m³) toluene (Taylor and Evans, 1985). Expired carbon dioxide increased in a dose-dependent manner from 100 to 3,000 ppm (400 to 11,000 mg/m³). The investigators stated that changes in expired carbon dioxide may provide evidence of combined behavioral, respiratory, sensory, and metabolic effects.

Dose-dependent decreases in behavioral performance and central nervous system depression were observed in mice and rats exposed by inhalation to toluene at concentrations ranging from 2,600 to 12,000 ppm (9,800 to 45,000 mg/m³) for up to 3 hours (Bruckner and Peterson, 1981). Younger animals were more susceptible to toluene toxicity and mice were more sensitive than rats of the same age.

Kishi *et al*. (1988) used the shock avoidance response test to study behavioral effects in rats. Inhalation exposure to 125 ppm (469 mg/m³) toluene for 20 minutes resulted in a considerable decrease in the effective avoidance response rate.

Hearing loss was observed in rats after exposure to 1,000 ppm (4,000 mg/m³) toluene, 14 hours per day for 2 weeks (Pryor *et al*., 1984).

VI.   Reproductive or Developmental Effects

Toluene is listed under the California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. Most of the information concerning the adverse developmental effects of toluene in humans comes from case reports among children of deliberate toluene "sniffers." Children whose mothers had inhaled large quantities of toluene during pregnancy were found to have microencephaly, facial and limb abnormalities, attention deficits, hyperactivity, developmental delay with greater language impairment, and growth retardation (Hersch *et al*., 1985; Hersch, 1989). Multiple solvent and/or other substance abuse may have contributed to the observed abnormalities. Growth retardation, craniofacial abnormalities, and hyperchloremic acidosis were observed in the children of women with severe renal tubular acidosis induced by chronic paint sniffing (Goodwin, 1988). Preterm delivery, perinatal death, and growth retardation were significantly increased among 21 newborns exposed to toluene as a result of maternal inhalation abuse (Wilkins-Haug and Gabow, 1991). A case-referent study of women occupationally exposed to organic solvents, including toluene, reported increased incidences of urogenital, gastrointestinal, and cardiac anomalies in their children (McDonald *et al*., 1987). Although toluene was considered to be the most likely teratogenic agent, concurrent exposures to other developmental toxicants make this conclusion difficult to support.

There are several animal studies of varying quality on the reproductive and developmental toxicity of toluene. A complete review of the developmental toxicology of toluene is available (Donald *et al*., 1991). Selected studies are summarized below.

Shigeta *et al*. (1982) reported statistically significant increases in the number of fetal resorptions observed in the offspring of mice exposed by inhalation to 100 ppm (400 mg/m³) toluene for 6 hours per day on days 1-17 of gestation. Exposure at 1,000 ppm (4,000 mg/m³) resulted in a statistically significant increase in the incidence of extra ribs.

A statistically insignificant increased incidence of extra ribs was observed in rats exposed by inhalation to 1,000 mg/m³ toluene for 24 hours per day on days 7-14 of gestation (Tatrai *et al*., 1980). Fused sternebrae and extra ribs were observed in rats exposed to 400 ppm (1,500 mg/m³) toluene for 24 hours per day on days 9-14 of gestation (Hudak and Ungvary, 1978). Skeletal retardation was observed in rats exposed to 266 ppm (1,000 mg/m³) toluene for 8 hours per day on days 1-21 of gestation and to 400 ppm (1,500 mg/m³) 24 hours per day on days 1-8. This same group exposed mice to 400 ppm (1,500 mg/m³) or to 133 ppm (500 mg/m³) toluene for 24 hours per day on days 6-13 of gestation. All dams died at the higher dose and a statistically significant decrease in fetal weight was observed at the lower dose.

Skeletal retardations were observed in the offspring of pregnant rabbits exposed by inhalation to concentrations of toluene ranging from 30 to 300 ppm (100 to 1,000 mg/m³), 6 hours per day on days 6-18 of gestation (Klimisch *et al*., 1992). These results were not dose-dependent and were not reproduced in two additional groups of rabbits exposed to 100 and 500 ppm (400 and 2,000 mg/m³) toluene.

A statistically significant increase in the number of animals showing a 13/13 rib profile (which is considered normal) was observed in mice exposed to 400 ppm (1,500 mg/m³) toluene, 7 hours per day on days 7-16 of gestation (Courtney *et al*., 1986). An increased number of resorptions

was observed in mice exposed to 400 ppm toluene on days 6-15 of gestation (Gleich and Hofman, 1983); the daily exposure duration was not specified.

These preceding animal studies support the association between toluene exposure and effects on somatic development of the fetus. However, the value of these studies is limited by issues such as unknown or unconventional exposure durations, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and purity of toluene used (Donald *et al*., 1991).

The best available study relating toluene exposure and retardation of somatic development is one in which adult rats of 2 generations were exposed for 6 hours per day to 0, 100, 500 or 2,000 ppm (0, 375, 1,875, or 7,500 mg/m³) toluene during an 80-day premating period and a 15 day mating period (IRDC, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. Exposure at this level to the male parent only did not result in any adverse effects. The NOAEL for fetotoxic effects in this study was 500 ppm.

In a recent teratogenicity study by inhalation, Ono *et al*. (1995) exposed pregnant Sprague-Dawley rats to 600 or 2000 ppm toluene for 6 h/day from day 7 to day 17 of pregnancy. The control group inhaled "conditioned" clean air. Maternal exposure to 2000 ppm caused significant toxic effects such as body weight suppression in dams and offspring, high fetal mortality, and embryonic growth retardation. However, no external, internal, or skeletal anomalies were observed in the fetuses of any treated group. In addition, there were no differences in the results of pre- and post-weaning behavioral tests of the offspring. No changes which could be related to toluene were apparent in the 600 ppm group. Thus 600 ppm is a NOAEL in this study.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 9.8 ppm (37,000 µg/m³)

Study	Andersen *et al*., 1983
Study population	16 young, healthy males
Exposure method	inhalation
Critical effects	impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication and slight eye and nose irritation
LOAEL	100 ppm
NOAEL	40 ppm
Exposure duration	6 hours
Extrapolated 1 hour concentration	98 ppm (40^2 ppm* 6 h $= C^2 * 1$ h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	9.8 ppm (37 mg/m³; 37,000 µg/m³)

Level Protective Against Severe Adverse Effects

In a 2-generation study, adult rats were exposed for 6 hours per day to 0, 100, 500, or 2,000 ppm (0, 375, 1875, or 7,500 mg/m³) toluene during an 80-day premating period and a 15 day mating period (International Research and Development Corporation, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. The NOAEL for fetotoxic effects in this study was 500 ppm. The NOAEL reported in the study, a chronic exposure study, was in the same concentration range as the LOAELs reported in other acute exposure studies addressing reproductive and developmental toxicity, summarized above. However, because the IRDC study was judged to be methodologically the most sound of all the studies considered for this endpoint (Donald *et al*., 1991), it was chosen as the basis for the severe adverse effect level. An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability. The 6-hour exposure serves as the basis for the level protective against severe adverse effects. This yields a 6-hour level protective against severe adverse effects of 5 ppm (19 mg/m³).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH for toluene of 500 ppm. According to NIOSH, "It has been reported that extreme fatigue, mental confusion, exhilaration, nausea, headache and dizziness resulted from exposures to 600 ppm by the end of 3 hours [von Oettingen *et al*. 1942]. In addition, the following observations have been made: some workers will tolerate concentrations ranging up to 200 ppm for 6 to 8 hours daily with no demonstrable ill effects; 200 to 500 ppm for 6 to 8 hours will cause tiredness and lassitude in most workers; and concentrations over 500 ppm for 1 to 3 hours are definitely dangerous and will cause symptoms attributable to depression of the central nervous system and the bone marrow [Wilson 1943]. It has also been reported that exposure to concentrations greater than 4,000 ppm for more than 5 minutes might limit self rescue ability [ANSI 1973]. After 20 minutes, exposures to concentrations at 300, 500, or 700 ppm resulted in significant increases in reaction times; a significant decrease in perceptual speed resulted after a 20-minute exposure to 700 ppm [Gamberale and Hultengren 1972]. .... The revised IDLH for toluene is 500 ppm based on acute inhalation toxicity data in humans [Gamberale and Hultengren 1972; von Oettingen *et al*. 1942; Wilson 1943]." Based on its documentation, the IDLH of 500 ppm, designed for a 30 minute exposure, does not appear to be low enough to protect the general public, especially sensitive individuals, from life-threatening effects for 1 hour. Therefore, no recommendation for a level protective against life-threatening effects is made at this time.

VII.   References

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CHRONIC TOXICITY SUMMARY

TOLUENE

(Methyl benzene; methyl benzol; phenyl methane; toluol)

CAS Registry Number: 108-88-3

I.   Chronic Toxicity Summary

Inhalation reference exposure level   **300 μg/m^3 (70 ppb)**

Critical effect(s)   Neurotoxic effects (decreased brain [subcortical limbic area] weight, altered dopamine receptor binding).

Hazard index target(s)   Nervous system; respiratory system; teratogenicity

II.   Physical and Chemical Properties (HSDB (1999) except as noted)

Description	Colorless liquid
Molecular formula	C_7H_8
Molecular weight	92.13 g/mol
Density	0.8661 g/cm^3 @ 20°C
Boiling point	110.6 ° C (CRC, 1994)
Melting point	−94.9° C (CRC, 1994)
Vapor pressure	28.1 torr @ 25°C (U.S. EPA, 1984)
Solubility	miscible in most organic solvents
Conversion factor	1 ppm = 3.76 mg/m^3 @ 25°C

III.   Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations; toluene is a major aromatic constituent of gasoline (HSDB, 1999). It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitor, adhesives and solvent based cleaning agents. Toluene is also utilized in printing operations, leather tanning and chemical processes. Benzene and other polycyclic aromatic hydrocarbons are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene in the context of air and water sample monitoring. In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of toluene was approximately 2.2 ppb. For 1998, annual statewide industrial emissions of toluene from facilities reporting under the requirements of the Air Toxics Hot Spots Act in California were estimated to be 5,176,626 pounds (CARB, 1999). Note that this estimate is for stationary sources, and does not include emissions from mobile sources.

IV.   Effects of Human Exposures

Neurological Effects
Most studies reporting adverse effects due to chronic toluene exposures involve either toluene-containing solvent abuse or occupational exposure to toluene. Solvent abusers are generally exposed to higher levels of toluene than are workers. A continuum of neurotoxic effects ranging from frank brain damage to degraded performance on psychometric tests which roughly track exposure levels has been observed.

Solvent abusers
Chronic toluene abuse has been shown to cause permanent changes in brain structure (loss of grey and white matter differentiation; cerebral, cerebellar and brainstem atrophy) which correlated with brain dysfunction as measured by magnetic resonance imaging (MRI) and brainstem auditory evoked response (BAER) evaluations (Caldemeyer *et al.*, 1996; Filley *et al.*, 1990; Ikeda and Tsukagoshi, 1990; Rosenberg *et al.*, 1988a; Rosenberg *et al.*, 1988b; Yamanouchi *et al.*, 1995; reviewed by Agency for Toxic Substances and Disease Registry (ATSDR), 1999).

Eleven chronic solvent (spray lacquer; $\approx$ 60% toluene, 10% dichloromethane) abusers were examined using MRI and BAER tests (Rosenberg *et al.*, 1988b). Neurological abnormalities were seen in four of 11 subjects and included brainstem, cerebellar, cognitive and pyramidal findings. Brain MRIs were abnormal in three of 11 subjects and indicated the occurrence of diffuse cerebral, cerebellar, and brainstem atrophy and loss of differentiation between the gray and white matter throughout the CNS. BAERs were abnormal in five of 11 individuals. All three individuals with abnormal MRI scans also had abnormal neurological examinations and BAERs. However, two of five individuals with abnormal BAERs had normal neurological examinations and MRI scans. The authors suggested that BAERs may detect early CNS injury from toluene inhalation, even at a time when neurological examination and MRI scans are normal.

Two subjects of a group of 22 hospitalized solvent abusers (primarily abusing toluene-based solvents) demonstrated decreases in intelligence quotient (IQ) as measured by the comparison of tests administered before the commencement of solvent abuse with tests administered during hospitalization for long-term solvent abuse (Byrne *et al.*, 1991).

Filley *et al.* (1990) studied 14 chronic toluene abusers using MRI and neuropsychological evaluations. The neuropsychological testing indicated that three patients functioned normally, three were in a borderline range, and eight were impaired. Independent analyses of white matter changes on MRI demonstrated that the degree of white matter abnormality was strongly correlated ($p < 0.01$) with neuropsychological impairment. The authors concluded that dementia in toluene abuse appears to be related to the severity of cerebral white matter involvement.

Six chronic toluene abusers were examined using MRI by Caldemeyer *et al.* (1996). All patients examined demonstrated white matter atrophy and T2 hyperintensity (T2: "Spin-spin" relaxation time; a time constant that reflects the rate at which protons stop rotating in phase with each other because of the local magnetic fields of adjacent nuclei; OTA, 1984), and five of six demonstrated

T2 hypointensity of the basal ganglia and thalami. The authors noted a correlation between the severity of white matter degeneration and degree of neurological dysfunction. However, there was no correlation between the severity of imaged white matter changes and the presence of T2 hypointensity or duration of toluene abuse. Additionally, no definite clinical evidence of damage to the basal ganglia and thalami was found despite the MR imaging finding of T2 hypointensity..

Ungar *et al*. (1994) developed a physical bilayered model of dipalmitoylphosphatidylcholine (DPPC) and toluene, and subjected DPPC control and toluene-mixed bilayers to MRI. T1 (T1: "Spin-lattice" relaxation time; a time constant that reflects the rate at which excited protons exchange energy with the surrounding environment; OTA, 1984) and T2 were measured as a function of toluene and lipid concentrations.   Measurements of the DPPC-toluene model indicated that toluene-containing lipid bilayers substantially shortened T2 and had little effect on T1. By comparison, DPPC alone had little effect on either T1 or T2. The authors believe that these results suggest that partitioning of toluene into the lipid membranes of cells in cerebral tissue may be responsible for the hypointensity of basal ganglia noted on T2-weighted MR images of brains of toluene abusers.

Occupational exposure

Solvent workers exposed to 42.8 ppm toluene (estimated as a time-weighted average) for an average duration of 6.8 years reported a significantly greater incidence of sore throat, dizziness and headache than controls; the sore throat and headache incidence demonstrated a rough dose-response (Yin *et al.*, 1987).

Orbaek and Nise (1989) examined the neurological effects of toluene on 30 rotogravure printers, 33-61 years of age (mean 50), employed at two Swedish printing shops for 4-43 years (median 29) in 1985. Mean exposure levels at the two printing shops were 43 and 157 mg/m^3 of toluene, respectively; however, before 1980 the exposure levels had exceeded 300 mg/m^3 in both shops. The authors noted that rotogravure printing provides an occupational setting with practically pure toluene exposure. Comparisons were made to a reference group of 72 men aged 27-69 (mean 47). The alcohol consumption of both the workers and referents was also determined (< 200 g/week or > 200 g/week). Neurological function in the workers and referents was evaluated using interviews and psychometric testing; the results from each of the two printing shops were pooled.   The printers reported statistically significantly higher occurrences of fatigue (60%), recent short-term memory problems (60%), concentration difficulties (40%), mood lability (27%), and other neurasthenic symptoms. The printers also scored significantly worse than referents in a number of psychometric tests, including synonym, Benton revised visual retention and digit symbol tests, even after adjustment for age.   For all comparisons, tests of interaction between the effects of toluene exposure and alcohol consumption were not statistically significant.

A battery of neurobehavioral tests was performed in 30 female workers exposed to toluene vapors in an electronic assembly plant (Foo *et al.*, 1990). The average number of years worked was 5.7 ± 3.2 for the exposed group and 2.5 ± 2.7 years for the controls. Study subjects did not smoke tobacco or drink alcohol, were not taking any medications, and had no prior history of central or peripheral nervous system illness or psychiatric disorders. The exposed group of workers inhaled a time-weighted average (TWA) of 88 ppm (330 mg/m^3) toluene while the

control workers inhaled 13 ppm (49 mg/m^3). A significant decrease in neurobehavioral performance was observed in the exposed workers in 6 out of 8 tests. Irritant effects were not examined, and concurrent exposures to other chemicals were not addressed. In this study, 88 ppm was considered a LOAEL for central nervous system effects. However, the workers designated by the authors to be controls did not comprise a true control group, since they were exposed to 13 ppm toluene. This may have resulted in an underestimation of the effects of exposure to 88 ppm toluene. Similar effects were noted in a follow-up study by Boey *et al.* (1997).

Abbate *et al.* (1993) evaluated alterations induced in the auditory nervous system by exposure to toluene in a group of rotogravure workers. A sample of 40 workers of normal hearing ability was selected from a group of 300 workers who were apparently in good health but were professionally exposed to toluene (12 – 14 years exposure, 97 ppm average exposure, exposure assessment not described). They were subjected to an adaptation test utilizing a BAER technique with 11 and 90 stimulus repetitions a second. The results were compared with an age and sex-matched control group not professionally exposed to solvents. A statistically significant alteration in the BAER results was noted in the toluene-exposed workers with both 11 and 90 stimuli repetitions. The authors suggested that these results can be explained as a toluene-induced effect on physiologic stimulus conduction mechanisms, even in the absence of any clinical sign of neuropathy. Furthermore, this effect could be observed in the responses of the entire auditory system, from peripheral receptors to brainstem nuclei.

A group of 49 printing-press workers occupationally exposed to toluene for approximately 21.6 years was studied by Vrca *et al.* (1997). Toluene exposure levels were determined from blood toluene and urinary hippuric acid levels, and were estimated to range from 40-60 ppm. No control group was used. Brain evoked auditory potential (BEAP; similar to BAER) and visual evoked potential (VEP) measurements were performed on a Monday morning after a nonworking weekend. There was a significant increase in the latencies of all the BEAP waves examined, except for P2 waves, as well as in the interpeak latency (IPL) P3-P4, while IPL P4-P5 decreased significantly with the length of exposure. No correlation was noted between the amplitude of BEAP waves and the length of exposure. The amplitude but not the latency of all the VEPs examined decreased significantly with the length of exposure.

The effects of acute and chronic toluene exposure on color vision were studied in a group of eight rotogravure printing workers (Muttray *et al.*, 1999). The workers had been employed as printers for an average of 9.8 years. The color vision acuity of the workers before and after an acute toluene exposure (28 – 41 minutes in duration, concentration 1115 – 1358 mg/m^3) was evaluated using the Farnsworth panel D-15 test, the Lanthony desaturated panel D-15 test, and the Standard Pseudoisochromatic Plates part 2. A control group of 8 unexposed workers was also tested. Acute toluene exposure had no effect on color vision. Print worker performance prior to acute toluene exposure (chronic effects) was similar to controls on the Farnsworth panel D-15 and Standard Pseudoisochromatic Plates part 2 tests. Print worker performance on the Lanthony desaturated panel D-15 test was worse than that of controls (median scores of 1.18 and 1.05 for exposed and controls (higher number indicates degraded performance), respectively, but not significantly ($p = 0.06$). The authors noted that the small number of subjects limited the statistical power of the study.

Zavalic *et al.* (1998) examined the effects of chronic occupational toluene exposure on color vision using a group of 45 exposed workers (mean toluene exposure concentration = 120 ppm) and 53 controls. Color vision was evaluated using the Lanthony desaturated panel D-15 test; test scores were age and alcohol consumption-adjusted. Color vision was significantly impaired in toluene-exposed workers (p < 0.0001) compared to controls. It was also observed that there was no significant difference between test scores on Monday morning (prework) and Wednesday morning. The authors stated that the effect of toluene on color vision can be chronic and that the possible recovery period is longer than 64 hours.

Hepatic Effects

Greenburg *et al.* (1942) reported liver enlargement in 32 of 106 (30.2%) painters employed in an aircraft factory compared to 7% in a control group. However, there was some exposure to other solvents (ethanol, ethyl acetate, butyl acetate) and paint ingredients such as zinc chromate.

Liver toxicity has been reported in toluene solvent abusers (Fornazzari *et al.*, 1983). Eight of 24 solvent abusers demonstrated abnormal results in three liver function tests; however, the tests used were not specified. The test parameters returned to normal after two weeks of toluene abstinence, suggesting that any liver damage caused by toluene abuse in those patients was not long lasting.

A cross-sectional study by Boewer *et al.* (1988) showed no significant correlation between toluene exposure and the levels of serum enzymes (serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyltransferase (GGT)) considered to be indicators of hepatic damage. In another cross-sectional study of 289 printing workers exposed to less than 200 ppm for 8 hours/day, 8 workers had significantly elevated serum enzymes (ALT/AST ratio, mean = 1.61) potentially indicative of liver damage. In each case, liver biopsy indicated a mild pericentral fatty change (Guzelian *et al.*, 1988). However, the mean toluene exposure concentration was not reported (only an upper bound), and no control group was included in the study.

V. Effects of Animal Exposures

Neurotoxic Effects
Sprague-Dawley rats (15/sex/group) were exposed to 0, 100, or 1481 ppm toluene for 6 hours/day, 5 days/week for 26 weeks (API, 1981). Neurohistopathological examinations were conducted in 3-5 rats/sex/group at weeks 9, 18, and 27. No significant treatment-related effects were reported. The study usefulness was limited because there were no other neurohistopathological examinations or organ weight measurements conducted on the animals.

Forkman *et al.* (1991) studied the potential neurotoxicity of toluene inhalation exposure (3700 mg/m^3 (1000 ppm), 21 hours/day, 5 days/week for 4 weeks) in male Sprague-Dawley rats. The rats were either trained in behavior meant to be performance tested and then exposed to toluene, or exposed and then trained. The rats were then subjected to several behavioral tests, including an operant test with baseline performance and extinction, motor coordination, and exploratory

activity. All tests were performed from 11 to 35 days after the end of the exposure. Exposure of trained rats to toluene resulted in a significantly different overall test performance when compared to controls. Rats trained after toluene exposure also had test performances different from controls, but the difference was not statistically significant.

Rats exposed to toluene concentrations of 1000 ppm or 100 ppm, 6 h/day, 5 days/week, for 3 or 6 months, respectively, demonstrated statistically significant decreased motor function as measured by degraded performance (approximately 60% and 65% of control at 1000 and 100 ppm toluene, respectively) on a rotarod performance test and decreases in spontaneous motor activity (approximately 62% of control at 100 ppm toluene) (Korsak *et al.*, 1992).

von Euler *et al.* (1993) studied the effects of subchronic toluene inhalation exposure (80 ppm, 4 weeks, 5 days/week, 6 hours/day) on spatial learning and memory, dopamine-mediated locomotor activity and dopamine D_2 agonist binding in rats. Spatial learning (postexposure days 3-6) and memory (postexposure day 14) were tested using a water maze. Spontaneous and apomorphine-induced locomotor activity was evaluated on postexposure day 17.   Effects on binding parameters of the dopamine D2 agonist S(-)[N-propyl- ^{3}H(N)]-propylnorapomorphine ([H]NPA) were determined using membrane preparations of the neostriatum of the rat brain. Toluene exposure caused a statistically significant impairment in spatial learning and memory. Toluene also significantly increased apomorphine-induced locomotion and motility but not rearing. Spontaneous locomotion, motility and rearing were not affected by toluene. Toluene exposure significantly increased the B_{max} and K_D values for [^{3}H]NPA binding. These results indicate that subchronic toluene exposure of rats to toluene causes persistent deficits in spatial learning and memory, a persistent increase in dopamine-mediated locomotor activity and an increase in the number of dopamine D_2 receptors in the neostriatum.

Male rat exposure to toluene (0, 40, 80, 160 or 320 ppm, 4 weeks, 6 hours/day, 5 days/week) , followed by a postexposure period of 29-40 days, resulted in decreased brain wet weights of the caudate-putamen (trend test for dose-response significant at $p < 0.05$) and subcortical limbic areas (trend test for dose-response significant at $p < 0.01$; significantly less than controls ($p < 0.001$) at concentrations of 80 ppm and higher) (Hillefors-Berglund *et al.*, 1995). Toluene exposure also significantly altered dopamine receptor activity (trend test for dose-response) as indicated by decreased IC_{50} (inhibition constant) (significantly less than controls ($p < 0.05$) at 80 ppm), K_H (inhibition constant for high-affinity receptor sites), K_L (inhibition constant for low-affinity receptor sites), and R_H% (high-affinity receptor site specific binding) values for dopamine competitive inhibition of [^{3}H]raclopride-binding in the caudate-putamen. Toluene exposure did not significantly affect the wet weights of the whole brain, serum prolactin levels, the K_D (disassociation constant) or the B_{max} (maximal specific binding) values of [^{3}H]raclopride-binding in the caudate-putamen and the subcortical limbic area, or the effect of dopamine on IC_{50} values at [^{3}H]raclopride-binding sites in the subcortical limbic area. Exposure to xylene or styrene (80 and 40 ppm, respectively; 4 weeks, 6 h/day, 5 days/week) followed by a postexposure period of 26-32 days had no effect on the parameters described above. The authors concluded that long-term exposure to low concentrations of toluene ($\geq$ 80 ppm), but not xylene (80 ppm) or styrene (40 ppm), leads to persistent increases in the affinity of dopamine D_2 agonist binding in the rat caudate-putamen. The authors also suggested that the enhancement of

apomorphine-induced locomotor activity seen after toluene exposure by von Euler *et al.* (1993) may be related to the increased D_2 agonist activity described above (*IC$_{50}$, K$_H$, K$_L$* values).

Respiratory Effects
A study of the chronic effects of toluene in rats (5-20 animals per group) exposed for 106 weeks to 0, 30, 100, or 300 ppm (0, 113, 375, or 1125 mg/m^3) toluene showed no treatment-related effects on histopathology of major organs, including the nasal turbinates (CIIT, 1980). In this study, the nasal histopathology examination sampling may have been inadequate to demonstrate the nasal lesions reported by the NTP (1990).

Rats (20 per group) exposed for 2 years to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/m^3) toluene 6.5 hours/day, 5 days/week for 103 weeks were examined for hematological and histopathological effects in addition to gross observations of toxicity (NTP, 1990). Significant erosion of the olfactory epithelium was observed in male rats while degeneration of the respiratory and nasal epithelium was observed in both sexes at 600 ppm.

Mice were exposed chronically to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/m^3) toluene 6.5 hours/day, 5 days/week, for 2 years (NTP, 1990). The only treatment-related effect was a significant increase in the number of animals with hyperplasia of the bronchial epithelium in the 1200 ppm exposure group.

Reproductive and Developmental Toxicity
Reproductive toxicity to maternal rats was observed during exposure to 1500 ppm toluene, 24 hours/day on days 9 to 14 of gestation (Hudak and Ungvary, 1978). Two dams out of 19 died during exposure. Fetuses from the 1500 ppm group showed increased incidence of sternebral alterations, extra ribs and missing tails. The same exposure on days 1 through 8 of gestation resulted in 5 deaths out of 14 dams. Fetuses in this regimen showed increased incidence of hydrocephaly and growth retardation compared to controls. A third regimen that exposed maternal rats to 1000 ppm on days 1 through 21 of gestation resulted in no maternal deaths or toxicity, and an increase in the incidence of skeletal variations in the fetuses. When exposed to 1500 ppm continuously, maternal mice died within 24 hours of exposure whereas exposure to 500 ppm had no apparent effect. Examination of the fetal mice showed significant growth retardation in the 500 ppm group.

A 2-generation study of the effects of 0, 100, 500, or 2000 ppm (0, 377, 1885, or 7538 mg/m^3) toluene in rats (males, 10-40 per group; females, 20-80 per group) was done by the American Petroleum Institute (API)(1985). Rats were exposed for 6 hours/day, 7 days/week for 80 days and a 15 day mating period. The mated females were then exposed to the same concentrations during days 1-20 of gestation and days 5-20 of lactation. After weaning, the F$_1$ pups were exposed 80 times to the appropriate exposure level and then randomly mated to members of the same exposure group. The F$_1$ generation showed significantly decreased body weight which persisted throughout lactation. No effects were observed on histopathology. No data were presented for the F$_2$ generation.

Da Silva *et al.* (1990) exposed rats and hamsters to 0 or 800 mg/m^3 toluene for 6 hours/day on gestation days 14-20 (rats), or days 6-11 (hamsters). Exposed rats demonstrated a significant

exposure-related decrease in birth weight compared with controls. In addition to low birth weight, the number of live pups was significantly lower in the 800 ppm group. No deficits in any parameter were noted in the hamsters. In this study, no neurobehavioral effects were noted in the offspring.

Hass *et al.* (1999) exposed rats to 0 or 1200 ppm toluene for 6 h per day from day 7 of pregnancy until day 18 postnatally. Developmental and neurobehavioral effects in the offspring were investigated using a test battery including assessment of functions similar to those in the proposed Organization for Economic Cooperation and Development (OECD) Testing Guidelines for Developmental Neurotoxicity Study (physical development, reflex development, motor function, motor activity, sensory function, and learning and memory). The exposure did not cause maternal toxicity or decreased offspring viability. However, lower birth weight, delayed development of reflexes, and increased motor activity in the open field was noted in the exposed offspring. The exposed female offspring had poorer scores on a Morris water maze test (they took longer to locate a hidden platform after platform relocation) at the age of 3.5 months indicating impaired cognitive function. The difference was not related to impaired swimming capabilities since swim speeds were similar to control values. The authors stated that exposure to 1200 ppm toluene during brain development caused long-lasting developmental neurotoxicity in rats.

Toluene has been listed under Proposition 65 as being known to the State of California to cause reproductive toxicity (OEHHA, 1999). Its NSRL is 7,000 micrograms per day.

VI.   Derivation of Chronic Reference Exposure Level (REL)

Study	Hillefors-Berglund *et al*. (1995); supported by Orbaek and Nise (1989), Foo *et al.* (1990)
Study population	Male Sprague-Dawley rats
Exposure method	Inhalation
Critical effects	Decreased brain (subcortical limbic area) weight, altered dopamine receptor (caudate-putamen) binding
LOAEL	80 ppm
NOAEL	40 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	4 weeks, followed by 29-40 days recovery
Average experimental exposure	7 ppm ($40 \times 6/24$ hours $\times$ 5/7 days)
Human equivalent concentration	7 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that $\lambda_a = \lambda_h$
Subchronic uncertainty factor	10
Interspecies uncertainty factor	1 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.07 ppm (70 ppb; 0.3 mg/m^3; 300 µg/m^3)

Supportive human study	Foo *et al.*, 1990
Study population	30 female workers in an electronic assembly plant
Exposure method	Occupational inhalation
Critical effects	Neurobehavioral deficits in 6 out of 8 tests
LOAEL	88 ppm
NOAEL	Not observed
Exposure continuity	10 m^3/day occupational inhalation rate, 5 days/week
Average occupational exposure	31.4 ppm (88 ppm x 10/20 x 5/7)
Exposure duration	5.7 $\pm$ 3.2 years (exposed group); 2.5 $\pm$ 2.7 years (controls)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.1 ppm (100 ppb; 0.4 mg/m^3; 400 µg/m^3)

The critical animal study (Hillefors-Berglund *et al*., 1995) used to derive an REL for toluene describes adverse neurological effects in rats after a well characterized inhalation exposure to toluene. The study results contain both a LOAEL and a NOAEL. Decreased brain (subcortical limbic area) weight and altered dopamine receptor binding compared to controls were noted at the NOAEL, but the changes were not statistically significant; this suggests that if a threshold for

adverse neurological effects exists in this study, it would be at or below the observed NOAEL. The study LOAEL for altered dopamine receptor binding agrees qualitatively with results from similar studies (von Euler *et al.*, 1994). Additionally, toluene-induced neurotoxicity has been described in many studies by a variety of endpoints in both animals and humans (ATSDR, 1999). The adverse neurotoxic effects associated with toluene exposure in the rat study by Hillefors-Berglund *et al.* (1995), decreased brain (subcortical limbic area) weight and altered dopamine receptor binding, occur in areas of the rat brain that are structurally and functionally similar to brain areas (basal ganglia, thalami) of some human toluene abusers that demonstrate MRI alterations (T2 hypointensity). The altered MRI parameters may be the result of the partitioning of toluene into the lipid membranes of brain cells (Ungar *et al.*, 1994). Table 1 lists several Reference Exposure Levels (RELs) calculated from the most sensitive animal and human neurotoxicity studies available. These RELs are also protective for other adverse endpoints, such as respiratory tract damage and teratogenicity.

Table 1: Reference Exposure Levels (RELs) from Selected Neurotoxicity Studies

Study	Duration	Effect	LOAEL (ppm)	LOAEL (ppm) (TWA)	NOAEL (ppm)	NOAEL (ppm) (TWA)	total UF[a]	REL (ppb)	REL ($\mu g/m^3$)
VonEuler *et al.* (1988)	4 weeks	rat: altered brain dopamine receptor binding	80	14.3			1000	14	54
Orbaek and Nise[b] (1989)	29 years	human: impairment on neuropsychometric tests	11.2 - 41	4 - 14.6			100	40 - 146	150 - 551
Foo (1990)	5.7 years	human: neurobehavioral tests	88	31.4			300	105	394
Korsak (1992)	6 months	rat: impaired motor function	100	17.9			100	179	671
Hillefors-Berglund (1995)	4 weeks	rat: decreased brain (subcortical limbic area) weight; altered brain dopamine receptor binding	80	14.3	40	7.1	100	71	271

LOAEL: Lowest Observable Effect Level; NOAEL: No Observable Effect Level
REL: Reference Exposure Levels; TWA: time-weighted average

a: Uncertainty Factors used to derive RELs

VonEuler *et al.* (1988)   LOAEL to NOAEL UF = 10, subchronic to chronic UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 1000.

Orbaek and Nise (1989)   LOAEL to NOAEL UF = 10, intraspecies variability = 10; total UF = 100

Foo *et al.* (1990)   LOAEL to NOAEL UF = 10, subchronic to chronic UF = 3, intraspecies variability = 10; total UF = 300

Korsak *et al.* (1992)   LOAEL to NOAEL UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 100.

Hillefors-Berglund *et al.* (1995)   subchronic to chronic UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 100.

b: Pooled psychometric data from two printing plants with different toluene concentrations (11.2 and 41 ppm) were used to determine significant neurotoxic effects by Orbaek and Nise (1989). The range of RELs derived from that study lists the upper and lower bounds for risk associated with the pooled population exposures. ATSDR (1999) used the Orbaek and Nise (1989) study data, assuming an exposure concentration of 11.2 ppm, to derive a chronic inhalation minimal risk level (MRL).

If both human and animal adverse effect data on a chemical are available, OEHHA prefers to use the human data to develop a REL when possible. However, the study by Hillefors-Berglund *et al*. (1995) provides data (decreased brain [subcortical limbic area] weight and altered brain dopamine receptor binding) which are specific and sensitive measures of neurotoxicity that would not be obtainable in human studies. In contrast, the psychometric tests used to generate the neurotoxicity data in the human occupational exposure studies described above tend to be less sensitive and suffer from greater measurement uncertainty. Additionally, the Hillefors-Berglund *et al*. (1995) study has better exposure characterization than the human occupational exposure studies. Nonetheless, the human studies are useful in supporting the derivation of the REL for toluene. Ordinarily, an interspecies uncertainty factor of 3 would be applied, in addition to the human equivalent concentration calculation, to reflect the uncertainty associated with extrapolating from animals to humans. However, in this case the uncertainty in the interspecies extrapolation is reduced by the availability of human epidemiological data with generally consistent effect levels, after appropriate duration corrections. Based on comparison of the data in both animals and humans, it appears that a REL of 271 μg/m^3 (rounded to 300 μg/m^3 in the final derivation) would protect exposed humans from experiencing chronic neurotoxic effects.

VII.   Data Strengths and Limitations for Development of the REL

The major strength of the REL for toluene is the use of an animal study with accurate exposure characterization and both LOAEL and NOAEL observations for an effect (neurotoxicity), supported by observations from other animal and human studies. A weakness is the uncertainty in predicting human health risk from animal adverse effect data. However, this is mitigated by the availability of human data showing effect levels that are, after appropriate corrections, broadly consistent with the animal data.

VII.   References

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ACUTE TOXICITY SUMMARY

VINYL CHLORIDE

(chloroethene; chloroethylene; vinyl chloride monomer; VC; VCM)

CAS Registry Number: 75-01-4

I.   Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **180,000 μg/m³**
Critical effect(s)   mild headache and dryness of eyes and nose in
                                          healthy human volunteers
Hazard Index target(s)   Eyes; Nervous System; Respiratory System

II.   Physical and Chemical Properties (HSDB, 1994 except as noted)

Description   colorless gas
Molecular formula C_2H_3Cl
Molecular weight   62.5
Density   2.56 g/L @ 25°C
Boiling point   -13°C
Melting point   -153.8°C
Vapor pressure   2,660 mm Hg @ 25°C
Flashpoint   -77.8°C (open cup) (ACGIH, 1991)
Explosive limits   4 to 22% by volume in air (ACGIH, 1991)
Solubility   soluble in alcohol, ethyl ether, carbon tetrachloride,
                          benzene
Odor threshold   3,000 ppm (Amoore and Hautala, 1983)
Odor description   sweet (AIHA, 1989)
Metabolites   chloroethylene oxide, chloroacetic acid
                          (Antweiler, 1976)
Conversion factor   1 ppm = 2.56 mg/m³ @ 25°C

III.   Major Uses or Sources

The chief use of vinyl chloride (VC) is in the production of polyvinyl chloride (PVC) resins used
for plastic piping and conduit (IARC, 1979). It is also used in the manufacture of methyl
chloroform. Vinyl chloride was used as a propellant until 1974 when this use was banned due to
its demonstrated carcinogenicity. The main toxicological concern for vinyl chloride is from
exposure to the monomer rather than the polymerized forms (i.e., PVC). Thermal decomposition
of VC produces hydrogen chloride, carbon monoxide, and traces of phosgene (ACGIH, 1991).

IV.   Acute Toxicity to Humans

The primary acute physiological effect of VC inhalation is CNS depression (Holmberg, 1984). Anesthesia may occur at high concentrations (7,000 - 10,000 ppm) for short durations in both animals and humans (Purchase *et al*., 1987).

In two accidental human poisonings, workers became incapacitated when exposed to high concentrations of VC gas (Anon., 1953). Following removal from exposure, one of the workers experienced tightness of the chest, nausea, abdominal pain, and headache. Before VC's relationship with certain forms of cancer was established, workers in at least one polyvinyl chloride manufacturing facility reportedly inhaled VC fumes for its euphoric effect, sometimes to the point of unconsciousness (Klein, 1976). Danziger (1960) reported a worker death associated with exposure to high concentrations of VC. Autopsy revealed cyanosis, local burns of the conjunctiva and cornea, congestion of internal organs (especially lung and kidneys), and failure of blood to clot.

Suciu *et al*. (1975) reported that factory workers exposed to high concentrations of VC experienced euphoria, giddiness, somnolence and, in some cases, narcosis. Yearly average concentrations reported at this factory were between 98 and 2,298 mg/m³ (38 to 898 ppm).

Two male volunteers exposed to 25,000 ppm (64,000 mg/m³) VC for 3 minutes reported the odor as pleasant, but became dizzy and disoriented to the space and size of surrounding objects. The men also reported a burning sensation on the soles of their feet (Patty *et al*., 1930).

In a controlled exposure, 6 adult volunteers (3 male, 3 female) were exposed to varying concentrations up to 20,000 ppm (51,200 mg/m³) of VC via an oral-nasal mask (Lester *et al*., 1963). The 5 minute exposures took place twice each day and were separated by 6-hour periods for 3 successive days. No CNS effects were reported at 4,000 ppm (10,240 mg/m³). Exposure to 12,000 ppm (30,720 mg/m³) resulted in complaints of dizziness and reeling in 2 subjects. A clear dose-response was observed in this study, but statistical comparisons were not made by the authors.

In a chamber exposure, human volunteers were exposed to 59, 261, 491, or 493 ppm VC for up to 7.5 hours (excluding a 0.5-hour lunch period) (Baretta *et al*., 1969). The subjects exposed to either 59 or 261 ppm VC reported no untoward effects. However, 2 of 7 subjects exposed to 491 ppm for 3.5 hours and 2 of 4 subjects exposed to 493 ppm for 7.5 hours reported mild headache and dryness of eyes and nose.

Vinyl chloride is known to cause "vinyl chloride disease" upon repeated exposures in workers. This multisystem disorder consists of Raynaud's phenomenon, acro-osteolysis, thrombocytopenia, splenomegaly, portal fibrosis, and hepatic and pulmonary dysfunction (IARC, 1979). This disease is likely an immune complex disorder from the adsorption of VC or a metabolite onto tissue proteins and is unlikely to occur following single acute exposure (Ward *et al*., 1976).

Differences in genetic susceptibility to hepatotoxicity of vinyl chloride have been described (Huang *et al*., 1997). Vinyl chloride is metabolized by cytochrome P450 2E1 (CYP2E1) to form

the toxic electrophilic metabolites, chloroethylene oxide and chloroacetaldehyde. These metabolites are detoxified by glutathione S-transferases (GSTs). A total of 251 workers from polyvinyl chloride plants were categorized into high or low exposure groups based on air exposure monitoring. Serum alanine aminotransferase (ALT) was used as an indicator of liver function. CYP2E1, GST theta, and GST mu were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) on peripheral white blood cell DNA. For the low vinyl chloride exposure group, positive GST theta (odds ratio = 3.8, 95% CI 1.2-14.5) but not CYP2E1 was associated with abnormal ALT levels in serum. For the high exposure group, a c2c2 CYP2E1 genotype was associated with an increased risk of abnormal ALT (odds ratio = 5.4, 95% CI 0.7-35.1), while a positive GST theta was associated with significantly reduced risk of abnormal ALT (odds ratio = 0.3, 95% CI 0.1-0.9).

Predisposing Conditions for Vinyl Chloride Toxicity

Medical: Inherited cytochrome P450 and glutathione S-transferase alleles may affect individual susceptibility (Huang *et al*., 1997).

Chemical: Inducers of hepatic cytochrome-P450 enzymes, such as phenobarbital, potentiate the hepatotoxic effects of inhaled VC in rats (IARC, 1979; Jaeger *et al*., 1974; Kappus *et al*., 1975). Liver damage was measured by the release of alanine alpha-ketoglutarate, SGOT, and SGPT enzymes.

Ethanol co-administration with VC resulted in greater toxicity to pregnant mice, rats, or rabbits than exposure to VC alone (John *et al*., 1981).

V.   Acute Toxicity to Laboratory Animals

A lethality study was carried out by Prodan *et al*. (1975) in which mice, rats, guinea pigs, and rabbits were exposed to VC for 2 hours. Deaths were due to respiratory failure. Animals that were still alive at the end of exposure recovered quickly following removal from the gas. However, no post-exposure observation period was included in the study to investigate possible delayed mortality. Table 1 below shows the LC_{50}, MLE_{05} (maximum likelihood estimate expected to produce a response rate of 5%), BC_{05} and BC_{01} (benchmark concentration at the 95% lower confidence interval of the 5% and 1% lethality level, respectively) as determined by log normal probit analysis (Crump, 1984; Crump and Howe, 1983).

Table 1.   Animal lethality benchmark concentration estimates from Prodan *et al*. (1975) for 2-hour vinyl chloride exposure

Species	LC_{50} (mg/m³ x 10^3)	MLE_{05} (mg/m³ x 10^3)	BC_{05} (mg/m³ x 10^3)	BC_{01} (mg/m³ x 10^3)
mouse	299	253	246	227
rat[1]	(394)	(329)	(292)	(260)
guinea pig	591	527	453	410
rabbit	600	545	466	424

[1] Log normal probit analysis indicates the data points for rats resulted in an unacceptable fit.

Exposure of rats, mice and guinea pigs to 100,000 ppm VC (5 animals/species) resulted in increased motor activity at 10 minutes but progressed to muscular incoordination, unsteady gait and pronounced tremor in all species 15 minutes into the exposure (Mastromatteo *et al*., 1960). Rats and mice became unconscious at 25 minutes while guinea pigs remained conscious during the entire 30 minute exposure period. At 200,000 and 300,000 ppm VC, rats and mice exhibited muscular incoordination at 2 and 1 minutes, respectively, following initiation of exposure. Guinea pigs were slightly more tolerant of the CNS depressant effects at these concentrations. Deaths in mice, rats and guinea pigs occurred at 200,000 ppm and above, 300,000 ppm and 400,000 ppm, respectively.

Exposure to 5,000 and 10,000 ppm vinyl chloride for 8 hours did not produce signs of CNS depression in guinea pigs (Patty *et al*., 1930). Inhalation of 25,000 ppm (64,000 mg/m³) (sample size unspecified) resulted in motor ataxia and unsteadiness by 5 minutes, deep narcosis without convulsions or twitching by 90 minutes, and death by respiratory paralysis by 6 hours. Gross pathological changes included congestion and edema in the lungs, and hyperemia in the liver and kidneys. Guinea pigs exposed to 100,000 ppm developed complete loss of coordination and incomplete narcosis 2 minutes into exposure.

Lester *et al*. (1963) showed that rats exposed to 50,000 ppm (128,000 mg/m³) VC for 2 hours exhibited moderate intoxication with loss of the righting reflex. Loss of the corneal reflex was apparent following a 2-hour exposure to 100,000 ppm (256,000 mg/m³). Exposure of these rats to 100,000 ppm (256,000 mg/m³) for two 8-hour periods resulted in mortality from a "pneumonic process."

Tatrai and Ungvary (1981) exposed mice, rats and rabbits to 1,500 ppm VC for up to 24 hours. Rats and rabbits were unaffected, but 90% of mice died following 12 hours of exposure and 100% of mice died following 24 hours of exposure. Pathological examination of mice revealed hemorrhages and vasodilatation in the lungs, suggestive of pulmonary edema.

Dermal exposure of monkeys to gaseous VC indicated that absorption of VC across the intact skin is very limited (Hefner *et al*., 1975).

Rhesus monkeys eliminate VC at approximately half the rate of mice and rats (Buchter *et al*., 1980). Rodents may therefore be less sensitive than primates to systemic VC toxicity.

VI.   Reproductive or Developmental Toxicity

In a review of the epidemiological data, Hemminki and Vineis (1985) concluded that there was inadequate evidence of increased teratogenesis in humans exposed to VC.

Animal studies have also failed to show significant association between VC exposure and teratogenesis. In rats, exposure to VC at a concentration of 1,500 ppm (3,840 mg/m³) for 24 hours/day during all three trimesters of pregnancy did not result in an increased incidence of birth defects (13-28 rats per group) (Ungvary *et al*., 1978). Pharmacokinetic studies showed that VC crossed the placental barrier of these rats, and was present in fetal blood.

John *et al*. (1981) showed that exposure of pregnant mice, rats or rabbits to 500 ppm (1,280 mg/m³) VC for 7 hours/day during organogenesis did not result in teratogenicity or embryotoxicity. Inhalation of 2,500 ppm (6,400 mg/m³) caused slight ossification changes in the offspring and maternal mortality in the mice. Co-administration of 15% ethanol in drinking water resulted in maternal toxicity, but no elevation in fetal effects above that seen for ethanol exposure alone.

Male mice exposed to 30,000 ppm (76,800 mg/m³) VC 6 hours/day for 5 days were mated to control females, with no resultant increase in spontaneous abortions (Purchase, 1975). However, Bi *et al*. (1985) showed that inhalation exposure of male rats to 100 ppm VC for 6 hours/day, 6 days/week for 3 months resulted in significant damage to seminiferous tubules compared to controls ($p < 0.05$).

VII.   Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 180,000 μg/m³

Study	Baretta *et al*., 1969
Study population	4-8 healthy human volunteers
Exposure method	(1) 7.5 hour exposures to 261 ppm VC
	(2) 3.5 hour exposures to 491 ppm VC
	(3) 7.5 hour exposures to 493 ppm VC
Critical effects	subjective reports of mild headaches and dryness of eyes and nose (groups 2 and 3); no effects reported by group 1
LOAEL	3.5 to 7.5 hour exposure to 491 or 493 ppm
NOAEL	7.5 hour exposure to 261 ppm
Exposure duration	7.5 hours
Equivalent 1 hour concentration	715 ppm ($C^2 * 1$ hr = $[261$ ppm$]^2 * 7.5$ hrs)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	72 ppm (180 mg/m³, 180,000 μg/m³)

Level Protective Against Severe Adverse Effects

Exposure of guinea pigs to 10,000 ppm VC for 8 hours did not produce signs of CNS depression (Patty *et al*., 1930). Exposure to 25,000 ppm produced motor ataxia and unsteadiness within 5 minutes and unconsciousness in 90 minutes. Exposure to 100,000 ppm produced motor ataxia within 2 minutes in guinea pigs (Patty *et al*., 1930) and motor ataxia with a pronounced tremor within 15 minutes in rats and mice (Mastromatteo *et al*., 1960). Higher concentrations of VC (200,000 and 300,000 ppm) reduced the onset of CNS depression to 1 to 2 minutes following initiation of exposure (Mastromatteo *et al*., 1960).

Based on the results of Patty *et al*. (1930), the NOAEL for motor ataxia, or muscular incoordination, in guinea pigs was 10,000 ppm for 8-hour exposure. The LOAEL was 25,000 ppm, which resulted in motor ataxia within 5 minutes and unconsciousness in 90 minutes. The NOAEL was adjusted to a 1-hour exposure by the formula $C^n \times T = K$ (where "n" = 2), which resulted in a concentration of 28,282 ppm VC. Applying uncertainty factors of 10 each to account for interspecies differences and increased susceptibility of sensitive human individuals results in a final value of 280 ppm (720 mg/m³) VC for a level protective against serious adverse effects.

Level Protective Against Life-threatening Effects

Log-normal analysis of lethality data for mice, guinea pigs, and rabbits (Prodan *et al*., 1975) yielded BC_{05} estimates of 246,000, 453,000, and 466,000 mg/m³, respectively. Mastromatteo *et al*. (1960) reported 30-minute no-observed-lethality levels of 100,000, 300,000, and 400,000 ppm, respectively, for mice, rats and guinea pigs.

The study by Prodan *et al*. (1975) provides data from which to derive an estimate for VC using the benchmark concentration approach. The BC_{05} of the most sensitive species, the mouse, was adjusted to a 1-hour equivalent exposure using the equation $C^n \times T = K$, where "n" = 2. Uncertainty factors of 3 and 10 were applied to the adjusted BC_{05} of 348,000 mg/m³ (136,000 ppm) to account for interspecies differences and increased susceptibility of sensitive human individuals, respectively. The resultant level protective against life-threatening effects is thus 4,500 ppm (12,000 mg/m³).

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VINYL CHLORIDE

CAS No: 75-01-4

I.   **PHYSICAL AND CHEMICAL PROPERTIES** (From HSDB, 1998)

Molecular weight	62.5
Boiling point	-13.37ºC
Melting point	-153.8°C
Vapor pressure	2660 mm Hg @ 25°C
Air concentration conversion	1 ppm = 2.56 mg/m^3

II.   **HEALTH ASSESSMENT VALUES**

Unit Risk Factor: 7.8 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Female mouse lung tumor incidence (Drew *et al*., 1983), extra risk calculated using a linearized multistage procedure (CDHS, 1990).]

III.   **CARCINOGENIC EFFECTS**

Human Studies

In 1974, Creech and Johnson described three cases of angiosarcoma of the liver (LAS) among workers at the B.F. Goodrich Tire and Rubber Co. in Louisville, Kentucky. Because LAS is a very rare cancer (20-25 cases per year in the U. S.), the clustering of three cases in one vinyl chloride (VC) polymerization facility indicated an abnormally high incidence of this cancer. Based on this report, as well as data indicating that VC is carcinogenic in laboratory animals, multiple studies of workers exposed to this agent were conducted. By 1985, at least 15 epidemiologic studies relating VC exposure to the incidence of various cancers had been completed. A summary of the data from these studies is provided in Table 1.

Between 1961 and 1977, 23 cases of LAS were reported among approximately 20,000 VC workers in the U.S. (Lelbach and Marsteller, 1981; Spirtas and Kaminski, 1978). The expected incidence of LAS is 0.014 cases per 100,000 per year in the general population in the U.S. (Heath *et al*., 1975). Based on analysis of these data, the relative risk for developing LAS following VC exposure among this country's VC workers is 483.

The epidemiologic studies also demonstrate a strong and consistent association between VC exposure and primary cancer of the liver. All of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMRs).   The average relative risk for liver cancer among VC workers is five to six times greater than the incidence of that seen in the general population. The evidence strongly suggests that exposure to VC can cause liver cancer. All reports published to date indicate that the SMRs of exposed workers are elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time.

Table 1: A Summary of Epidemiologic Data for Occupationally Exposed Vinyl Chloride Workers

Study	Place	Cohort	Deaths (%)	Exposure in years	SMR				
					All Sites	Liver (LAS)	Brain	Lung	Lymphoma
Tabershaw and Gaffey[1] (1974)	U.S.	8,384	352 (4.7)	>1 10.2%>20 yrs	110	94[3] (6)	155[4]	112	106
Duck et al. (1975)	U.K.	2,122	152 (7.2)	>0	96	93[3] (0)	--	103	--
Nicholson et al. (1975)	U.S.	257	24 (9.3)	>5	231	- (3)	--	--	--
Ott et al.[2] (1975)	U.S.	594	79 (13.3)	>0	81	- (0)	--	77	--
Byren et al. (1976)	Sweden	771	58 (75)	>0	--	413[a] (2)	612[a]	168	--
Waxweiler et al. (1976)	U.S.	1,294	136 (10.5)	>5 (f/u > 10 yrs)	149[a]	1,155[b] (11)	329[a5]	156	159
				>5 (f/u > 15 yrs)	189[b]	1,606[b] -	498[a]	194[a]	176
Fox and Collier (1977)	U.K.	7,717	409 (5.3)	>0 8% > 20 yrs	90.7	1,408[a] (2)	54.6	89.8	90.9
EEH (1975)[1]	U.S.	10,173	707 (6.9)	>1 19.3%>20 yrs	104	75[3] (5)	203[a]	107	112
Buffler et al. (1979)	Texas	464	28 (6.0)	>0	138	- (0)	--	208[a]	--
Bertazzi et al. (1979)	Italy	4,777	62 (1.3)	> 0.5	97	800[a] (3)	125	81	133
Masuda et al. (1979)	Japan	304	26 (8.5)	>1	138	500[a] (0)	--	125	--
Weber et al. (1981)	Germany	7,021 production	414 (5.9)	>0	112	1,523[b] -	162	--	214[a]
		4,007 processing	360 (9)	>0	85	434[a] -	535[a]	--	34
		4,910 unexposed	417 (8.5)	n/a	83	401[a] -	184	--	77
Cooper[1] (1981)	U.S.	10,173	707 (6.9)	>1	104	75[3] (8)	203[a]	107	112
Heldaas et al. (1984)	Norway	454	50 (11)	>1	114	- (1)	--	180	--
						Relative Risk			
Theriault and Allard (1981)	Canada	451 exposed	59 (2.6)	>5	1.48	6.25[a] (10)	--	.36	--
		871 unexposed	233 (26.8)	n/a					

Table 1 (continued):   A Summary of Epidemiologic Data for Occupationally Exposed Vinyl Chloride Workers

LAS = angiosarcoma of the liver; f/u = follow-up
[1]The studies of Cooper and EEH are reanalyses of the Tabershaw and Gaffey Cohort
[2]SMR subjects also in the Tabershaw and Gaffey Cohort
[3]SMR is for the "digestive system cancer", not liver cancer
[4]SMR is for "other and unspecified cancer", 40% of which were brain cancer
[5]SMR is for cancer of CNS, not brain
[a] $p < 0.05$ [b] $p < 0.01$

The association between VC exposure and increased risk for other cancers is not as clear as that for liver cancer. Some evidence associates exposure to VC with increased mortality ratios for brain cancer, lung cancer, and lymphoma. Since these cancers appear more commonly in the general population than LAS and primary liver cancer, it becomes more difficult to show increased risk.

Workers exposed to VC appear to be at greater risk for brain cancer than do non-exposed populations. Of the six studies that assessed the risk of brain cancer, five showed a positive trend for increased risk of this cancer type following exposure to VC, with four demonstrating statistical significance ($p < 0.05$). Cancer risk increased an average of four times above that expected in the general population in those studies that exhibited a significantly increased risk. Of the two studies not showing a significant increase in risk for brain cancer, statistical power in the Bertazzi and associates study was only about 35% (Bertazzi *et al*., 1979), while that of Fox and Collier (1977) was approximately 80% (Beaumont and Breslow, 1981). In the Fox and Collier study, the number of deaths overall was low and, most importantly, a large percentage of workers in the cohort was very recently employed in the VC industry and thus had a short follow-up time. These factors may partially explain why this study failed to detect an association between VC exposure and brain cancer.

The evidence linking VC exposure with lung cancer remains inconclusive. Analyses of SMRs for cancer of the lung were performed in 12 studies. Of these, seven studies showed an increased risk for lung cancer, but only one was statistically significant at the 5% level (Buffler *et al*., 1979). This increased risk persisted after adjusting for personal smoking habits (for this particular cohort). However, this cohort was small and the study was unable to demonstrate an increased risk for any other cancer. The Waxweiler *et al*. (1976) cohort (which had a follow-up period greater than 15 years) also used a small group.

An association between VC exposure and lymphoma has not been established. Five studies evaluated the risk of lymphoma development among workers occupationally exposed to VC. Four of the studies showed a positive trend for lymphoma among VC workers, but statistical significance was noted only by Weber *et al*. (1981). However, the statistical power in all of these studies was less than 80% to demonstrate a relative risk of two, and less than 40% to show a relative risk of 1.5.

Animal Studies

Reviews of VC carcinogenicity data from exposed laboratory animals available at the time the document "_Health Effects of Airborne Vinyl Chloride_" (CDHS, 1990) was released include those by Kalmaz and Kalmaz (1984), IARC (1979), SRI (1983), Kuzmack and McGaughy (1975), and Purchase _et al_. (1987). Adequate experimental evidence exists to indicate that VC is carcinogenic in mice, rats, and hamsters when given orally and by inhalation. VC has been found to cause tumors in a dose-related manner at several sites, including liver, lung and mammary gland. The oncogenic response appears to be a function of the site, VC concentration, tumor type, species of animal, and route of administration.

Although some evidence of VC-induced carcinogenesis has been observed by all routes of administration and in all species tested, important discrepancies in the protocols of many studies have limited their usefulness in quantitative risk assessment. These discrepancies include the lack of appropriate control groups, insufficient exposure time, or incomplete histopathology of the animals. Studies that have been used previously in risk assessment include feeding studies (Feron _et al_., 1981; Til _et al_., 1983) and a series of inhalation studies (Maltoni _et al_., 1984).

Groups of 60-80 male and 60-80 female five-week old Wistar rats were fed polyvinyl chloride powder (10% of diet) with or without a high VC monomer content (0 to 4000 ppm) in the diet for their lifetimes (Feron _et al_., 1981). The actual doses of VC given to rats in the feed were 0, 1.7, 5.0, and 14.1 mg/kg/day.

Necrosis, centrilobular degeneration and mitochondrial damage were seen in the hepatic parenchyma of rats administered VC. Significantly increased incidences of liver and lung angiosarcomas and hepatocellular carcinomas were observed in both male and female rats. Tumor incidences are listed in Table 2. It is possible that underreporting of tumors at all sites occurred because of the incomplete histopathology performed and the fact that only the longest-surviving high-dose animals were chosen for complete histopathology.

As a follow-up to the study of Feron and co-workers (1981), groups of 100 male and 100 female Wistar rats (except for the top-dose group, which was composed of 50 animals of each sex) were fed polyvinyl chloride (up to 1% of diet) with a high content of VC monomer for up to 149 weeks (Til _et al_., 1983). Levels of VC administered in the powder were 0, 0.017, 0.17, and 1.7 mg/kg/day for 149 weeks. Actual oral exposure to VC monomer (calculated by measuring the evaporative loss of VC during the four-hour feeding periods, the rate of food intake, and the level of VC in the feces) was estimated to be 0.014, 0.13, or 1.3 mg VC/kg/day for the low, middle, and high dose groups, respectively.

The results of this study demonstrated increases in the incidences of hepatic foci or cellular alteration, neoplastic nodules, hepatocellular carcinomas, liver-cell polymorphism, and cysts in the highest dose group. Two females and one male in this group developed liver angiosarcomas. Females, but not males, of the low- and mid-dose groups developed a higher incidence of hepatic basophilic foci of cellular alteration. No pathologic effects in other organ systems were attributed to VC exposure (Til _et al_., 1983). Histopathology of all organs was not performed on all animals; therefore, tumors not grossly observable or palpable could have been missed.

Because of the shortcomings of the study, its utility for the evaluation of carcinogenic risk is limited.

Several researchers have investigated the potential carcinogenicity of VC administered by inhalation (Viola, 1977; Caputo *et al.*, 1974; Keplinger *et al.*, 1975; Lee *et al.*, 1977; Hong *et al.*, 1981; Suzuki, 1981; Groth *et al.*, 1981; Drew *et al.*, 1983; Maltoni *et al.*, 1984; Bi *et al.*, 1985). All experiments confirm the carcinogenicity of VC, although only a few of the studies are adequate for a quantitative evaluation of carcinogenic risk. This summary will concentrate on the studies (Drew *et al.*, 1983; Maltoni *et al.*, 1984; Bi *et al.*, 1985) used by CDHS (1990) for quantitative risk assessment purposes.

Table 2: Tumor incidences in male and female Wistar rats exposed to dietary vinyl chloride (Feron *et al.*, 1981).

	Incidence[1] Vinyl chloride (mg/kg-day)			
Tumor type/Sex	0	1.7	5.0	14.1
Liver angiosarcoma				
male	0/55	0/58	6/56[*2]	27/59[***]
female	0/57	0/58	2/59	9/57[**]
Hepatocellular carcinoma				
male	0/55	1/58	2/56	8/59[**]
female	0/57	4/58	19/59[***]	29/57[***]
Neoplastic nodules				
male	0/55	1/58	7/56[**]	23/59[***]
female	2/57	26/58[***]	39/59[***]	44/57[***]
Lung angiosarcoma				
male	0/55	0/58	4/56[*]	19/59[***]
female	0/57	0/58	1/59	5/57[*]
Abdominal mesotheliomas				
male	3/55	1/58	7/56	8/59
female	1/57	6/58[*]	3/59	3/57
Mammary tumors[3]				
female	3/57	2/58	5/59	9/57

[1] Number in denominator = number of animals necropsied.
[2] values marked with asterisks differ significantly from controls as determined using the Chi-square test. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
[3] Including mammary adenomas, adenocarcinomas and anaplastic carcinomas.

Bi *et al.* (1985) evaluated the tumorigenic potential of VC in male Wistar rats following inhalation exposure to 0, 10, 100 or 3000 ppm (six hours/day, six days/week) for up to 12 months. The incidence of liver angiosarcomas was 0/19, 0/20, 7/19 and 17/19 for the four exposure groups, and 0/19, 0/20, 2/19 and 9/20 for lung angiosarcomas, respectively. The incidence of liver angiosarcomas in the 100 and 3000 ppm groups was significantly greater than controls ($p = 0.004$, $p < 0.001$, respectively); the incidence of lung angiosarcomas in the 3000 ppm group was also significantly greater than controls ($p = 0.001$). This study probably

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underestimated the carcinogenic potential of VC because of the less-than-lifetime exposure and the small number of animals per group.

Drew *et al*. (1983) examined the effect of age and exposure duration on VC oncogenicity in females of several different species of rodents. Groups of female CD-1 Swiss mice, B6C3F$_1$ mice, Fischer 344 rats, and Golden Syrian hamsters (n = 54 for mice, n = 56 for rats and hamsters) were exposed to VC for six hours/day, five days/week for six, 12, 18, or 24 months, beginning at eight weeks of age, and observed for their lifespans. Other groups were held until six or 12 months of age, exposed for six or 12 months, and then observed for the remainder of their lifespans. The exposures were conducted at a single dose level for each species; mice, rats and hamsters were exposed to 50, 100, and 200 ppm VC, respectively. All animals exposed to VC at age eight weeks (the start of the experiment) exhibited decreased survival relative to controls (Drew *et al*., 1983). B6C3F$_1$ mice experienced the most significant life-shortening regardless of the age at which exposure was begun. No significant decrease in survival was observed in rats, hamsters, or Swiss mice initially exposed after six months of age. Other clinical signs of VC toxicity were not evident and liver necrosis was not observed.

In rats, exposure to VC was associated with hemangiosarcomas, mammary gland adenocarcinomas and adenomas, and hepatocellular carcinomas. The incidence of hemangiosarcomas was a function of the duration of exposure and age at start of exposure; the longer the exposure period the greater the incidence of hemangiosarcomas. A six-month exposure produced a low incidence of hemangiosarcomas and hepatocellular carcinomas only if begun early in life. One-year exposures produced a significant incidence of tumors, especially if begun early in life. The incidence of mammary gland adenocarcinomas and fibroadenomas was not always related to exposure duration, but the incidence was higher in rats whose exposure began at eight weeks of age. Hepatocellular carcinomas were induced in a dose-related manner in rats when exposures began at eight weeks. Tumor incidences in VC-exposed rats are listed in Table 3.

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with VC exposure (Drew *et al*., 1983). The highest incidence of hemangiosarcomas and stomach adenomas occurred in animals exposed early in life for only six months. The highest incidence of mammary gland carcinomas was seen in animals exposed at an early age for up to twelve months. Exposure beginning at or after eight months of age resulted in a markedly lower tumor incidence, possibly because the lifespans of chronically exposed hamsters were significantly reduced to the point that late-appearing tumors would not be expressed. Tumor incidences in VC-exposed hamsters are listed in Table 4.

Mice, especially the B6C3F$_1$ strain, appeared to be the species most sensitive to the carcinogenic effects of VC (Drew *et al*., 1983). Hemangiosarcomas and mammary gland carcinomas in both strains and lung carcinomas in Swiss mice were associated with VC exposure. In B6C3F$_1$ mice, exposure to VC for six months resulted in 60-70% incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in B6C3F$_1$ mice was

Table 3:   Tumor incidences in 100 ppm vinyl chloride-exposed female Fisher 344 rats (Drew *et al*., 1983).

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Liver hemangiosarcomas	control	0	1/112 (0.9)
	6	4.5	4/76 (5.3)
	12	8.9	11/55 (20.0)[***]
	18	13.4	13/55 (23.6)[***]
	24	17.9	19/55 (34.7)[***]
Mammary adenocarcinomas	control	0	5/112 (4.5)
	6	4.5	6/76 (7.9)
	12	8.9	11/56 (19.6)[**]
	18	13.4	9/55 (16.4)[*]
	24	17.9	5/55 (9.1)
Hepatocellular carcinomas	control	0	1/112 (0.9)
	6	4.5	3/75 (4.0)
	12	8.9	4/56 (7.1)[*]
	18	13.4	8/54 (14.8)[***]
	24	17.9	9/55 (16.4)[***]

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
[*] $p < 0.05$; [**] $p < 0.01$; [***] $p < 0.001$ (Fisher's exact test)

Table 4:   Tumor incidences in 200 ppm vinyl chloride-exposed female Golden Syrian hamsters (Drew *et al*., 1983).

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Hemangiosarcomas (all sites)	control	0	0/143 (0)
	6	8.9	13/88 (14.8)[***]
	12	17.9	4/52 (7.7)[**]
	18	26.8	2/103 (1.9)
Mammary carcinomas	control	0	0/143 (0)
	6	4.5	28/87 (32.2)[***]
	12	8.9	31/52 (59.6)[***]
	18	13.4	47/102 (46.1)[***]
Skin carcinomas	control	0	0/133 (0)
	6	4.5	2/80 (2.5)
	12	8.9	9/47 (18.8)[***]
	18	13.4	3/90 (3.3)

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
[**] $p < 0.01$; [***] $p < 0.001$ (Fisher's exact test)

greatest when the animals were exposed early in life. Lower incidences of this tumor were seen when initial exposure occurred at a later age. In Swiss mice, exposure to VC at an early age resulted in the highest incidence of hemangiosarcomas, mammary gland carcinomas, and lung carcinomas, regardless of duration of exposure. Lower incidences of all tumors were observed in animals exposed later in life. Tumor incidences in VC-exposed mice are listed in Table 5.

Table 5: Tumor incidences in 50 ppm vinyl chloride-exposed female B6C3F$_1$ and CD-1 Swiss mice (Drew *et al*., 1983).

Strain/Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
B6C3F$_1$ hemangiosarcomas (all sites)	control	0	4/69 (5.8)
	6	2.23	46/67 (68.7)***
	12	4.46	69/90 (76.7)***
	18	--	--
mammary carcinomas	control	0	3/69 (4.3)
	6	2.23	29/67 (43.2)***
	12	4.46	37/90 (41.1)***
	18	--	--
CD-1 Swiss hemangiosarcomas (all sites)	control	0	1/71 (1.4)
	6	2.23	29/67 (43.3)***
	12	4.46	30/47 (63.8)***
	18	6.69	20/45 (44.4)***
mammary carcinomas	control	0	2/71 (2.8)
	6	2.23	33/67 (49.3)***
	12	4.46	22/47 (46.8)***
	18	6.69	22/45 (48.9)***
	control	0	9/71 (12.7)
	6	2.23	18/65 (27.7)*
	12	4.46	15/47 (31.9)*
	18	6.69	11/45 (24.4)

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
* $p < 0.05$; *** $p < 0.001$ (Fisher's exact test)

Maltoni and co-workers performed a series of chronic inhalation studies on rats, mice, and hamsters in the Bentivoglio Laboratories (BT) or the Bologna Institute of Oncology (Maltoni *et al*., 1984). The investigators studied the effects of exposure to 14 concentrations of VC (1-30,000 ppm) in male and female rats and six concentrations of VC in male and female mice and male hamsters. In each experiment, animals were exposed to VC for four hours daily, five days per week for various durations, and observed for the rest of their lives. A number of the experimental procedures were not described or were inadequately described in the report by Maltoni *et al*. (1984). Details of the experimental protocol for the BT experiments are provided in Table 6.

Data on noncarcinogenic toxic effects of vinyl chloride were sparsely reported in the Maltoni BT experiments. Vinyl chloride appeared to be toxic at the higher concentrations, but reportedly the high mortality at these dose levels was due to a high incidence of vinyl chloride-induced tumors. The available information on survival, including Kaplan-Meier survival curves, indicates that vinyl chloride decreased survival in a dose-dependent manner.

Table 6: Experimental protocol for vinyl chloride inhalation studies performed by Maltoni *et al.* (1984).

Experiment number	Dose (ppm)	Exposure duration (weeks)[1]	Species/ strain	Starting exposure age (weeks)	animals/exposure concentration[2]
BT1	0, 50, 250, 500, 2500, 6000, 10000	52	rat/SD	13	30 M, 30 F
BT2	1, 100, 150, 200	52	rat/SD	13	60 M, 60 F (85 M, 85 F)
BT3	0, 50, 250, 500, 2500, 6000, 10000	17	rat/SD	12	30 M, 30 F
BT4	0, 50, 250, 500, 2500, 6000, 10000	30	mouse/ Swiss	11	30 M, 30 F (80 M, 70 F)
BT5	6000, 10000	1	rat/SD	19 (fetus)	30 F 13-29 M, F (no controls)
BT6	30000	52	rat/SD	17	30 M, 30 F (no controls)
BT7	0, 50, 250, 500, 2500, 6000, 10000	52	rat/ Wistar	11	30 M (40 M)
BT8	0, 50, 250, 500, 2000, 6000, 10000	30	hamster/ Syrian Golden	11	30 M (62 M)
BT9	0, 50	52	rat/SD	13	150 M, 150 F (50 M, 50 F)
BT14	6000, 10000	5	rat/SD	21 (parents)	6 F (no controls)
		5		1day (offspring)	21-22 M, F (no controls)
BT15	0, 1, 5, 10, 25	52	rat/SD	13	60 M, 60 F
BT4001	0, 2500	76	rat/SD	13	54 F (60 F)
		69		1 day	68 M, 68 F (158 M, 149F)
BT4006	0, 2500	15	rat/SD	1 day	60 M, 60 F

[1] Exposures were for four hours/day, 5 days/week. [2] Number in parentheses = number of control animals when not equal to number of animals in experimental groups.

In the Maltoni experiments, exposure to vinyl chloride was associated with an increased incidence of malignant tumors at a variety of tissue sites in all of the species tested. A summary of these tumor sites is provided in Table 7 (Maltoni *et al.*, 1984). A direct relationship between exposure levels and tumor incidence was apparently demonstrated, although no statistical tests for trends were performed. Results of experiments on Sprague-Dawley rats exposed to vinyl chloride for 52 weeks were statistically analyzed using the Fischer exact probability test. A summary of the lowest concentrations at which a statistically significant excess of tumors was

observed is given in Table 8. When adjusted to average lifetime exposure, the lowest concentration associated with tumor production is 0.06 ppm (1 ppm * 4/24 * 5/7 * 12/24 - 0.3 ppm).

Table 7: Tumors correlated to inhalation exposure to vinyl chloride in rats, mice, and hamsters in the BT experiments (Maltoni *et al*., 1984).

Tumors	Rat	Mouse	Hamster
Liver angiosarcomas	+	+	+
Hepatomas	+	(+)	
Encephalic neuroblastomas	+		
Lung adenomas		+	
Lymphomas/leukemias			(+)
Angiosarcomas at other sites	+	+	(+)
Zymbal gland epithelial tumors	+		
Nephroblastomas	+		
Cutaneous epithelial tumors	(+)	(+)	(+)
Mammary adenocarcinomas	+	+	
Forestomach papillomas, acanthomas	+	(+)	+

+   Tumor incidence was statistically significant ($p < 0.05$) by the Fisher exact test.
(+)   Association was not statistically significant, but was considered biologically significant.

Table 8: Lowest concentration of VC at which a significant incidence of tumors ($p < 0.05$) was reported by Maltoni *et al*. (1984) at specific sites in Sprague-Dawley rats.

Tumor type	Vinyl chloride concentration (ppm)
forestomach papilloma	30,000 (male, female)
Zymbal gland carcinoma	10,000 (male, female)
neuroblastoma	10,000 (female)
nephroblastoma	250 (female)
liver angiosarcoma	200 (male); 25 (female)
mammary adenocarcinoma	1 (female)

Experiment BT1
Most previous risk assessments have been based on the data from experiment BT1 (Maltoni *et al*., 1984). In this study, 30 Sprague Dawley rats of each sex were exposed to concentrations of vinyl chloride ranging from 50 to 10,000 ppm for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age. A positive control group received 2,500 ppm of vinyl acetate. After treatment the animals were observed for their lifespans up to 135 weeks. Survival of both males and females decreased in a dose-related manner, especially at concentrations above 500 ppm. Vinyl chloride was more toxic to females than to males in this experiment. Vinyl chloride was associated with an increased incidence of liver angiosarcomas in a dose-related fashion. These results are presented in Table 9 (Maltoni *et al*., 1984). In addition to liver angiosarcomas, vinyl chloride (at concentrations above 2500 ppm) caused an increased incidence of zymbal gland carcinomas, nephroblastomas, hepatomas, and neuroblastomas. The incidence of liver angiosarcomas was probably underestimated at the higher exposure levels due to mortality resulting from tumors at other sites.

Table 9: Incidence of liver angiosarcomas (LAS) in male and female Sprague-Dawley rats exposed to 52 weeks to vinyl chloride (Maltoni *et al*., 1984)

Study	Exposure level (ppm)	LAS incidence[1]		corrected LAS incidence[2]	
		male	female	male	female
BT1	0	0/30	0/30	0/22	0/29
	50	0/30	1/30	0/26	1/29
	250	1/30	2/30	1/28	2/26
	500	0/30	6/30	0/22	6/28
	2,500	6/30	7/30	6/26	7/24
	6,000	3/30	10/30	3/17	10/25
	10,000	3/30	4/30	3/21	4/25
BT2	0*	0/85	0/100	0/61	0/68
	100	0/60	1/60	0/37	1/43
	150	1/60	5/60	1/36	5/46
	200	7/60	5/60	7/42	5/44
BT6	30,000	5/30	13/30	5/22	13/24
BT9	0	0/50	0/50	0/29	0/38
	50	1/150	12/150	2/70	12/110
BT15	0	0/60	0/60	0/25	0/44
	1	0/60	0/60	0/48	0/55
	5	0/60	0/60	0/43	0/47
	10	0/60	1/60	0/42	1/46
	25	1/60	4/60	1/41	4/40
LAS incidence in historical controls		1/1179	2/1202	1/364	2/541

[1] Number in denominator - number of animals necropsied.

[2] Number in denominator - number of animals alive when first liver angiosarcoma was observed.

Experiment BT 15

Groups of 60 male and 60 female Sprague-Dawley rats were exposed to 0, 1, 5, 10, or 25 ppm of vinyl chloride for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age (Maltoni *et al*., 1984). Following exposure the animals were observed for the remainder of their lives (up to 147 weeks). Available data,. including Kaplan-Meier survival curves, indicated that vinyl chloride did not affect survival at the concentrations tested.

No statistical analyses of mortality and body weight data were reported. Mortality was greater in the male control group than in the treated groups: the time at which 50% of the male control group had died was week 72, compared with week 100 in the 25-ppm vinyl chloride group. No explanation was given for this decreased survival. The incidence of mammary gland carcinomas in treated females was higher than in controls at all concentrations of vinyl chloride exposure. The differences from control values were statistically significant at concentrations of 1 ppm and above. The mammary gland adenocarcinoma incidence for this and the other relevant BT experiments are presented in Table 10.

Table 10:   Incidence of mammary gland carcinomas in female Sprague-Dawley rats and
Swiss mice exposed by inhalation to vinyl chloride (Maltoni *et al.*, 1984)

Study No.	Experimental Dose Level (ppm)	Tumor Incidence[1]	Corrected Tumor Incidence[2]
BT1 (Rat)	0	0/30	0/29
	50	2/30	2/30
	250	2/30	2/27
	500	1/30	1/28
	2,500	2/30	2/25
	6,000	0/30	0/28
	10,000	3/30	3/29
BT2 (Rat)	0	2/60	2/100
	100	4/60	4/60
	150	6/60	6/60
	200	5/60	5/60
BT6 (Rat)	30,000	2/30	2/30
BT9 (Rat)	0	9/50	9/43
	50	59/150	59/142
BT15 (Rat)	0	6/60	6/60
	1	14/60	14/60
	5	22/60	22/60
	10	21/60	21/60
	25	16/60	16/60
Tumor Incidence in Historical Controls		100/1202	100/1202
BT4 (Mice)	0	1/80	1/67[3]
	50	12/30	12/30[3]
	250	13/30	13/29[3]
	500	10/30	10/28[3]
	2,500	9/30	9/30[3]
	6,000	9/30	9/28[3]
	10,000	14/30	14/28[3]
Tumor Incidence in Historical Controls		21/554	21/554[3]

[1] Number in denominator - number of animals examined.
[2] Number in denominator - number of animals alive when first malignant mammary tumor was observed (type unspecified).
[3] Number in denominator - number of animals alive when first mammary tumor was observed (type unspecified).

Experiment BT4

Thirty male and 30 female Swiss mice were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm of vinyl chloride four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age (Maltoni *et al.*, 1984). The study was terminated 81 weeks after the exposure period began. Vinyl chloride was highly toxic to both males and females, but males appeared more sensitive than females to the toxic effects of vinyl chloride. Survival decreased in a dose-related manner, although statistical analysis apparently was not performed on the data presented.

A very high incidence of lung adenomas was observed in vinyl chloride-treated male and female mice. A statistically significant increase in the incidence of liver angiosarcomas was seen in male and female mice exposed to vinyl chloride, but a dose response was not seen in the male animals. In addition, a high incidence of mammary gland adenocarcinomas occurred in treated female mice. These results are presented in Table 10 (data from Maltoni *et al*., 1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Human occupational studies demonstrate a strong and consistent association between VC exposure and primary cancer of the liver. All of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMRs). The average relative risk for liver cancer among VC workers is five to six times greater than the incidence of that seen in the general population. The evidence strongly suggests that exposure to VC can cause liver cancer. All reports published to date indicate that the SMRs of exposed workers are elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time. CDHS (1990) decided that the Waxweiler *et al*. (1976) study was most suitable for quantitative risk assessment use.

Three sets of animal cancer bioassays (Drew *et al*., 1983; Maltoni *et al*., 1984; Bi *et al*., 1985) were also considered by CDHS (1990) to provide adequate data for quantitative risk assessment purposes. The Maltoni *et al*. experiments together provide an unusually large set of data on cancer incidence in both males and females rats over a large range of exposures at many concentrations - altogether fifteen groups beyond the four control groups. The Drew *et al*. experiments provide incidence data on female rodents for an unusual exposure protocol in that the duration varied for two or three groups beyond controls, while the concentration remained fixed for each species. The Bi *et al*. experiments provide incidence data on male rats for three exposures beyond controls. CDHS (1990) chose to develop cancer risk estimates for VC using both the human and animal data described above.

Methodology

Human-derived risk estimates

The review of the epidemiological studies strongly suggests a causal association between vinyl chloride and several different types of cancer, including liver, lung, and brain. However, none of the occupational cohort studies presented exposure data for a large enough cohort to derive a dose-response curve; so the CDHS (1990) analysis used historical industrial hygiene data to reconstruct a range of likely exposures, from which risk estimates can be extrapolated.

This risk analysis proceeds by selecting the Waxweiler *et al*. (1976) study of 1294 workers who experienced high sustained exposures to vinyl chloride and who were followed long enough (10 years) to develop substantial numbers of cancers that appeared to be related to the exposure. The retrospective estimates of Barnes *et al*. (1976) for the relevant industrial processes furnished

concentrations of the exposures of vinyl chloride, having an overall average value of 647 ppm. The analysis converts these annual average exposure estimates to a lifetime daily equivalent tissue exposure of 3.6 ppm on the assumption of a saturable metabolic process (Michaelis-Menten) leading to active carcinogens. This is based on extrapolated measurements of binding rates to macromolecules (Gehring *et al*. 1977). The seven liver cancer deaths reported for that cohort project to a lifetime risk of .039 (.089 upper confidence limit) per worker for liver cancers. That risk divided by the overall lifetime daily equivalent of effective exposure yields unit risk estimates for that malignancy.

The calculations provided the following upper confidence limits (UCL) on unit risks: 2.5×10^{-5} ppb^{-1} for liver cancers, and 4.5×10^{-5} ppb^{-1} for three sites of cancer combined, liver, lung and brain. Each of these three sites of cancer had a significantly elevated SMR when calculated for a 15-year follow up time. The unit risks calculated in this manner are about six times greater than would be calculated by using actual exposures instead of the effective exposures that take account of the metabolic saturation in the tissue.

Animal-derived risk estimates

The animal bioassay-based quantitative risk assessment analyses performed by CDHS (1990) used the computer program GLOBAL86 to calculate potential risks using a linearized multistage procedure that were associated with vinyl chloride exposure. Significant trends for liver angiosarcoma dominated the results of the modeling. All three analyses of female rats and two of the three analyses of male rats met the statistical criterion ($p > 0.05$) for goodness of fit of the dose-dependent response of liver angiosarcoma (LAS) to vinyl chloride. In addition, the following experimental groups met that criterion: lung carcinoma in the Swiss mice of Drew *et al*. (1983), lung angiosarcoma in the Wistar rats of Bi *et al*. (1985), and mammary tumors in both the Sprague Dawley rats of Maltoni *et al*. (1984) and the F-344 rats of Drew *et al*. (1985).

Table 11 gives unit risk estimates calculated by using the linearized multistage procedure for LAS and other tumor types from both male. and female rats and for female mice for inhalation experiments done by Maltoni *et al*. (1984), Bi *et al*. (1985), and Drew *et al*. (1983). The entries in Table 11 include all those instances in which an adequate fit of the data is achieved by the model using all data points for each species, sex, and tumor type at exposures not greater than 500 ppm, when practical. This exposure limitation tends to reduce the effects of the parent compound (including mortality) at the higher exposure levels. The analyses did include one higher exposure, the 3000 ppm exposure of Bi *et al*., which was retained in order to obtain an adequate number of exposure groups (four) to establish a clear trend.

The results of Table 11 do not include the analyses for angiosarcoma and mammary tumors in mice or the angiosarcoma, skin carcinoma, and mammary tumors in hamsters. The estimates for q_1^* for angiosarcomas and mammary tumors in mice were in the range of 20×10^{-5} to 50×10^{-5} ppb^{-1}, greatly elevated above those for rats while the estimates for those tumors in hamsters (6×10^{-5} and 1×10^{-4}) were about the same as the highest results in rats. None of these analyses met the stringent criteria for goodness of fit of the MLE as defined above, so they were not included in the tabulation of risk estimates.

Table 11: Risks of carcinogenicity from vinyl chloride exposure estimated from rodent data

Experiment	Strain/species, sex	Tumor	Rodent q_1^* (10^{-5} ppb^{-1})	Human[a] q_1^* (10^{-5} ppb^{-1})
Maltoni *et al.*, (1984)				
BT-1,2 ($\leq$ 500 ppm)	SD/rat, female	LAS	1.9	4.9
	SD/rat, female	mammary	1.4	3.7
BT-9, 15	SD/rat, female	LAS	6.7	18.0
	SD/rat, male	LAS	2.5	6.5
Bi *et al.* (1985)	Wi/rat, male	LAS	5.0	13.0
	Wi/rat, male	lung angiosarcoma	1.7	4.5
Drew *et al.* (1983)	F344/rat, female	LAS	3.2	8.4
	F344/rat, female	hepatocellular carcinoma	1.7	4.4
	F344/rat, female	mammary	1.6	4.2
	Sw/mouse, female	lung	6.9	20.0

[a] Determined by multiplying by the scaling factor on rodent dose.
SD = Sprague-Dawley; Wi = Wistar; F344 = Fischer 344; Sw = Swiss; LAS = liver angiosarcoma.

The effect of combining the BT (Maltoni *et al.* 1984) experiments was to lower the value of the resulting q_1^* by a modest amount. Thus BT-1 and BT-2 individually yielded values of 2.5×10^{-5} and 2.2×10^{-5} ppb^{-1} respectively, compared to 1.9×10^{-5} ppb^{-1} when combined. Also, BT-9 and BT-15 individually yielded values of 6.9×10^{-5} and 1×10^{-4} ppb^{-1}, compared to 6.7×10^{-5} ppb^{-1} when combined. The use of metabolized exposure rather than ambient exposure had the effect of increasing the values of q_1^* by about 30-50% in the BT-1 and BT-2 experiments. The effect on BT-9 and BT-15 was virtually negligible because of the much lower exposures experienced in those experiments.

Uncertainties in estimates of unit risk arise from uncertainties mentioned earlier about the accuracy of the model used to determine metabolized exposure. Departures from the present fit of the Michaelis-Menten model could cause calculations of risk to lose accuracy. Cumulative effects or different metabolism, for example, may cause the true risk to differ from that predicted. Nevertheless, uncertain as it is, the metabolic model appears much more likely to provide a more accurate measure of risk than does ambient exposure.

Final cancer unit risk calculation

Cancer risk estimates for VC derived from human and animal data provided the range of 95% UCLs on cancer unit risk for humans: from 2.5×10^{-5} to 2×10^{-4} ppb^{-1}. Because many of the tumors associated with vinyl chloride exposure (particularly LAS) exhibit a long latency period, exposure at an early age would produce a greater risk. The average latency period for the development of LAS in one study of occupationally exposed vinyl chloride workers was determined to be 22.1 years (Stafford, 1983). Drew *et al.* (1983) demonstrated that in rats, mice and hamsters, the highest incidence of neoplasms was observed when vinyl chloride exposure

was started early in life. Exposures early in life may produce up to a 10-fold greater incidence in tumors compared to exposures late in life.

Because of these considerations, CDHS decided that the best estimate of unit risk coincided with the top of the range, which was, when rounded, 2×10^{-4} ppb^{-1}, or 7.8×10^{-5} (μg/m^3)$^{-1}$. This is approximately the value obtained from the more recent Maltoni *et al*. experiments, with lower exposure concentrations than the previous experiments. That result is at the top of the range of six experiments that provided clear dose response relationships for liver cancer. The selected top of the range, 2×10^{-4} ppb^{-1} is also equal to the Drew *et al*. result for lung carcinoma in mice. That result is one of the lowest for mice. The other, higher results for mice are not explicitly reported in the present risk analysis because of scattering of points in each case not providing a clear exposure-response trend. The results for hamsters, not reported quantitatively for the same reason, were close to those for the rats. This approach was considered to provide adequately health protective estimates of human unit risks, which represent the 95% upper confidence limits for risk calculations.

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