Voluntary Children's Chemical Evaluation Program (VCCEP) Tier 1 Pilot Submission

Toluene (CAS No. 108-88-3)

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American Chemistry Council

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GLOSSARY OF TERMS

μg	Microgram
ACGIH	American Conference of Governmental Industrial Hygienists
ACH	Air Changes per Hour
ADD	Average Daily Dose
AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
BMCL	Benchmark Concentration Level (frequently used in reference to the lower confidence limit level from benchmark model)
CAA	Clean Air Act
CARB	California Air Resources Board
CAS	Chemical Abstract Service
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFM	cubic feet per minute
CNS	Central Nervous System
CPSC	Consumer Product Safety Commission
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
EU	European Union
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act
g	Gram
GC/MS	Gas Chromatograph/Mass Spectrometry
GD	Gestation Day
HEC	Human Equivalent Concentration
HI	Hazard Index
High-end exposure	An exposure that was calculated using exposure concentrations representative of a 90th or 95th percentile of the range of values in a given dataset, depending on availability in the published.
HQ	Hazard Quotient
I-O	Indoor-Outdoor (ratio)
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUR	Inventory Update Rule (TSCA)
kg	Kilogram
kHz	Kilohertz (thousands of cycles per second)
LD	Lactation Day
LOAEL	Lowest observable adverse effect level
MACT	Maximum Achievable Control Technology
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	Milligram
mL	Milliliter
MSDS	Material Safety Data Sheet
MSHA	Mine Safety and Health Administration
MTD	Maximum Tolerated Dose
NATA	National Air Toxics Assessment

NCEA	National Center for Environmental Assessment
NCOD	National Drinking Water Contaminant Occurrence Database
NESCAUM	Northeast States for Coordinated Air Use Management
NHANES	National Health and Nutrition Examination Survey
NHEXAS	National Human Exposure Assessment Survey
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organization of Economic Cooperation and Development
OEHHA	Office of Environmental and Human Health Assessment (Cal.)
OPPTS	Office of Pollution Prevention and Toxic Substances (EPA)
OSHA	Occupational Safety and Health Administration
NESHAPs	National Emission Standards for Hazardous Air Pollutants
NIOSH	National Institute of Occupational Safety and Health
PAMS	Photochemical Assessment Monitoring Stations
PBPK	Physiologically-Based Pharmacokinetic (models, modeling)
PEL	Permissible Exposure Limit (OSHA)
POD	Point of Departure
ppb	Part Per Billion
ppm	Part Per Million
PPPA	Poison Prevention Packaging Act
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Limit
RfC	Inhalation Reference Concentration
RfD	Oral Reference Dose
RFG	Reformulated Gasoline
SARA	Superfund Amendments and Reauthorization Act
SD	Standard Deviation
SDWA	Safe Drinking Water Act
SDWIS	Safe Drinking Water Information System
SEM	Standard Error of the Mean
SIAM	SIDS Initial Assessment Meeting
SIAP	Screening Information Assessment Profile
SIAR	Screening Information Assessment Report
SIDS	Screening Information Data Set
STEL	Short-Term Exposure Limit
TEAM	Total Exposure Assessment Method
TERA	Toxicology Excellence for Risk Assessment
TLV	Threshold Limit Value
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
Typical Exposure	An exposure that was calculated using the average or median exposure concentrations in a given dataset (depending on availability) and average or median values for exposure parameters.
UCMR	Unregulated Contaminant Monitoring Rule
UF	Uncertainty Factor
USGS	United States Geological Survey
VOC	Volatile Organic Compound
VCCEP	Voluntary Children's Chemical Evaluation Program

WAGM	Weighted Average Geometric Mean
WHO	World Health Organization

1. Executive Summary

This submission is by the American Chemistry Council Benzene, Toluene & Xylene VCCEP Consortium (the "Consortium") and covers the Tier 1 review of toluene (CAS No. 108-88-3) under the VCCEP Pilot Program. Toluene was included in the VCCEP Pilot Program because the National Health and Nutrition Examination Survey III (NHANES III) detected toluene in human blood, the Total Exposure Assessment Methodology (TEAM) project detected toluene in indoor air and exhaled breath, toluene was identified in the National Drinking Water Contaminant Occurrence Database, and toluene was reviewed under the Organization for Economic Cooperation and Development (OECD) High Production Volume (HPV) Screening Information Data Set (SIDS) Program.

Production and Use

About 89% of the toluene produced in the United States annually is not as an isolated chemical, but is as part of an aromatic hydrocarbon stream added to gasoline to improve octane ratings. The remaining 11% of toluene production consists of isolated commercial toluene for use as an intermediate feedstock in the production of other chemicals such as benzene and xylenes, as a solvent in products such as paints, or for other miscellaneous uses such as the production of pharmaceuticals. The majority of toluene production is from petroleum streams, though it can also be manufactured as a byproduct of coke production.

Hazard

A large number of toxicology and epidemiology studies have been conducted on toluene, including studies on all of the endpoints in the VCCEP. In reviewing these data, the Consortium organized the hazard assessment around the toxicology data available for the VCCEP endpoints (based on the tiers listed in the December 26, 2000 VCCEP Federal Register notice) and included human health experiences for additional consideration and comparison.

Observations of effects of toluene in humans correlate fairly well with results in laboratory animals. Symptoms of acute toxicity are similar – CNS effects, respiratory tract irritation, eye and skin irritation and intoxication at high doses. From animal and human data, toluene can be characterized as a neurotoxic chemical at moderate/high doses, inducing neuromuscular effects and impairment of speech, vision and hearing. Based on the weight-of-evidence, toluene exposure does not appear to affect the immune system in either animals or humans. Toluene has not demonstrated genotoxic activity, and animal studies indicate that inhalation of toluene does not cause systemic cancer.

Reproductive effects have been reported in pregnant toluene inhalant abusers following very high (intentional abuse) exposures. Possible decreased fecundity and increased spontaneous abortion have also been reported in occupationally exposed female workers, though the limitations of these data make causal interpretation and quantitative analysis difficult. No association between subfecundity and occupational exposure to toluene, at concentrations up to 200 ppm, has been reported in male workers. Reports of other reproductive effects (e.g., congenital malformations and low birth weight) associated with occupational toluene exposures are limited and inconclusive due to confounding exposures, recall bias and other limitations. No toluene-induced malformed offspring or significant effects on fertility have been observed in

animal studies. Toluene did not induce adverse reproductive effects in males (humans or rodents). Postnatal neurobehavioral effects in offspring of female animals treated with high doses of toluene, and animals exposed at very young ages have been reported but these results are not consistently observed.

Overall, it appears that neurological toxicity (especially color vision and other sensory endpoints) constitutes the most sensitive endpoint for toluene exposure in both animals and humans. Neurotoxicity studies demonstrate the lowest NOAELs of all toxicity endpoints. Similar workplace NOAELs for color vision impairment (32–56 ppm; Zavalic et al, 1998a; Schaper et al., 2004) and for auditory impairment (45 ppm; Schaper et al., 2003) provide crude quantitative estimates of the association with human workplace exposures, which are suitable for use in risk assessment. However, it is important to remember that these are observational (not experimental) studies, so that issues of bias must always be addressed.

Exposure

Toluene exposure may occur in indoor, outdoor, and in-vehicle air due to a variety of sources such as solvent-based products, combustion sources (automobile exhaust, cigarettes, biomass burning), and stationary sources. Toluene exposure may occur during gasoline refueling or in the workplace. Food and water are also possible sources of exposure.

A child-centered approach was used to define exposure scenarios for children's interaction with toluene sources including environmental (ambient) sources, and use of consumer products. Under this approach children and their parents are assumed to be exposed to background or ambient sources that affect all individuals on a daily basis. A child's/parent's background/ambient sources include air (indoor and outdoor), diet, and water. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to toluene in microenvironments from specific activities such as transportation via gasoline powered vehicles, use of toluene-containing consumer products, or living in a home where tobacco smoking occurs. This exposure assessment did not consider exposures from accidental or intentional misuse of toluene containing products.

Sources of toluene exposure may vary by age. This age variation occurs because individuals interact with different sources in different ways at different ages. For example, an older child (teenager) might receive a direct exposure when using certain consumer products (automotive or painting products) or smoking, whereas a small child would only be passively exposed to toluene in the home when a product is used or tobacco smoke is present. In addition, infants would be the only group expected to be exposed via human milk. Age variation also occurs because exposure/dose related characteristics such as body weight, breathing rate, and diet vary with age. Because of these various factors, exposures were evaluated by different age groups from birth to adulthood.

Childhood exposure to toluene has been quantified in terms of background exposures (i.e., ambient air, food, and water) and specific source exposures, some of which are associated with toluene chain of commerce (i.e., consumer products) and some that are non-chain of commerce sources (i.e., gasoline, and tobacco smoke). Except for breastfeeding infants of occupationally exposed mothers, the exposure source that contributes the most to children's overall background toluene exposures is residential indoor air. For infants of occupationally exposed mothers who breastfeed, ingestion of human milk is the more dominant pathway of toluene exposure, followed by closely by inhalation of indoor air. In terms of source-specific exposures,

toluene exposure from mainstream cigarette smoke is similar to or greater than that received from use of consumer products. Toluene exposures during gasoline refueling are elevated above ambient levels, though given the short duration of these exposures they have little impact on total exposure.

Risk

Non-cancer health risks for toluene exposures have been evaluated in the risk assessment using the Hazard Index (HI) approach, using two different dose metrics:

- An external dose/concentration based dose metric. These external oral and inhalation exposures are compared with the RfD and RfC, respectively, to derive HIs;

- An internal dose metric in which an age-specific PBPK model was used to predict blood levels resulting from the aggregated exposure scenarios. These blood levels are compared to the steady-state blood level associated with exposure at the RfC (RfC_{blood}) to derive a HI. An internal dose metric provides greater insights into age-dependent toluene pharmacokinetics and potential health risks.

The information in the risk assessment and the underlying hazard and exposure assessments demonstrate the following:

- Very low toluene exposures are received from everyday background sources of exposure such as ambient air, water, food and in-vehicle exposures. Aggregated background doses result in HIs that are less than 0.009;

- Chronic, source-specific, inhalation exposures from tobacco smoking and vehicle refueling scenarios do not result in exceedances of the calculated systemic reference doses, including when combined with background ambient doses. Tobacco smoke HIs range from 0.0001 for a child exposed only to ETS to 0.009 for an adult exposed to ETS and mainstream smoke. Refueling HIs do not exceed 0.003 for a high-end exposure;

- Chronic and acute inhalation exposures from toluene-containing consumer products do not result in exceedances of short-term (AEGL-1) and chronic (IRIS RfC) health benchmarks;

- Infants' exposure to toluene via human milk was evaluated from occupationally and non-occupationally exposed mothers. The highest overall HIs are for infant children (7 to 12 weeks old) ingesting milk from occupationally exposed mothers. The HIs are 0.3 and 0.9 for typical and high-end occupationally exposed mothers, respectively, when total aggregate toluene doses are evaluated. These estimates are expected to be conservative given the nature of the scenario and modeling used to derive them. Further, when these exposures are evaluated on the basis of peak and average blood levels achieved compared to the RfC_{blood}, the HIs for infants exposed to the high-end estimated human milk levels are 0.1 or less.

The quantitative risk characterization indicates that reasonably anticipated children's exposures to toluene from the ambient background environment and specific sources such as gasoline during refueling and consumer product use are unlikely to pose significant health risks.

VCCEP Data Needs

Toxicity data on toluene are available for all the Tier 1 VCCEP endpoints and all of the higher tiered endpoints, including subchronic and chronic repeated-dose, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, carcinogenicity and metabolism. Importantly, epidemiology and other human health data on toluene are extensive and have been used as the basis for human risk assessment for this VCCEP assessment and other assessments, such as the U.S. EPA IRIS assessment. As such, this Submission concludes no further testing is needed on the VCCEP endpoints.

For compounds, like toluene, which are used in consumer products and occur in many environments, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is adequate to demonstrate that reasonably anticipated exposures to the compound from environmental sources are not likely to present significant health risks to children. In addition, doses from typical and reasonably worst case exposures from use of consumer products that are consistent with product label information are not likely to present significant health risks to children. Accordingly, the VCCEP sponsors believe additional exposure assessment work should be a low priority.

2. Basis for Inclusion of Toluene in VCCEP Pilot Program

In selecting compounds for the VCCEP Pilot Program, EPA relied on biomonitoring and environmental monitoring databases that it considered relevant to assessing the potential for children's exposure. *See* VCCEP Federal Register Notice (Dec. 26, 2000), at III.Q. Availability of hazard data was an additional factor that influenced chemical selection decisions; EPA stated that it wanted to select chemicals for which Tier I hazard data was available. Toluene was selected for the following reasons: (1) it has been evaluated under the Organization for Economic Cooperation and Development (OECD) SIDS Program; (2) toluene was found in human blood in the NHANES biomonitoring study; (3) toluene was reported in human exhaled air in the TEAM study; (4) toluene has been detected in drinking water; and (5) it has been detected in indoor air. The following is a summary of the EPA review of the available biomonitoring and environmental monitoring database for toluene. The previous review under the OECD SIDS program is discussed in Section 3.

Table 2.1: The results of EPA's VCCEP candidate chemical selection process for Toluene

Table 4: Working List of Candidate Chemicals to be Addressed by the Voluntary Children's Chemical Evaluation Program									
CAS No.	CHEMICAL NAME	Chemicals found in Human Tissues					Chemicals Found in Drinking Water, Food and/or Indoor Air		
		NHANES	NHAT	NHEXAS	TEAMS	Human Milk	NCOD	EAFUS	INDOOR AIR
108-88-3	Toluene	Y			Y		Y		Y

Reference: EPA VCCEP Website.

2.1 National Health and Nutrition Examination Survey III (NHANES III)

NHANES III was conducted between 1988 through 1994 on 33,994 people and focused primarily on basic health and nutritional parameters such as blood pressure, immunization status, and nutritional blood measures. NHANES III included a special study that looked at the blood levels of 32 volatile organic compounds (VOCs) in a sample of about 800 volunteers from the overall NHANES study. Eleven compounds were found with high frequency and the data on these 11 compounds were sufficient to establish reference levels (e.g. median, 95th percentile) for the nonoccupationally exposed U.S. population. Another five compounds were found in at least 10% of the samples.

Results on toluene from NHANES III were published in Ashley et al. (1994) and are presented in Table 2.2 (from the EPA VCCEP website). These blood concentrations are consistent with low level toluene exposures and are further discussed in Section 7.3.

Table 2.2: Blood Concentrations for Toluene from NHANES III Study reported on EPA's VCCEP website

Table 6: Frequency of Detection and Tissue Concentration of Select VCCEP Pilot Chemicals in Human Monitoring Studies				
CAS No.	**CHEMICAL NAME**	**MEDIUM**	**DETECTION FREQUENCY**	**CONCENTRATION**
108-88-3	Toluene	blood	≥ 75% of 804	med = 0.28 ppb

2.2 Total Exposure Assessment Methodology Data

The Total Exposure Assessment Methodology (TEAM) study was designed to develop methods to measure individual total exposure (exposure through air, food, and water) and to apply these methods within a probability-based sampling framework to estimate the exposures of urban populations in several U.S. cities. The TEAM Study reports the results of eight monitoring studies performed in five communities during different seasons of the year. The exposure information on toluene collected through the TEAM study effort is limited. However, extensive information on toluene exposure is available and is presented in Section 7.

2.3 National Drinking Water Contaminant Occurrence Database

The National Drinking Water Contaminant Occurrence Database (NCOD) provides data on the occurrence and concentration of unregulated contaminants in drinking water. NCOD was developed to satisfy the statutory requirements set by Congress in the 1996 SDWA amendments. The purpose of the database is to support EPA's decisions related to identifying contaminants for regulation and subsequent regulation development. The NCOD contains occurrence data from both Public Water Systems and other sources (like the U.S. Geological Survey National Water Information System) on physical, chemical, microbial and radiological contaminants for both detections and non-detects.

NCOD contains occurrence monitoring from sampling locations throughout a Public Water System, therefore a detection value does not necessarily mean the contaminant would be found at the tap. There are some summary statistics, but no actual analysis of the data is provided. Also, NCOD contains data for only unregulated contaminants required to be monitored by public water systems, even though EPA has not set health-based drinking water maximum contaminant levels for this subset of contaminants. This subset is covered by the Unregulated Contaminant Monitoring Rule, or UCMR. Currently the NCOD does not contain occurrence data for all water systems and all states. The only Public Water System data contained in NCOD is data that has been reported by States to the Safe Drinking Water Information System (SDWIS). Historical data goes back to 1983.

Information on toluene in drinking water is addressed in Section 7.2.1.2 of the exposure assessment.

2.4 Air Monitoring Data

Several of the air monitoring references cited by EPA for the VCCEP program provide data on indoor and/or outdoor air concentrations of toluene. The air data samples reported in these studies were generally collected between the mid -1980's and 1991. The most recent study cited by EPA was conducted by Shields et al. (1996) in March and April 1991 at telecommunication center, data centers, and administrative offices. Daisey et al. (1994a) collected indoor and outdoor air samples at 12 office buildings in the San Francisco Bay area between June and September 1990, including several buildings with indoor air quality complaints. Brown et al. (1994) compiled the results of several previous indoor air studies on established and new buildings and reported toluene air concentrations for dwellings, offices and a hospital. Samfield (1992) and Shah and Singh (1988) also compiled the results of numerous indoor and outdoor air monitoring studies. These studies generally reported average air concentrations in the low part per billion (ppb) range. The results of these and other exposure studies are presented in Section 7.

3. Previous and On-Going Assessments

This section reviews the previous and on-going assessments for toluene

3.1 Integrated Risk Information System (IRIS)

The EPA's Integrated Risk Information System (IRIS) is an online database of human health effects of various chemicals that may be present in the environment (www.epa.gov/iris/). EPA has recently updated the toluene IRIS database in September 2005, including the derivation of a chronic inhalation reference concentration (RfC) and a chronic oral reference dose (RfD). In assessing the toxicology database for the toluene RfC, EPA noted that there are a number of occupational studies that have examined effects from inhalation exposure to toluene. EPA concludes, "The most sensitive effects from these studies are neurological effects, including altered vision, dizziness, fatigue, headache, and decreased performance in neurobehavioral tests. Exposure to higher levels in humans and animals have resulted in respiratory tract irritation. Animal studies have also demonstrated effects on other organ systems, but only at high exposure levels (generally above 600 ppm or greater)." Based on this human epidemiology data, EPA derived a chronic human NOAEL of 34 ppm and used this to establish the RfC. EPA further stated that, "Confidence in the (inhalation) database is high; several chronic studies in humans are available that examine neurotoxicity and effects on color vision, and numerous reproductive and developmental studies, as well as a 2-generation reproductive toxicity study, exist." EPA used kidney effects from an NTP (1990) 13-week rat gavage study as the key effect for establishing the RfD. The RfC and RfD are discussed in greater detail in the Risk Assessment (Section 8.0).

3.2 AEGL Committee

The National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL) first met in June 1996 with the purpose of developing and recommending airborne guideline levels for short-term exposures to hazardous substances to the U. S. Environmental Protection Agency (EPA). It was intend that these levels could also be used by other federal, state and local agencies and the private sector for emergency planning, prevention and response activities (U.S. EPA http://www.epa.gov/oppt/aegl/history.htm). There are three AEGL levels:

AEGL-1 - is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience notable discomfort, irritation, or asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 - is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience life-threatening health effects or death.

The AEGL development process consists of four basic stages: (1) draft AEGLs, (2) proposed AEGLs, (3) interim AEGLs, and (4) final AEGLs. Toluene has gone through the first three

stages of the AEGL process. In December 2002, the AEGL committee approved the following interim AEGLs for toluene (see Table 3.1).

Table 3.1: Toluene AEGL Values (Interim)					
Ppm					
	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	200	200	200	200	200
AEGL 2	990	570	510	510	510
AEGL 3	** see below	4,200*	2,900*	1,500*	1,500*

Lower Explosive Limit (LEL) = 11,000 ppm
* = ≥ 10% LEL; ** = ≥ 50% LEL
AEGL 3 - 10 min = ** 7,200 ppm
For values denoted as * safety considerations against the hazard(s) of explosion(s) must be taken into account.
For values denoted as ** extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

3.3 Other Reviews

There have been a number of other previous reviews of toluene by organizations such as IARC, California Office of Environmental and Human Health Assessment (OEHHA), the European Union (EU), the OECD SIDS program, and the Agency for Toxic Substances and Disease Registry (ATSDR). IARC reviewed toluene in 1999 and classified it as a Class 3 carcinogen, "not classifiable as to its carcinogenicity to humans." A summary of the toluene IARC review can be viewed on the IARC website (www-cie.iarc.fr/htdocs/monographs/vol71/030-toluene.html). OEHHA determined neurotoxic effects were the critical effect when it established a chronic recommended exposure limit (REL). In 2003, the European Union (EU) published its risk assessment of toluene. An earlier version of the EU risk assessment was also provided to the OECD for consideration under the SIDS program. The EU risk assessment of toluene considers some of the same toxicology data reviewed in this assessment and includes some exposure information and assessment, though the focus of this risk assessment was not on children. ATSDR released a Toxicology Profile on toluene in September 2000, which provided a review of hazard, exposure and pharmacokinetic data on toluene.

4. Regulatory Overview

This section provides an overview of the extensive federal environmental, health and safety, and related regulations controlling toluene exposures.

Toluene is broadly regulated by many federal agencies, including the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), the Occupational Safety and Health Administration (OSHA), and the Department of Housing and Urban Development (HUD). Given the number, and in some cases, the complexity of these regulations, this overview necessarily is not an exhaustive survey of all regulations relating to toluene.

4.1 EPA Regulation

EPA regulates toluene under numerous statutes, including the Clean Air Act, 42 U.S.C. §§ 7401 *et seq.*; the Clean Water Act, 33 U.S.C. §§ 1251 *et seq*.; the Safe Drinking Water Act, 42 U.S.C. §§ 300f *et seq.* (SDWA); the Resource Conservation and Recovery Act, 42 U.S.C. §§ 321 *et seq.* (RCRA); the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. §§ 9601 *et seq.* (CERCLA, or Superfund); the Superfund Amendments and Reauthorization Act, 42 U.S.C. §§ 9601 *et seq.* (SARA); the Emergency Planning & Community Right-To-Know Act (EPCRA), 42 U.S.C. §§ 11011 *et seq.*; the Pollution Prevention Act, 42 U.S.C. §§ 13101 *et seq.* (PPA); and the Toxic Substances Control Act, 15 U.S.C. §§ 2601 *et seq.* (TSCA).

4.1.1 Clean Air Act

The Clean Air Act regulates toluene emissions from stationary sources (e.g., factories, refineries, and power plants) and mobile sources (e.g., trucks, cars, motorcycles) and as volatile organic compounds in products. Under the Clean Air Act, toluene is variously referred to as a Hazardous Air Pollutant (HAP), a volatile organic compound (VOC), or a Mobile Source Air Toxic (MSAT).

4.1.1.1 Hazardous Air Pollutant Regulation

Section 112 of the Clean Air Act establishes a two-step process for protecting the public and the environment from the effects of toxic air pollutant emissions from stationary sources. First, EPA promulgates extensive National Emission Standards for Hazardous Air Pollutants (NESHAPs), better known as Maximum Achievable Control Technology (MACT) standards, as required by section 112(d) of the Act. These technology-based MACT standards are imposed on specific manufacturing sectors on a category-by-category basis. (See generally 40 C.F.R. Parts 61, 63.) Second, within the eight years following the promulgation of each technology-based MACT standard, EPA has to regulate any remaining (or "residual") risk with an "ample margin of safety" (CAA § 112(f), 42 U.S.C. § 7412(f)). In this second phase, EPA applies a risk-based approach to assess whether the MACT technology-based emission limits sufficiently reduce health and environmental risks.

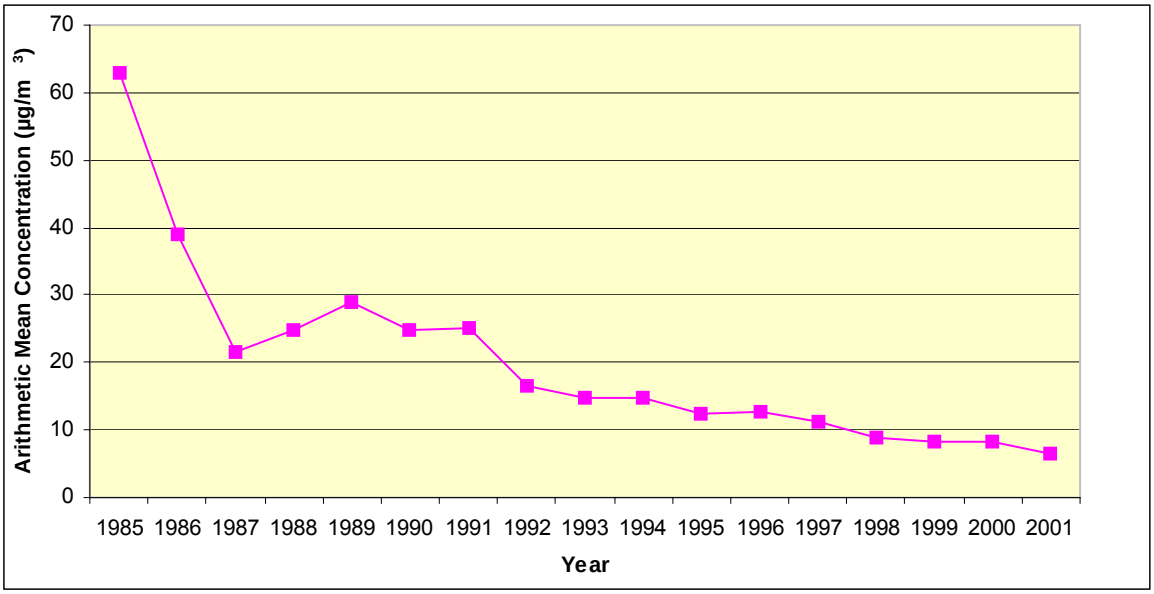
Thus, toluene emissions from stationary sources are subject to both stringent, manufacturing-sector-specific MACT-based standards and any further regulation that EPA determines is necessary to ensure an ample margin of safety. Virtually all of the MACT standards have been published, and EPA is in the process of considering where residual risk rules for facilities will be

needed. For example, on June 14, 2006, EPA promulgated a proposed residual risk rule amending the synthetic organic chemical manufacturing industry NESHAP, also known as the hazardous organic NESHAP. (See 71 Fed. Reg. 34422.)

4.1.1.2 Volatile Organic Compound Regulations

Numerous regulations affect VOCs in regions where ozone formation is a concern. While these regulations are not necessarily specific to toluene, they do affect many consumer and commercial products that contain toluene and many commercial or industrial operations that emit toluene. (See, e.g., 40 C.F.R. Part 59, National VOC emission standards for consumer and commercial products, 40 C.F.R. Part 60, VOC standards for new stationary sources involving certain activities.) In general, the overriding effect of these regulations is a reduction of toluene emissions. The nationwide decline in toluene concentrations was assessed through the use of EPA's AirData database (http://www.epa.gov/aqspubl1/annual_summary.html; accessed 8/20/03). This database contains annual summaries from air monitoring stations, pulling data from three EPA databases: 1) Air Quality System, 2) National Emissions Trends and 3) National Toxics Inventory. The AirData database shows the average ambient toluene concentration to have decreased by 90%, from 63 µg/m^3 in 1985 to 6.4 µg/m^3 in 2001. This decline is illustrated in Figure 4.1 [below/on the following page].

Figure 4.1: Trends in U.S. Toluene Air Concentrations From 1985 to 2001[1]



[1]For the year 1989, two data points from a New York monitoring station were determined to be national average outliers and were excluded from this analysis. Both data points were three orders of magnitude greater (14,948 µg/m^3 and 12,538 µg/m^3) than the national average without them (15.6 µg/m^3).

This trend has been particularly strong since the implementation of the 1990 Clean Air Act Amendments. When considering historic exposure data, even data from the mid-1990s, this is an important consideration.

4.1.1.3 Mobile-Source Air Toxics, Reformulated Gasoline, and Limits on Gasoline Volatility

"Nationwide, mobile sources represent the largest contributor to air toxics" (EPA, Mobile Source Emissions – Past, Present, and Future). The Clean Air Act requires EPA to promulgate regulations to control hazardous air pollutants from motor vehicles and motor vehicle fuels. The regulations must reflect the greatest degree of emission reduction achievable, considering "the availability and costs of the technology, and noise, energy, and safety factors, and lead time" (CAA § 202(l)(2), 42 U.S.C. § 7521(l)(2)). As a result, numerous regulations reduce emissions of mobile-source air toxics such as toluene, including EPA's reformulated gasoline ("RFG") program, limitations on gasoline volatility, and other provisions that affect MSATs.

On passage of the 1990 CAA amendments, EPA established the RFG program. This program requires the reformulation of gasoline to reduce emissions of smog-forming and toxic pollutants (see generally 40 C.F.R. Part 80).

Other regulations limit gasoline volatility, thereby reducing evaporative emissions (see, e.g., 40 C.F.R. § 80.27). Volatility is a measure of how easily gasoline evaporates. When gasoline evaporates, toxics such as toluene that are present in the gasoline are released to the air. EPA regulates the Reid vapor pressure of gasoline, a common measure of gasoline volatility, from May through September each year for certain "designated volatility nonattainment areas" and "designated volatility attainment areas" as defined in 40 C.F.R. § 80.2(cc) and 40 C.F.R. § 80.2(dd), respectively. Moreover, many classes of motor vehicles are required to have evaporative emission controls, thereby further reducing the amount of gasoline volatiles that get into the air (see, e.g., 40 C.F.R. §§ 86.1811-01(d), 86.1811-04(e), 86.1812-01(d), 86-1813-01(d), 86.1814-01(d), 86.1814-02(d), 86.1815-01(d), 86.1815-02(d), 86.1816-05(d), 86.1816-08(d)).

In 2001, EPA promulgated a mobile-source air toxics final rule that identified 21 MSATs, including toluene, and set new gasoline toxic emission performance standards (see 66 Fed. Reg. 17230 (March 29, 2001)). This rule establishes a framework for EPA's national mobile-source air toxics program and requires that refineries maintain the toxics performance of the gasoline they produced during the baseline period 1998–2000. The rule also contains a plan for continuing research and analysis on all MSATs.

In February 2006, the EPA Administrator signed another proposed mobile source air toxics rule designed to reduce emissions of toluene and other MSATs. The proposed rule "would significantly lower emissions of … air toxics … by reducing exhaust emissions from passenger vehicles operated at cold temperatures (under 75 degrees F); and … by reducing emissions that evaporate from, and permeate through, portable gasoline containers (gas cans)." EPA Fact Sheet: Control of Hazardous Air Pollutants from Mobile Sources, Office of Transportation and Air Quality, EPA420-F-06-021 (Feb. 2006). EPA projects "[t]otal reductions in mobile source air toxics would be 147,000 tons in 2015 and over 350,000 tons in 2030." (71 Fed. Reg. 15804 (March 29, 2006).

Table 4.1: Timeline of Mobile-Source Regulatory Actions that Resulted in Reductions of VOCs in Emissions

Year	Description
1970	The Clean Air Act Amendments of 1970 set the first standards for emissions from motor vehicles. The standards are phased in over the next 5 years.
1971	New cars must meet evaporative emissions standards for the first time.
1975	New cars are required to use catalytic converters.
1981	New cars meet the amended Clean Air Act standards for the first time.
1983	Second-generation catalytic converters required for new cars.
1983	First inspection and maintenance programs established in areas with air pollution problems.
1989	EPA sets first fuel volatility limits aimed at reducing evaporative emissions.
1990	Clean Air Act Amendments of 1990 require further reductions in hydrocarbons, lower tailpipe standards, more stringent emission testing procedures, expanded I/M programs, new vehicle technologies, and clean fuels programs. California adopts a low emission vehicle (“LEV”) program.
1991	EPA establishes lower tailpipe standards for hydrocarbons.
1992	Winter oxygenated fuel program begins in cities with high carbon monoxide levels. California has a similar "Phase I gasoline" program (oxygenated fuel required to limit carbon monoxide emissions also has a lower hydrocarbon content).
1994	Progressive introduction begins of national Tier 1 emission limits for light duty vehicles. On-board diagnostic systems become a requirement for light duty vehicles and trucks.
1995	Phase I RFG is required to be sold in areas of ozone non-attainment (Phase I RFG has lower volatility and contains oxygenated compounds). California transitional gasoline introduced as a transition from Phase I to Phase II RFG.
1996	California Phase II RFG is introduced. (Phase II RFG has reduced vapor pressure and lower hydrocarbon content.) National Tier 1 emission limits introduced progressively from 1996 for light duty trucks. Phase-in begins of revised procedures and limits for evaporative emissions for light and heavy-duty vehicles. Dispensing rates for gasoline and methanol pumps are regulated.
1998	Federal Tier 1 tailpipe emissions standards go into effect. California's Low Emission Vehicles (“LEV”) fleet averaging program begins. National hydrocarbon emission limits introduced for vehicles using clean alternative fuels (provisions under LEV program). Voluntary Agreement for Cleaner Cars: Northeastern states agree to put cleaner cars on the road before they could be mandated under the CAAA. The first National Low Emissions Vehicles (NLEVs) under this agreement were released in New England in 1999 and were available nationwide in 2001.
1998	Phase-in begins of on-board refueling controls on passenger vehicles (1998–2000).
2000	NLEV program starts. California hydrocarbon emission limits introduced for vehicles using clean alternative fuels – provisions under LEV program.
2001	Phase-in begins of on-board refueling controls on light light-duty trucks (2001–2003).
2001	Japanese electric-gasoline hybrid automobiles become available.
2003	Federal Tier 2 tailpipe emissions standard phase-in begins.

Table 4.1 (cont.)

Year	Description
2003	Phase-in of California's LEV II program begins.
2003	California requires a maximum level of sulfur in RFG of 600 ppm.
2004	Phase-in begins of on-board refueling controls on heavy light-duty trucks (2004–2006).
2004	For refiners and importers, EPA requires a maximum level of sulfur in gasoline of 300 ppm, and an average of 120 ppm.
2005	California requires a maximum level of sulfur in RFG of 30 ppm.
2005	For refiners, EPA requires an average level of sulfur in gasoline of 30 ppm. For importers, the average requirement is 90 ppm, and the maximum is 300 ppm.
2006	For refiners, EPA requires a maximum level of sulfur in gasoline of 80 ppm. For importers, the average is set at 150 ppm.
2006	Phase-in of California's LEV II program complete.
2006	EPA proposes rule on MSATs with standards to reduce exhaust emissions from passenger vehicles operated at cold temperatures and reduce emissions from portable gas cans.
2007	Importers must meet the 30-ppm average and 80-ppm maximum sulfur content in gasoline.
2007	Planned finalization of EPA's proposed rule on MSATs.
2010	Federal Tier 2 tailpipe emissions standard phase-in complete.

This list also includes regulatory actions that reduce sulfur in gasoline. Lower sulfur content increases catalytic converter efficiency, thus decreasing hydrocarbon emissions. Therefore, the new sulfur regulations have also been included in the table.

4.1.2 Clean Water Act

The Clean Water Act, originally enacted as the Federal Water Pollution Control Act Amendments of 1972, establishes the basic structure for regulating discharges of pollutants into the navigable waters of the United States. It prohibits any person from discharging any pollutant from a point source into navigable waters except as in compliance with the Act's permit requirements, effluent limitations, and other relevant provisions. The Act also grants EPA the authority to set wastewater standards for industry and water quality standards for all contaminants in surface waters.

Toluene has been designated a hazardous substance under the Clean Water Act (see 40 C.F.R. § 116.4). Because of this designation, discharges are regulated, and certain releases must be reported. Direct discharges of wastewater from sources using end-of-pipe biological treatment cannot exceed a toluene concentration of 80 μg/L on any particular day and a monthly average of 26 μg/L (see 40 C.F.R. § 414.91). For indirect-discharge sources and direct-discharge sources that do not use end-of-pipe biological treatment, the maximum toluene concentrations are 74 μg/L on any particular day and a monthly average of 28 μg/L (see 40 C.F.R. §§ 414.101, 414.111). Other EPA regulations permit ocean dumping of wastewater containing toluene, but only when toluene is present in concentrations below its solubility in seawater (see 40 C.F.R. § 227.7(a)). Releases in excess of 1,000 pounds of toluene from any facility must be reported (see 40 C.F.R. § 117.3).

In addition, EPA has established water quality standards, which vary by body of water, for states that do not comply with federal guidance for establishing their own standards under the Clean Water Act (see 40 C.F.R. §§ 131.31–.40).

4.1.3 Safe Drinking Water Act

The Safe Drinking Water Act creates a comprehensive scheme for regulating drinking water and its sources. Under the authority of the Act, EPA sets standards for approximately 90 contaminants in drinking water and its sources—rivers, lakes, reservoirs, springs, and groundwater wells. For each of these contaminants, EPA sets an enforceable limit, called a maximum contaminant level (MCL), and a non-enforceable public health goal, called a maximum contaminant level goal (MCLG), which allows for a margin of safety.

EPA has set both the MCLG and MCL for toluene in public drinking water sources at 1.0 mg/L, (see 40 C.F.R. §§ 141.50, 141.61). The permissible level of toluene in bottled water products is also 1.0 mg/L (see 21 C.F.R. § 165.110(b)(4)(iii)(B)).

In addition to MCLGs, MCLs, and other similar drinking-water standards, EPA also promulgates health advisories, or guidance values, based on non-cancer health effects for different durations of exposure (e.g., one-day, ten-day, and lifetime exposures). These health advisories provide technical guidance to EPA, state and local government, and other public health officials regarding "health effects, analytical methodologies, and treatment technologies associated with drinking water contamination." EPA has promulgated several health advisory values for toluene (see Office of Water, EPA, 2004 Edition of the Drinking Water Standards and Health Advisories, EPA 822-R-04-005 (Winter 2004)).

4.1.4 Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act regulates the transportation, storage, treatment, and disposal of hazardous wastes. RCRA includes toluene on its list of hazardous constituents (see 40 C.F.R. Pt. 261 App. VIII). Moreover, toluene and certain substances containing toluene are identified on two of RCRA's three hazardous waste lists—hazardous wastes from nonspecific sources (see 40 C.F.R. § 261.31) and commercial chemical products (see 40 C.F.R. § 261.33). Toluene also is on the groundwater monitoring list for owners and operators of hazardous waste facilities (see 40 C.F.R. Pt. 264 App. IX). Thus, toluene is subject to a variety of RCRA controls relating to its transportation, storage, treatment, and disposal.

4.1.5 Comprehensive Environmental Response, Compensation, and Liability Act

The Comprehensive Environmental Response, Compensation, and Liability Act, as amended by the Superfund Amendments and Reauthorization Act, provides EPA broad authority to respond directly to releases and threatened releases of hazardous substances, pollutants, and contaminants that may endanger public health or the environment.

Toluene also has been designated as a hazardous substance under CERCLA (see 40 C.F.R. § 302.4). As a result, toluene is subject to monitoring and numerous other requirements relating to releases and threatened releases. For example, releases of toluene in excess of 1,000 pounds from any facility must be reported (see 40 C.F.R. Part 302). In addition, certain amounts of other products containing toluene are reportable. Moreover, toluene present at listed Superfund sites is subject to varying levels of cleanup.

4.1.6 The Emergency Planning and Community Right-To-Know Act And The Pollution Prevention Act

The Emergency Planning and Community Right-To-Know Act, also known as Title III of SARA, was enacted by Congress to help inform local communities of chemical hazards in their areas. Section 313 of EPCRA requires EPA and state governments to annually collect data on releases and transfers of certain toxic chemicals from industrial facilities. These data are available to the public in the Toxics Release Inventory ("TRI"). In 1990, Congress amended these reporting requirements by passing the Pollution Prevention Act ("PPA"). Section 6607 of the PPA requires facilities to provide information on pollution prevention and recycling for each toxic chemical subject to reporting under TRI (see 42 U.S.C. § 13106).

Toluene is one of the more than 650 chemicals and chemical categories subject to reporting under TRI (see 40 C.F.R. § 372.65; EPA, 2004 Reporting Year List of TRI Chemicals). Thus, producers and users of toluene in many industries, such as petroleum refineries, manufacturers, miners, petroleum bulk terminals, and chemical wholesalers, are subject to these reporting requirements.

4.1.7 Toxic Substances Control Act

The Toxic Substances Control Act authorizes EPA to obtain information on all new and existing chemical substances that could cause an unreasonable risk to public health or the environment and to regulate their manufacture, use, distribution, and disposal. Under TSCA, EPA classifies chemical substances as either "existing" chemicals or "new" chemicals. Existing chemicals are those listed on the Toxic Substances Control Act Chemical Substance Inventory, or TSCA Inventory, which EPA must compile, keep current, and publish (see TSCA § 8(b), 15 U.S.C. § 2607(b)). TSCA provides authority to EPA to regulate and seek various kinds of safety and health data on existing chemicals, which include mandatory reporting under Section 8, 15 U.S.C. § 2607, and testing under Section 4, 15 U.S.C. § 2603.

4.2 CPSC Regulation

The Consumer Product Safety Commission regulates toluene in consumer products under the Federal Hazardous Substances Act, 15 U.S.C. §§ 1261 *et seq.* (FHSA), and the Poison Prevention Packaging Act, 15 U.S.C.§§ 1471 *et seq.* (PPPA).

The FHSA requires precautionary labeling on the immediate containers of hazardous household products to help consumers safely store and use these products and to provide consumers information about immediate first aid steps in the event of an accident. Implementing regulations require special labeling of certain products containing toluene. Given that substances containing 10% or more by weight of toluene are "hazardous," products containing toluene at or above 10% require special labels, including "danger," "vapor harmful," "poison," and "harmful or fatal if swallowed" (16 C.F.R. § 1500.14(a), (b)).

The PPPA requires that certain products be packaged in child-resistant packaging to protect children under five from possible poisoning and death in the event that they open containers of hazardous products and eat or drink the contents. CPSC regulations impose special packaging requirements for numerous substances, including solvents for paint or other similar surface-coating materials that contain 10% or more by weight of toluene, or combinations of toluene and

certain other solvents, and that have a viscosity of less than 100 Saybolt universal seconds at 100 °F (see 16 C.F.R. § 1700.14(a)(15)).

4.3 FDA Regulation

FDA regulates a myriad of products ranging from food ingredients and drugs to medical and surgical devices; therefore, only a sample of FDA's regulations relating to toluene are discussed below.

In general, FDA limits the amount, if any, of toluene that food and drugs can contain. Toluene is not an approved food additive that can be added directly to food for human consumption (see 21 C.F.R. Part 172). Moreover, only limited amounts of toluene are permitted as indirect food additives, for example, as a result of processing equipment or packaging (see, e.g., 21 C.F.R. §§ 176.180, 177.1010, 177.1200).

Although there is no specified limit to the amount of toluene that is permitted in food adhesives, the regulations do provide guidelines to limit the amount of toluene. These guidelines state that the adhesive should be separated from the food by a functional barrier, or that in dry foods, the quantity of adhesive that contacts the food shall not exceed the limits of good manufacturing practice, and that in fatty and aqueous foods, the quantity of adhesive that contacts foods shall not exceed the trace amount at seams and at the edge exposure between packaging laminates that may occur within the limits of good manufacturing practice. *See* 21 C.F.R. § 175.105. Similar guidance, with no specified limit, is provided for the use of toluene in the food-contact surfaces of packaging for processing, transporting, or holding certain foods (see 21 C.F.R. §§ 176.180). FDA limits the amount of toluene in food packaging cellophane (see 21 C.F.R. § 177.1200). FDA also limits the permissible amount of toluene in bottled water products to 1.0 mg/L (see 21 C.F.R. § 165.110(b)(4)(iii)(B)).

Furthermore, FDA also provides guidance on the amounts of residual solvents that are considered safe in pharmaceuticals. According to FDA, toluene in pharmaceutical products should be limited. If, however, its use is unavoidable, then the toluene level should be no more than 890 ppm (FDA, Guidance for Industry, Q3C—Tables and List).

4.4 OSHA Regulation

The Occupational Safety and Health Administration is the primary federal agency responsible for establishing and enforcing workplace standards, including exposure limits for many substances. The National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) also develop and recommend exposure limits for worker protection, although these limits are not enforceable.

OSHA sets both permissible exposure limits (PELs) and short-term exposure limits (STELs). A PEL is the maximum concentration to which workers may be exposed in any 8-hour work shift of a 40-hour work week, and a STEL is the maximum 15-minute concentration to which workers may be exposed during any 15-minute period of the workday.

For toluene, OSHA has set the PEL at 200 ppm as an 8-hour time-weighted average (TWA) concentration, an acceptable ceiling of 300 ppm, and an acceptable maximum peak above this ceiling of 500 ppm for a maximum duration of 10 minutes (see 29 C.F.R. § 1910.1000, Table Z-2).

The NIOSH-recommended exposure limit (REL) for toluene is 100 ppm as a TWA for up to a 10-hour work shift and a 40-hour work week and 150 ppm (655 mg/m^3) for 15 minutes as a short term limit (see NIOSH Pocket Guide to Chemical Hazards).

ACGIH has assigned toluene a Threshold Limit Value® (TLV®) of 50 ppm as a TWA for a normal 8-hour workday and a 40-hour work week (see ACGIH, 2005 TLVs® and BEIs®).

4.5 HUD Regulation

The Department of Housing and Urban Development attempts to minimize exposure to toluene through regulations relating to the location of HUD-assisted projects. These regulations help calculate the acceptable separation distance between HUD-assisted projects and hazardous operations that store, handle, or process hazardous substances and provide guidance for identifying and assessing these hazardous operations. Toluene is one of the hazardous substances addressed by these regulations (see 24 C.F.R. Part 51, Subpart C, App. I).

4.6 State Regulation

In addition to the federal regulatory programs described briefly above, toluene is subject to a wide variety of state regulations. A description of such programs is well beyond the scope of this regulatory overview, but in many instances, these regulatory programs are more stringent than federal requirements. Many federal statutes, such as the Clean Air Act and the Occupational Safety and Health Act, permit or, in some instances, require states to apply additional regulatory measures. For example, California has extensive air toxics and VOC regulations that go well beyond federal requirements. These include specific air toxics programs, stringent mobile-source (both fuels and vehicle) controls, and other regulatory controls. In recent years, many of these California programs have been adopted or extended by other states, particularly those in the Northeast. More recently, several localities have enacted local air toxics programs that provide further controls on releases of toluene to the environment.

5. Chemical Overview

This section provides information regarding the chemical identity, physical and chemical properties of toluene and data regarding its fate and transport in the environment. The data presented here are primarily based on information compiled in the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Toluene (2000). The original sources cited by ATSDR are also noted in the tables.

This section presents a summary on the extraction, production and uses of toluene in the chain of commerce and the releases to the environment from these processes. A detailed description of the various chain-of-commerce sources of toluene can be found in Chemical Economic Handbook – Toluene (CEH, 2003). Detailed sector notebooks are also available for several specific industries related to toluene (e.g., the chemical industry, petroleum refining industry, and printing industry) from the EPA Office of Compliance (EPA, 1995a, 1995b, 2002a).

For the facilities that reported year 2003 Toxic Release Inventory (TRI) data, on-site air emissions accounted for 96% of total facility emissions. Since the majority of toluene released to the environment partitions into the air (ATSDR, 2000), this section focuses primarily on air releases of toluene to the air. Releases to water and soil are discussed briefly at the end of this section.

5.1 Physical, Chemical, and Environmental Fate Properties

The information pertaining to the physical and chemical properties of toluene is presented in Table 5.1 below.

Table 5.1: Physical and Chemical Properties of Toluene

Property	Value	Reference
Molecular weight	92.14	CRC, 1994
Vapor pressure (25°C)	28.5 mM Hg	CRC, 1994
Density (25°C)	0.8647 g/cm^3	CRC, 1994
Solubility (25°C)	535 mg/L	Howard, 1990
Henry's law constant (25°C)	5.94 x 10^{-3} atm-m^3/mol	Howard, 1990
Log K_{ow} (octanol-water partitioning)	2.73	Howard, 1990
Log K_{oc} (organic carbon-water partitioning)	1.57- 2.25	Howard, 1990
Physical state at room temperature	Clear, colorless liquid	NFPA, 1994. (in ATSDR, 1995)
Melting point	-95 °C	Howard, 1990
Boiling point	110.6 °C	Howard, 1990
Odor	Aromatic, benzene-like, mild-solvent like	NFPA, 1994 (in ATSDR, 2000)

Property	Value	Reference
Odor threshold	2.9 ppm	EPA, 2003a
Flashpoint	4 °C	NFPA, 1994 (in ATSDR, 2000)
Flammability limits in air	Lower:1.2%; Upper: 7.1 %	NFPA, 1994 (in ATSDR, 2000)

NFPA = National Fire Protection Association
CRC = CRC Press

The environmental fate and transport characteristics of toluene are summarized in Table 5.2. As indicated by this information, when toluene is released to the environment it rapidly partitions to the air. Toluene's presence in surface waters is limited by its solubility in water and its high vapor pressure. Toluene released to groundwater is relatively mobile, but biodegrades under both aerobic and anaerobic conditions. Toluene does not bioconcentrate appreciably in marine organisms or plants. Once in the atmosphere, toluene degrades rapidly due to reaction with atmospheric hydroxyl radicals and has a half-life of 10 to 104 hours (ATSDR, 2000). Due to the fate and transport characteristics of toluene, most human exposure occurs by the inhalation pathway.

Table 5.2: Environmental Fate and Transport Characteristics of Toluene

Characteristic	Description*	Reason
Volatility	Moderate-high	High vapor pressure of 28.5 mM Hg @ 25°C.
Solubility	Low-moderate	Slight solubility of 535 mg/l @ 25°C.
Propensity of toluene to partition to the atmosphere from surface water	Moderate-high	High Henry's Law constant of 5.94 x 10^{-3} atm-m^3/mol. Half-life of several hours (turbulent water) or several days (static water) (ATSDR, 2000).
Groundwater mobility	High	Low Log K_{oc} of 1.6 to 2.3.
Propensity of toluene released to the environment to partition into the air	High	High volatility and Henry's Law Constant; Low solubility.
Fraction of human exposure that occurs via the inhalation pathway	High	High fraction of toluene that partitions to the air (ATSDR, 2000).
Biodegradation potential of toluene in groundwater	Moderate	Toluene biodegradation characterized by half-life of 7 to 28 days under favorable conditions (e.g. presence of appropriate

Characteristic	Description*	Reason
		electron acceptors and acclimated microbial populations, or level of methanogeneic activity)(ATSDR, 2000).
Persistence of toluene in the atmosphere	Short (half life of less than one week)	Rapid chemical degradation reactions with hydroxyl radicals (ATSDR, 2000).
Propensity of toluene to bioaccumulate in marine organisms	Low	Low log K_{ow} of 2.73. High rate of metabolism (ATSDR, 2000).
Bioconcentration potential of toluene in plants	Low	Low potential for root uptake since most toluene rapidly volatilizes from surface soils.

[a] The descriptions are based on the rankings reflective of those generally accepted in the scientific literature.

5.2 Toluene Production and Demand

About 89% of the toluene produced in the United States annually is not as an isolated chemical, but is as part of an aromatic stream added to gasoline to improve octane ratings. The remaining 11% of toluene production consists of isolated commercial toluene for use as an intermediate feedstock in the production of other chemicals such as benzene and xylenes, as a solvent in products such as paints, or for other miscellaneous uses such as the production of pharmaceuticals. Toluene is produced by the petrochemical industry and to a lesser degree, by the steel industry as a byproduct of coke production (Table 5.3). The major chemical processes used in toluene production include catalytic reforming (dehydrogenation of straight-run light naphtha in presence of hydrogen), hydrotreating (subjecting liquid hydrocarbon stream to hydrogen with a catalyst at an elevated temperature and pressure), distillation (chemical separation from crude or light oils based on boiling points), and destructive distillation (separation at high temperature in the absence of oxygen).

Table 5.3: Industrial Sources of Commercial Toluene

Industry	Process	Inputs	Percentage of 2002 U.S. toluene production (CEH, 2003*)
Petroleum	Catalytic reforming	Hydrotreated light naphthas (e.g., methylcyclohexane)	89%
Petroleum	Hydrotreating/ distillation	Pyrolysis gasoline (unsaturated aliphatic hydrocarbons produced by steam cracking of gas oil or heavy naphtha)	7%
Steel	Destructive distillation	Coal	<1%

* The population balance not represented in these tables was obtained as a by-product of styrene and xylene isomerization manufacture and from coke-over light oil.

Historical toluene demand levels are available from trade publications. It is important to note that as of Oct. 1, 1996, the International Trade Commission no longer collects or publishes annual synthetic organic chemical data. Aggregate production volume data is available under the EPA's inventory update rule (IUR) every four years. However, to protect confidential business information (CBI), the production volumes are reported in broad ranges. For toluene in the year 1998, the IUR database indicates that production volume was greater than 1 billion pounds (> 140 million gallons).

Between 1990 and 1999, toluene production increased at an annualized rate of 1.4%, while at the same time, annual air emissions, as reported to the Toxic Release Inventory (TRI) decreased nearly 64% (EPA, 2003b). (See Table 5.4)

Table 5.4: Annual U.S. Demand for Commercial Toluene

Year	Demand (million gallons/year)[a]	Total TRI Air Emissions (million lbs)[b]
1990	1,110	250
1991	1,103	213
1992	1,125	198
1993	1,108	180
1994	1,275	172
1995	1,302	148
1996	1,224	128
1997	1,560	114
1998	1,455	100
1999	1,652	92
2000	1,776	82
2001	1,093	72
2002	1,460	64

[a] Data from CEH, 2003.
[b] Original TRI industries (primarily SIC Codes 20-39).

CEH (2003) provides information on isolated commercial toluene production capacity by producer and city (Table 5.5). In general, demand appears to be about 50-70% of the total capacity. Most of the toluene production capacity is found in Texas (18 facilities), Louisiana (4 facilities), and Ohio (2 facilities).

Table 5.5: U.S. Toluene Production Capacity (2003)

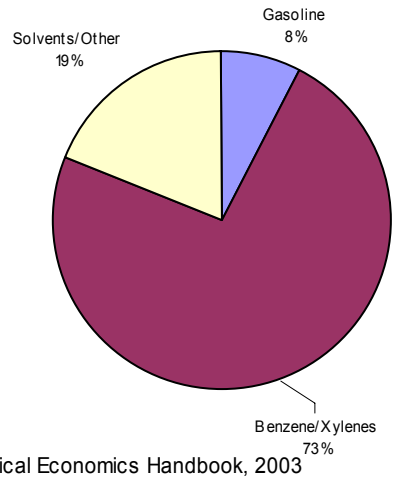
Producer	City	State	2003 Capacity[a] (million gallons)
BP Chemicals	Texas City	TX	245
Chevron Phillips Chemical Co.	Port Arthur	TX	40
CITGO Petroleum Corp.	Corpus Christi	TX	69
	Lemont	IL	19
ConocoPhillips	Alliance	LA	65
	Sweeny	TX	104
Dow Chemical U.S.A.	Plaquemine	LA	14
Equistar Chemicals, LP	Channelview	TX	40
	Chocolate Bayou	TX	15
	Corpus Christi	TX	10
ExxonMobil Chemical Co.	Baton Rouge	LA	30
	Baytown	TX	184
	Beaumont	TX	60
	Chalmette	LA	111
Flint Hills Resources	Corpus Christi	TX	193
Frontier El Dorado Refining Co.	El Dorado	KS	11
HOVENSA, LLC	St. Croix	VI	90
	Corpus Christi	TX	55
Lyondell-Citgo Refining, LP	Houston	TX	37
Marathon Petroleum LLC	Catlettsburg	KY	30
	Texas City	TX	16
The Premcor Refining Group Inc.	Lima	OH	107
Shell Chemical Company	Deer Park	TX	30
Sunoco	Marcus Hook	PA	85
	Toledo	OH	64
	Westville	NJ	30
Total Petrochemicals	Port Arthur	TX	52
Valero Energy Corp.	Corpus Christi	TX	23
	Three Rivers	TX	45
Total Capacity (2003)			1,907
Total Demand (2002)			1,460

[a]Does not include idled plants.

5.3 Production and Uses of Isolated Commercial Toluene

Most isolated commercial toluene is used as a feedstock for the production of other chemicals, benzene and xylenes in particular; lesser amounts are used in solvent applications or blended back into gasoline to meet octane specifications. The U.S. consumption of isolated commercial toluene is shown graphically in Figure 5.1.

Figure 5.1
2004 U.S. Consumption of Toluene[a]



Source: Chemical Economics Handbook, 2003
[a] Based on consumption of recovered toluene

The chemicals and derived products for which toluene is a building block are summarized in Table 5.6 (ATSDR, 1998; CMR, 2000; EPA, 1998a).

Table 5.6: Major Uses of Isolated Commercial Toluene

End Use or Chemical Produced from Toluene	Description of End Use or Typical Use for Derived Chemical
Benzene	Intermediate for chemicals such as ethylbenzene, cumene, cyclohexane and nitrobenzene, which are used to manufacture products such as plastics, nylon, resins and dyes.
Xylenes	Mixed xylenes are used a solvent in certain paints and coatings. Xylene isomers used as intermediates in production of chemicals used in the manufacture of polyesters, plasticizers, pharmaceuticals and insecticides.
Solvents	Used as a solvent in some consumer and commercial products such as printing press inks, adhesives, spray paints, carburetor cleaner or engine cleaner.
Toluene diisocyanate	Primarily used in the manufacture of flexible urethane foams in furniture, carpet underlay or bedding.
Gasoline blending	Added to gasoline to improve octane ratings.
Other	Used in production of benzoic acid (which is used in production of phenol and food preservatives), benzyl chloride (which is used as intermediate in manufacture of dyes and pharmaceuticals), benzaldehyde (which is used as food additive and in manufacture of perfumes) and toluene sulfonic acid (which is used as a catalyst).

[a]Chemical Week, March 6, 2002.

5.4 Petroleum Products Which Contain Toluene

As stated previously, the majority of toluene production (89%) is not as an isolated chemical, but as a constituent in petroleum products. The petroleum product that is most likely to contain toluene is gasoline. Unleaded automobile gasoline generally has a toluene content of about 5% by weight (ATSDR, 1995a). Toluene may also be found in smaller amounts in the aromatic fraction of commercial and military jet fuel (ATSDR, 1995b, 1998). In some cases, toluene (<1% by volume) is added to jet fuel (e.g. JP-8) as a component to help dissipate the static electricity that may be generated by high flow rates in fuel loading systems (U.S. Navy, 2003). In addition to the toluene that is found in crude oil, a small portion of isolated toluene is also blended into automobile gasoline to increase the octane rating (see Table 5.5). Aromatic hydrocarbons such as toluene contribute to the anti-knock properties (prevention of engine pinging or rattling due to secondary detonations) of unleaded automobile gasoline. Table 5.7 summarizes petroleum based fuel production and consumption volumes (DOE, 2000).

Table 5.7: U.S. Petroleum-Based Fuel Production and Consumption

Economic Activity	U.S. Production or Consumption Rate, 1999 (million gallons per day)[a]			
	Motor Gasoline	Jet Fuel	Kerosene	Distillate fuel oil
Consumption (demand)	354	70	3.1	143
Production (supply)	341	66	2.8	150
Net import to U.S. to meet demand	13	5	0.3	7.3

[a]Consumption and production volumes based on assumption of 42 gallons per barrel.

5.5 Toluene Releases to Ambient Air

Toluene is released to ambient air during a number of processes including toluene production, toluene use, combustion of fuel (mobile and non-mobile sources), biomass combustion and miscellaneous processes such as operation of printing presses or disposal of municipal solid waste. Each of the various sources of toluene emissions to air is described in detail by the EPA in "Locating and Estimating Air Emission Sources of Toluene" (1994). Table 5.8 lists various emission sources of toluene and the section number where more information can be found in this EPA reference. The emissions from most of these identified sources are regulated and limited by the federal government. Environmental regulations governing the toluene production industry were discussed in Section 4.

Table 5.8: Summary of Sources of Toluene to Ambient Air

Type of Activity	Process or Source	Section of EPA (1994)
Releases from toluene production	Hydrotreating (pyrolysis or straight run gasoline)	Section 4.1.1: Hydrotreating
	Catalytic reforming (straight run gasoline)	Section 4.1.2: Catalytic reforming
	Secondary hydrogenation (pyrolysis gasoline)	Section 4.1.3: Secondary hydrogenation (for pyrolysis gasoline)
	Liquid-liquid extraction or distillation	Section 4.1.4: Toluene recovery
	Destructive distillation (coke oven)	Section 4.2 Toluene from coal
	Styrene production (toluene by-product)	Section 4.3: Toluene production from styrene
Releases from toluene use	Benzene production	Section 5.1: Benzene production
	Toluene diisocyanate production	Section 5.2: Toluene diisocyanate production
	Trinitrotoluene production	Section 5.3: Trinitrotoluene production
	Benzoic acid production	Section 5.4: Benzoic acid production
	Benzyl chloride production	Section 5.5: Benzyl chloride production
	Production of other chemicals (e.g. mono-, di-nitrotoluene or toluene sulfonic acid)	Section 5.6: Toluene derivatives
	Manufacture of paint and ink	Section 5.7: Paint and ink manufacturing
	Surface cleaning or degreasing	Section 5.8: Solvent cleaning operations
	Miscellaneous solvent uses in adhesives, rubbers, photographic film and agricultural sprays	Section 5.9 Other solvent uses
Releases from use of toluene-containing products	Application of surface coatings (e.g. paint, varnish, lacquer or primer)	Section 6.1: Surface coating operations
	Operation of printing presses (i.e. gravure printing)	Section 6.2: Printing and publishing
	Use of building materials containing residual toluene (e.g. particle board, plywood, or synthetic rubber adhesive)	Section 6.5: Other sources of residual toluene emissions
Releases from mobile sources	On-road and off-road sources	Section 6.3 Gasoline and automotive emissions
Releases from combustion sources	Waste incineration	Section 7.2: Hazardous and solid waste incineration
	Coal combustion	Section 7.1: Coal combustion
Other activities	Storage and distribution of gasoline (marine vessel loading, bulk gasoline plants, terminals and service stations)	Section 6.4: Gasoline marketing
	Wastewater treatment	Section 7.3: Wastewater treatment processes

The EPA Office of Air Quality Planning and Standards (OAQPS) collects emissions inventory data for hazardous air pollutants (HAP) pursuant to the 1990 amendments to the Clean Air Act. The most recent emissions inventory available in final form is the September 21, 2001 revision to the 1996 National Toxics Inventory (NTI). The NTI emissions estimates are based on the following sources of data:

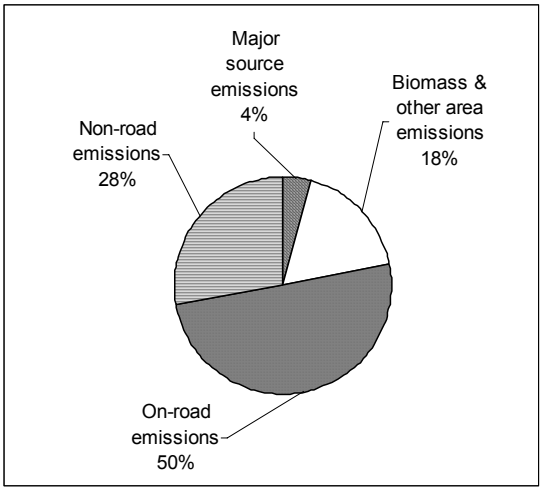
- State and local air pollution control agency HAP inventories;
- OAQPS Maximum Achievable Control Technology (MACT) databases;
- Toxic Release Inventory (TRI) data;
- Mobile source estimates from the EPA's Office of Mobile Sources; and
- Area source emission estimates using emissions factors and activity data.

Emission quantities for four general source categories are provided for the chemicals in the NTI database, including:

- Major sources (stationary facilities with potential to emit 10 tons of any one toxic air pollutant or 25 tons of more than one pollutant);
- Area and other sources (such as biomass burning including wildfires and agricultural burning, as well as small facilities such as dry cleaners with emissions less than that of major sources);
- On-road mobile sources (vehicles that travel on roads and highways such as cars, trucks and buses); and
- Non-road mobile sources (mobile sources that are not found on roads such as lawn mowers, snowmobiles and heavy construction vehicles).

Figure 5.2 shows the relative contribution of the various sources to the total toluene emissions on a nationwide basis based on the NTI 1996 database (EPA, 2000). It should be noted that the contribution from biomass and other area sources is greater in rural areas, as there is less of a contribution from motor vehicles and more likely to be biomass burning.

Figure 5.2: Relative Contribution of Various Toluene Emission Sources to Total Toluene Emissions



5.6 Releases of Toluene to Soil and Water

Toluene can be released to surface water by discharges of industrial or municipal wastewater that contains toluene or accidental spills during transfer of petroleum or chemical products (ATSDR, 2000). Sources of toluene to groundwater include leaks of gasoline underground storage tanks, accidental spills and leachate from landfills (ATSDR, 2000). Toluene is also disposed in on-site industrial underground injection wells as part of the EPA Underground Injection Control (UIC) Program, which is regulated under the Safe Drinking Water Act. Under this program, liquids are pumped into deep, confined and isolated formations that are located beneath potable water supplies. EPA's Underground Injection Control Program regulates the location, construction, operation and enclosure of injection wells to insure that underground drinking water supplies are protected. Toluene can be released to soils as a result of land disposal of toluene containing wastes or from gasoline as a result of a leaking underground storage tank (ATSDR, 2000). The amount of toluene released to soil is considered negligible (ATSDR, 2000).

The 2003 TRI estimates for toluene releases are summarized below in Table 5.9. Facilities that are subject to TRI reporting are those with ten or more full-time employees (or the equivalent in man-hours), those that exceed any one threshold for manufacturing (including importing), processing, or otherwise using a toxic chemical listed in 40 CFR Section 372.65, and that fall under the covered SIC codes below:

- Manufacturing (SIC codes 20 through 39);
- Metal mining (SIC code 10, except for SIC codes 1011, 1081, and 1094);
- Coal mining (SIC code 12, except for 1241 and extraction activities);
- Electrical utilities that combust coal and/or oil for the purpose of generating electricity for distribution into commerce (SIC codes 4911, 4931, and 4939);
- Resource Conservation and Recovery Act (RCRA) Subtitle C hazardous waste treatment and disposal facilities (SIC code 4953);

- Chemicals and allied products wholesale distributors (SIC code 5169);
- Petroleum bulk plants and terminals (SIC code 5171);
- Solvent recovery services (SIC code 7389 limited to facilities primarily engaged in solvent recovery services on a contract basis); and
- Federal facilities that meet the thresholds also must report by Executive Order.

Releases from facilities that are not required to submit reports (i.e., those with few employees or chemical usage/production rates below regulatory threshold) are not expected to have a major impact on the overall evaluation because they would represent minor toluene sources.

Table 5.9: Toluene Releases for All Industries Reporting TRI data for 2003

Type of Release	Release Amount (million pounds/year)	Percent of Total Release
Total air emissions	55	96%
Surface water discharges	0.023	0.04%
Underground injections	0.30	0.5%
Releases to land	0.94	1.6%
Transfer to disposal	1.03	1.8%
Total	57.4	100%

6. Hazard Assessment

6.1 Toluene Health Assessment Summary

This toluene hazard assessment considers both animal toxicology data related to the VCCEP endpoints and human clinical and epidemiological data. Sections 6.2-6.12 review the extensive animal toxicology data and Section 6.13 reviews the numerous human studies. Overall, human and animal data demonstrate similar responses from exposure to toluene. Sections 6.1.1 and 6.1.2 provide a summary of the results used in the hazard assessment. Table 6.1 lists representative key animal studies and conclusions from those studies addressing each biological endpoint in the VCCEP tier approach.

6.1.1 Animal Studies

Acute Toxicity (Tier 1): Toluene induces minimal oral (rats), dermal (rabbits) or inhalation (rats) acute toxicity, slight to moderate skin and eye irritation (rabbits) and no skin sensitization (guinea pigs).

Repeat Dose Studies (Tier 1 and 2): Inhalation studies of 13 weeks or longer duration in rats demonstrated a LOAEL ≥ 1000ppm, characterized by increased relative kidney and liver weights (NTP, 1990), changes in blood parameters (NTP, 1990; API, 1981b; Korsak et al., 1992), and central nervous system (API, 1981b) and neurobehavioral effects (rotarod, Korsak et al., 1992). The NOAEL value varied from 100 – 625ppm, depending on the range of doses tested. Mice, exposed for 14 weeks in the NTP (1990) study were more sensitive to toluene toxicity with a NOAEL of 100ppm and deaths at 625ppm. Oral treatment of rats and mice with toluene for 13 weeks (NTP, 1990) resulted in a NOAEL of 325mg/kg and a LOAEL of 625mg/kg for rats based on increased kidney weights and deaths at higher doses. Mice appeared again more sensitive than rats with a LOAEL of 312mg/kg based on increased liver weights in females and clinical signs in both sexes at higher doses.

Genetic Toxicity (Tier 1 and 2): *In vitro* and *in vivo* genotoxicity studies of toluene indicate that toluene is not genotoxic. Genetic effects were not observed in *in vitro* systems including gene mutations or DNA repair mediated toxicity in bacteria, or gene conversion in yeast, and cytogenetic damage in mammalian cells. In animal studies toluene did not induce biologically significant effects, measured by chromosome aberrations, micronuclei, or sister chromatid exchange in bone marrow, peripheral blood or liver, and did not cause reproductive toxicity indicative of sperm damage in a dominant lethal assay in mice. Toluene was also not genotoxic when combined with other chemicals. Gad-El-Karim et al. (1984) demonstrated that toluene did not cause increased micronuclei or chromosome aberrations in bone marrow of mice but actually reduced the clastogenic effect of benzene when given in combination.

Reproductive and Developmental Toxicity (Tiers 1 and 2): Reproduction parameters in rats were not adversely affected by exposure to toluene in several fertility studies (Ono et al., 1996; Thiel and Chahoud, 1997) or in a 2-generation study at concentrations up to 2000ppm, although decreased pup weight in the F1 generation exposed to 2000ppm was reported during the first 15 weeks of life (API, 1985; Roberts et al., 2003). Significantly decreased sperm count and reduced epididymal weight reported in rats exposed to 2000ppm for 90 days did not affect reproductive performance (Ono et al., 1996).

Developmental effects in offspring are expressed primarily after high exposures to dams, often accompanied by maternal toxicity (API, 1992). Neurobehavioral changes in neonates have been reported when dams were exposed to ≥800ppm (DaSilva et al., 1990; Hass et al., 1999, Hougaard et al., 1999). Increases in spontaneous abortions, resorptions, decreased pup body weight and organ weight and altered pup development occurred when maternal exposure was ≥1000ppm (Dalgaard et al., 2001; Ono et al., 1995, 1996).

In rabbits, no maternal toxicity, fetal toxicity or developmental effects were observed at concentrations as high as 500ppm (Klimisch et al, 1992).

Immunotoxicity (Tier 2): Toluene does not appear to affect the immune system of animal or humans, although a few positive findings have been reported. Inhalation exposure resulted in a decreased thymus weight in male rats exposed to 2000ppm toluene for 90 days and to pregnant rats at 600ppm administered on gestation days 7-17 (Ono et al., 1995). These findings were not consistent with results of studies by NTP (1990) or API (1985) in which no thymus effects were observed in rats or mice exposed at high doses of 1000-3000ppm for period of 15 weeks to 2 years. A study by Aranyi et al. (1985) suggested that toluene might compromise disease resistance based on increased but not dose-related susceptibility to respiratory infection over a range of inhaled doses from 2.5 – 500ppm for up to 4 weeks. Studies from Hsieh et al. have given variable results. Hsieh at al (1989) reported that exposure of mice for 28 days to 105mg/kg/day in drinking water caused decreased relative thymus weight and decreased plaque-forming cell (PFC) responses with an NOAEL = 22mg/kg. However, in a subsequent study (Hsieh et al., 1990b) exposure to toluene at concentration of 85mg/kg did not cause decreased relative thymus weight or significant decreases in PFC responses, suggesting the likelihood of a NOAEL higher than 22mg/kg for these endpoints. Furthermore, oral gavage studies at much higher dose levels, did not show immunotoxic effects from toluene. An oral gavage dose of 600mg/kg toluene for 14 days showed no effects on relative thymus weight, PFC formation or host resistance responses in mice (Burns et al., 1994) and oral doses of toluene up to 2500mg/kg/day for 13 weeks did not adversely affect spleen or thymus weights or histopathology of these organs (NTP, 1990).

Adult Neurotoxicity and Auditory Effects (Tier 3): Neurotoxicity has been investigated in both general toxicity studies and in mechanistic studies. These experimental findings are in concert with human observations that toluene can induce neurotoxicity. Mechanistic research studies indicate that neurological effects can be observed at concentrations that are lower than the NOAELs established in the general toxicity studies. But it is not known whether these effects cause the long-term or irreversible changes that have been observed or are merely reflections of temporary intoxicating effects of CNS depression. For example, Ladeforged et al., (1991) reported that norepinephrine, dopamine, and 5-hydroxytryptamine levels were altered in various brain regions in rats exposed to 500 or 1500ppm toluene, although no neurobehavioral or gross histopathological changes were seen. Von Euler et al. (1993) reported changes in water maze performance of rats exposed to 80ppm toluene, and apomorphine-induced motor activity was enhanced in treated rats.

Auditory impairment in rats induced by toluene exposure has been described in numerous studies. In the rat, functional and morphological auditory impairment induced by toluene could be enhanced by exposure to noise and n-hexane (Nylén et al., 1994). Behavioral indices of effects were present 2.5 months after exposure was terminated, indicating long-lasting, irreversible ototoxic impairment. Estimates of threshold concentrations for hearing loss are LOAEL = 1000ppm and NOAEL = 700ppm (Johnson et al., 1988; Pryor et al., 1984a,b). Very

young animals may be more sensitive to this effect of auditory impairment than older animals (Pryor et al., 1984a).

Developmental Neurotoxicity (Tier 3): This endpoint was frequently incorporated into studies evaluating all developmental toxicity endpoints with toluene exposure from gestation day 7 – 20, or in some studies, treatment was initiated during the final trimester of gestation. Effect of toluene on cognitive function has been demonstrated at prenatal exposure concentrations of 1800ppm (Hougaard et al., 1999) and pre- and post-natal concentrations of 1200ppm (Hass et al., 1999). However, other studies employing exposures at concentrations that overlap those listed above, did not affect spontaneous activity or visual learning (Thiel and Chahoud, 1997). Although a LOAEL of 1200ppm could be established, there were not sufficient data to establish a NOAEL. Perinatal treatment of dams with toluene in drinking water at doses up to 400ppm through gestation and lactation and of offspring to weaning can also affect behavioral performance in offspring at 35-55 days of age, in the absence of maternal or general offspring toxicity (Kostas and Hotchin, 1981).

Chronic Toxicity and Carcinogenesis (Tier 3): When administered by inhalation for 2 years to rats and mice at concentrations up to 1200ppm (NTP, 1990) toluene did not affect survival or induce increases in tumor types in rats. In female mice, an increase in benign adenomas of the pituitary gland was seen at 600ppm but not at 1200ppm and was not considered toxicologically significant. Toluene has also been used as a vehicle and diluent in dermal cancer studies in mice. The irritation caused by repeated exposure to shaved skin has resulted in a low incidence of skin tumors in 4/50 mice with the likely mode of action being cancer promotion caused by chronic skin irritation. As discussed in Section 3.3, IARC (1989) concluded that toluene is not classifiable as to its carcinogenicity noting that the evidence suggests a lack of carcinogenicity in humans and inadequate evidence in animals. ACGIH also designated toluene as A4 –not classifiable as a human carcinogen.

Metabolism (Tier 2): The metabolism and pharmacokinetics of toluene have been extensively studied in animals (WHO, 1985; US EPA 2005). After absorption by the oral, respiratory or dermal routes, toluene undergoes rapid metabolism to hydroxylated or oxidized metabolites like benzyl alcohol, cresols or benzoic acid, which in turn, are conjugated and eliminated in the urine. Hippuric acid is the major urinary metabolite of toluene (Antti-Poika, et al. 1985). In rats, toluene is extensively absorbed via the lungs (Benignus et al., 1984) and the gastrointestinal tract (Turkall et al. 1991; Gospe and Al-Bayatl 1994). Oral administration can produce blood levels similar to those after inhalation in rats (Gospe and Al-Bayatl, 1994). Absorption of toluene through the skin occurs slowly relative to absorption by the respiratory or oral routes (Morgan et al. 1991). Toluene is distributed in blood, plasma and various other tissues such as liver, brain, kidney, stomach, adipose fat, and bone marrow (Pyykko, et al. 1977; Bergman 1979). Metabolism of toluene in animals occurs via initial oxidative pathways carried out by P450 enzymes, primarily in the liver, to benzyl alcohol; o- and p-cresol are minor metabolites. Further oxidation of benzyl alcohol leads to benzoic acid. Conjugation of benzoic acid with glycine produces hippuric acid (predominant urinary metabolite). To a minor extent, conjugation of benzyl alcohol, benzoic acid and cresol can occur with glucuronide, sulfate or glutathione (mercapturic acid) leading to the formation of corresponding conjugates, which are water-soluble and also excreted in the urine. Overall, toluene is rapidly metabolized to hippuric acid, which is excreted in the urine; this represents the major metabolic route of toluene detoxification and elimination in animals.

6.1.2 Human Experience Summary

Effects of toluene on humans have been evaluated with volunteers under controlled experimental conditions of acute/short duration, from toxicological outcomes of toluene abuse, and by occupational studies in which actual exposures have generally been to mixtures of compounds rather than to pure toluene. These latter data suggest that results may be indicative of solvents exposure generally, rather than toluene exposure specifically. In addition to co-exposure with other materials, worker exposure studies are also complicated by confounding from smoking, alcohol and other lifestyle factors; as well as issues of selection and measurement bias.

Short-term exposure to toluene at concentrations of 75ppm and above can induce headache, dizziness, intoxication, sleepiness and eye irritation; below 40ppm, no central nervous system effects were observed. Dermally, toluene may cause skin irritation by removing skin lipids.

Repeated exposure to moderately high airborne concentrations of toluene may alter neuromuscular development and cause central nervous system (CNS) effects. High-level toluene exposure has been reported in the literature to produce acute and/or long-lasting CNS dysfunction, including ataxia and tremors; cerebral atrophy; and impaired speech, color discrimination, and hearing loss.

Toluene alone does not induce consistent genetic damage in occupational settings, especially under current low exposure levels. No evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene was reported by Forni et al. (1971) and Mäki-Paakkanen et al. (1980). Occasional high excursion levels may have caused positive results reported by Pelclová et al. (1990) or by Schmid et al (1985). Negative results in occupational settings are further supported by negative results in controlled laboratory studies using human volunteers (Richer et al., 1993) and *in vitro* studies of cultured human lymphocytes where no elevation of chromosomal aberrations or sister chromatid exchanges were observed (Gerner-Smidt and Friedrich, 1978; Richer et al., 1993).

Toluene abuse during pregnancy can result in children with deformities (Arnold et al., 1994; Pearson et al., 1994). Spontaneous abortion from workplace toluene exposures has been reported (e.g., Ng et al., 1992a), but the limitations of this database make definitive conclusions impossible. Retrospective interviews with women exposed to low levels of toluene have suggested decreases in fecundity, but there is considerable potential for bias in these studies, which detracts from any causal interpretation. No association between subfecundity and occupational exposure to toluene concentrations up to 200ppm have been demonstrated for men and their partners (Plenge-Bönig and Karmaus, 1999). Reports of other reproductive effects (e.g., congenital malformations and low birth weight) associated with occupational toluene exposures are sparse and inconclusive. A review of available occupational exposure studies through the year 2000 concluded that data were insufficient to define the role of toluene exposure in adverse reproductive outcomes (Bukowski, 2001).

Limited data on immunological effects of inhalation exposure to toluene in humans is available and results are as equivocal as those seen in animal studies. Based on the weight-of-evidence, toluene exposure does not appear to affect the immune system.

Results from clinical experiments and human epidemiological studies suggest that high-level toluene exposure may be associated with subjective complaints and subtle neurobehavioral

effects. Common symptoms include mucosal irritation, headache, dizziness, and lapses in short-term memory or concentration. The most common association on neurobehavioral tests was for short-term memory, although associations with other neurobehavioral endpoints have also been reported. For example, workers exposed to toluene at concentrations greater than 80ppm have demonstrated decrements in neurobehavioral performance tests addressing memory, perception, or psychomotor function (Foo et al., 1990; Eller et al., 1999). These findings agree fairly well with the results of laboratory experiments, where high-level exposures can induce CNS effects, sensory impairment, mucosal irritation, and acute intoxication. However, several high-exposure epidemiological studies reported totally or largely negative neurobehavioral findings (Cherry et al., 1984; Chia et al., 1987; Deschamps et al., 2001). Those exposed to less than 50ppm were generally comparable to reference subjects for neurobehavioral effects (e.g., Seeber et al., 2004 & Zupanic et al., 2002).

Auditory toxicity has also been documented among workers exposed to concentrations greater than 50ppm, and the role of co-exposure to other solvents and noise have been examined. For example, Morata et al. (1993, 1997) reported increased incidence of mild high-frequency hearing loss in printing plant workers exposed to both noise and greater than 75ppm toluene and noise. However, it should be noted that Schaper et al. (2003) found neither significant hearing loss nor interaction between toluene and noise intensity in workers exposed to toluene at concentrations as high as 45ppm.

Alteration of color vision may be a particularly sensitive endpoint in evaluating the neurological impact of toluene exposure. The body of literature on color discrimination suggests an effect from chronic high-level toluene exposures above 100 ppm, but results near the TLV are inconsistent (i.e., both positive and negative findings). For example, Zavalic et al. (1998a,b) reported color vision decrements in workers exposed to 132ppm toluene over 18 years of employment, but little effect on color vision at 32ppm exposure. These results are consistent with the findings of other authors, (e.g., Nakatsuka et al., 1992; Schaper et al., 2004) who reported no statistically significant associations with color vision in workers exposed to levels near the TLV. However, other authors (Cavalleri et al., 2000; Campagna et al., 2001) have reported associations with color vision from toluene exposures as low as 36 ppm. Overall, these inconsistencies and the substantial potential for bias (especially selection bias) in these studies preclude any firm or definitive conclusions about lower-level exposures.

Conclusion

From animal and human data, toluene can be characterized as a neurotoxic chemical at moderate/high doses, inducing neuromuscular effects and impairment of speech, vision and hearing. Toluene does not appear to significantly affect the immune system of either animals or humans. Toluene has not demonstrated genotoxic activity, and animal studies indicate that inhalation of toluene does not cause systemic cancer.

Reproductive effects have been reported in pregnant toluene inhalant abusers following very high (intentional abuse) exposures. Possible decreased fecundity and increased spontaneous abortion have also been reported in occupationally exposed female workers, though the limitations of these data make causal interpretation and quantitative analysis difficult. No association between subfecundity and occupational exposure to toluene, at concentrations up to 200 ppm, has been reported in male workers. Reports of other reproductive effects (e.g., congenital malformations and low birth weight) associated with occupational toluene exposures are limited and inconclusive due to confounding exposures, recall bias and other limitations. No toluene-induced malformed offspring or significant effects on fertility have been observed in

animal studies. Toluene did not induce adverse reproductive effects in males (humans or rodents). Postnatal neurobehavioral effects in offspring of female animals treated with high doses of toluene, and animals exposed at very young ages have been reported but these results are not consistently observed.

Overall, neurotoxicity is the most sensitive endpoint to evaluate toluene toxicity in animals and humans. Table 6.1 demonstrates that neurotoxicity studies report the consistently lowest NOAELs of all endpoints. Similar workplace NOAELs for color vision impairment (32–56 ppm; Zavalic et al, 1998; Schaper et al., 2004) and for auditory impairment (45 ppm; Schaper et al., 2003) provide crude quantitative estimates of the association with human workplace exposures, which are suitable for use in risk assessment. However, it is important to remember that these are observational (not experimental) studies, so that issues of bias must always be addressed.

Table 6.1. Toluene VCCEP Hazard Endpoints: Key Studies & References

Endpoint	Study	Result	Reference
TIER 1			
Acute Toxicity Inhalation	Rat 4 hour	LC50 = 12-33g/m3	BASF, 1980; Carpenter et al., 1976; Pozzani et al., 1959
	Mouse 6-7 hour	LC50 = 19.9 – 27.9g/m3	Bonnet et al., 1979, 1982; Svirbely et al., 1943
Oral	Rat	LD50 = 5-7g/kg	Wolf et al., 1956; Smith et al., 1969; Kimura et al., 1971; Ungváry et al., 1982, Withey & Hall, 1975
Dermal	Rabbit	LD50 = 12.4g/kg	Smyth et al., 1969
Repeat Dose Screening Studies: Superseded by definitive subchronic, reproductive and developmental studies			
Genetic Toxicity Bacterial Reverse Mutation In Vitro cytogenetics	 Ames Assay Human lymphocytes	 Negative Negative	 Haworth et al., 1983 Richer et al., 1993
TIER 2			
Subchronic Toxicity	Rat/Mouse 15 week inhalation	NOAEL rat = 625 ppm; NOAEL mouse = 100 ppm	NTP, 1990
Developmental toxicity	Rat Rabbit	NOAEL = 600 ppm NOAEL = 500 ppm	Ono et al., 1995 Klimisch et al, 1992
Reproductive and Fertility	Rat: 2-generation	NOAEL F1 = 500 ppm	Roberts et al., 2003
Immunotoxicity	Mouse drinking water Mouse oral gavage	NOAEL =22 - 85 mg/kg-day NOAEL = 600 mg/kg/day	Hsieh et al., 1989, 1990 Burns et al., 1994
In vivo Cytogenetics	Chrom. aberr - mice oral SCE - humans (3 day exposure)	NOAEL = 1720 mg/kg NOAEL = 50 ppm (only dose)	Gad-El-Karim et al., 1984 Richer et al., 1993
Metabolism/ Pharmacokinetics (PK)	Multiple studies PK and Toxicokinetics	Rapidly metabolized, conjugated and eliminated as hippuric acid in the urine	Reviews in EPA 2005, ATSDR 2000; PBPK in Appendix C.
TIER 3			
Neurotoxicity	Rat 6 mon inhalation Rat 4 wks Inhalation Rat Auditory Toxicity (Inhal)	NOAEL behavior = 1500 ppm; NOAEL brain physiology <500 ppm LOAEL=80 ppm (only dose) LOAEL=1000 ppm NOAEL=700 ppm	Ladefoged et al., 1991 Von Euler et al., 1993, 1994 Pryor et al., 1983a, 1984a
Chronic/Carcinogenesis	Rat/mouse 2 year inhalation	NOAEL tumors = 1200 ppm	NTP, 1990
Developmental Neurotoxicity	Mouse – drinking water Rat Inhalation	NOAEL develop=400 ppm LOAEL open field behavior =400 ppm LOAEL = 1200 ppm	Kostas & Hotchin, 1981 Hass et al., 1999

6.2 Acute Toxicity (see Table 6.2)

Inhalation: Toluene-induced acute inhalation toxicity in rats ranged from 3338-8800ppm (12.5-33g/m^3) in four studies performed at 4 hours exposure. Of these four, the BASF (1980) study closely approximates the EU guideline B2. Test atmospheres were 6.08, 20.00, 23.98, 38.87, and 61.80mg/l of 99.5% pure toluene for 4 hrs; rats were observed for 14 days post-exposure. At concentrations of 20.0g/$m^3$and above, clinical signs included watery discharge from eyes and nose, unrest, increased respiration, rocking gait, narcosis, startle movements and hyperemia of ears and extremities. LC50 by probit analysis was 28.1g/m^3 (7503ppm). Results are comparable to 33g/m^3 [8800ppm](Carpenter et al., 1976), and 12.5 – 28.8g/m^3 (Pozzani et al., 1959) and 22 – 23.5g/m^3 [5874-6275ppm] for a 6hr exposure (Bonnet et al., 1982). LC50 values in mice were similar, ranging from 19.9-27.9g/m^3 [5320-7449ppm] with exposures of 6-7 hr duration (Svirbely et al., 1943: Bonnet et al., 1979, 1982).

Oral: Oral LD50 in rats ranged from 5.5 (Kimura et al., 1971; Withey and Hall., 1975 and) to 7.5g/kg (Wolf et al., 1956; Smyth et al., 1969) and intraperitoneal values were 1.3-1.64g/kg in rats (Fodor, 1972; IUCLID, 1994) and 2.15g/kg in mice (Koga and Ohmiya, 1978).

Dermal: Dermal LD50 in rabbits was reported to be 14.1ml/kg =12.4g/kg (density 0.876) (Smyth et al., 1969).

Skin Irritation: In animals, repeated application of undiluted toluene to rabbit ears or shaved skin caused slight to moderate irritation (Wolf et al., 1956). Exxon (1988), using the EU Annex V, B2 method, demonstrated toluene to be a moderate skin irritant in rabbits, causing significant inflammation of skin reflected in a mean erythema score of 2.43 at 72 hr and on day 7. Using OECD method 404, Guilott et al. (1982a) injected toluene under the skin of rabbits and reported toluene to be slightly irritating by OECD criteria and moderately irritating by other methods. Results in guinea pigs from Kronevi et al. (1979) and Anderson et al. (1986) similarly demonstrated toluene to be slightly to moderately irritating to skin.

Eye Irritation: In animals, instillation of 0.1ml toluene in one eye of a rabbit (other eye was untreated control) induced slight to moderate irritation that resolved in 7-21 days (Wolf et al., 1956; Hazleton Labs, 1962; Exxon, 1995; Sugai et al., 1990). Rinsing of the treated eye at 4 or 30 seconds after instillation did not change the level of toluene-induced irritation (Guillot et al., 1982b).

Skin Sensitization: Toluene was evaluated in a guinea pig maximization test (EU guideline B6). Himilayan guinea pigs were intradermally injected with a 10% moderately irritating concentration of toluene and epidermally exposed to undiluted toluene; control animals were given corn oil. Two weeks later the treated animals were challenged with 50% or 25% toluene, except for erythema in on guinea pigs exposed to 50%, no other effects were observed. Toluene was not a skin sensitizer (NoTox, 1996.)

Table 6.2: Hazard Assessment Studies for Toluene Toxicity: Acute (Tier 1)

Study Type	Species/Route of Exposure	LD50/LC50	Comments	Reference
Acute: Inhalation	Rat/Inhalation	28.1g/m^3 l (7503 ppm)	4 hr exposure	BASF, 1980
	Rat/Inhalation	33g/m^3 (8800 ppm)	4 hr exposure	Carpenter et al., 1976
	Rat/Inhalation	12.5-28.8g/m^3 (3338-7690 ppm)	4 hr exposure	Pozzani et al., 1959
	Ra/Inhalation	22 –23.5g/m3 (5874-6275 ppm	G hr exposure	Bonnet et al., 1982
	Mouse/Inhalation	19.9 g/m^3 (5320 ppm)	7 hr exposure	Svirbely et al, 1943
	Mouse/Inhalation	26.0g/m^3 (6942 ppm)	6 hr exposure	Bonnet et al, 1979
	Mouse/Inhalation	24.0-27.9g/m^3 (6480 -7449 ppm)	6 hr exposure	Bonnet et al, 1982
Acute:Oral	Rat/Oral	5500 mg/kg	.	Kimura et al., 1971
	Rat/Oral	5580 mg/kg		Withey & Hall., 1975
	Rat/Oral	5900 mg/kg	.	Ungváry et al., 1982
	Rat/Oral	7000 mg/kg		Wolf et al., 1956
	Rat/Oral	7500 mg/kg		Smyth et al., 1969
Acute: IP	Rat/Intraperitoneal	1600 mg/kg		Fodor, 1972
	Rat/Intraperitoneal	1330-1640 mg/kg		IUCLID, 1994
	Mouse/ Intraperitoneal	2159 mg/kg		Koga and Ohmiya, 1978
	Rabbit/Dermal	12,400 mg/kg	14.1ml/kg (d=0.876)	Smyth et al., 1969
Irritation:	Rabbit/Skin Irritation	Moderate skin irritant. erythema score > 2; persistent inflammation	EU Annex V, B2 method; 0.5ml on clipped back for 4 hr, semi-occluded; observe 7 days, Draize score	ExxonMobil, 1988
	Rabbit/Eye Irritation	Slight eye irritant: Scores for redness & chemosis, <2.5 and 2.0 respectively	OECD 405 method; 0.1ml instilled in one eye; other eye is control; conjunctival redness, discharge at 1-48 hr; no effect 7da	ExxonMobil, 1995

6.3 Repeated Dose Toxicity - Subchronic Toxicity

Repeat dose toxicity studies have been conducted by oral and inhalation routes in both rats and mice; there are no data by dermal or other routes of administration (see Table 6.3).

Inhalation:
There are data for four subchronic studies of 13 week or longer duration performed with toluene: 3 in the rat and one in mice.

Rat: The studies are: 1) exposure of groups of 10 male and female rats at 0, 100, 625, 1250, 2500 and 3000ppm (0, 377, 2355, 4711, 9422 and 11,307mg/m^3) toluene for 6.5hr/day, 5 days/wk for 15 weeks (NTP, 1990), 2) exposure of 15M, 15F rats at 0, 100 and 1500ppm (0, 377 and 5654mg/m^3) for 6hr/day, 5d/wk for 8, 17 and 26 weeks with subgroups at each dose and sacrifice time allowed a 2-week recovery (API, Bio/dynamics Inc., 1981b), and 3) exposure of groups of 12 male rats to 0 or 1000ppm (3770mg/m^3), 6hr/day, 5days/wk for 3 months or 100ppm, 6hr/day, 5days/wk for 6 months (Korsak et al., 1992).

The most thorough study was the 15-week GLP study conducted by the NTP (1990) in which 625ppm was found to be the NOAEL. Rats were observed for clinical signs daily, and weighed once/week. All rats were necropsied. Histopathological examination was performed on the standard group of organs and tissues in the controls and the 2500 and 3000ppm exposure groups. Eight male rats died during wk 2 at 3000ppm. Mean body weight of rats exposed to 2500 and 3000ppm were significantly reduced by 15-25%. Clinical observations included dyspnea in most of the exposed groups, and ataxia at 2500 and 3000ppm. Relative kidney weight was significantly increased at 1250ppm and higher in both sexes (3-21%). Males at 1250ppm and higher had significantly increased relative liver weight (9-33%); females at 2500ppm and higher also showed this effect (16-21%). Relative weight of brain, heart, and lung were significantly increased in both sexes at 2500 and 3000ppm. Relative testes weight was significantly increased at 2500ppm and 3000ppm. In males, hematological parameters and clinical chemistry values were not considered to be biologically meaningfully changed by exposure. However, in females, plasma cholinesterase activity decreased at 3000ppm, and leukocyte count decreased at 1250ppm and higher. No effects were observed on sperm or estrus cycle. No toxicological effects were found at 625ppm in either sex.

The API, Bio/dynamics study (1981b) was similar to the NTP study, but was conducted at fewer and more widely spread doses. The high dose was initially set at 2000ppm, but after ataxia, tremors and prostration (signs of CNS depression) were seen, the dose was lowered to 1500ppm. Hematology and clinical chemistry parameters were evaluated in 10 rats/sex/group after 13 weeks and in 5 rats/sex/group after 26 weeks of exposure; there were sporadic significant changes in several parameters that were not dose related. However, blood glucose was decreased in all exposed rats (significantly only in females at 1500ppm) after 26wk. At sacrifice, brains were saved for microscopic evaluation and no exposure related neurohistopathological changes were found.

Korsak at al. (1992) studied the effects of toluene (as well as m-xylene, and a 1:1 mixture) on body weight, organ weight, hematology, clinical chemistry, spontaneous motor activity, and rotarod performance. After 3 or 6 months of exposure to toluene, there were no significant differences observed in body weight or absolute and relative organ weight (heart, lung, liver, spleen, kidneys, adrenals, or testes) or in clinical chemistry values (aspartate aminotransferases, alkaline aminotransferases, alkaline phosphatase, sorbitol dehydrogenase, total protein, albumin, glucose, triglicerides). However, 3-month exposure to 1000ppm produced significantly decreased circulating lymphocytes (~17%), and increased monocytes (~76%), and caused significant decrement in rotarod performance, and caused reduced spontaneous motor activity.

Mouse: NTP (1990) conducted a comprehensive 14-week inhalation study in mice. Groups of 10 male and 10 female mice were exposed to 0, 100, 625, 1250, 2500, and 3000ppm (0, 377, 2355, 4711, 9422 and 11,307mg/m^3) toluene for 6.5hr/day, 5d/wk. Fatalities were observed in groups receiving 625ppm and higher (6 males and all females at 3000ppm, 7 females at 2500ppm, 1 male and 1 female at 1250ppm, and 1 female at 625ppm). Final body weight in all exposed groups were 7-13% lower than controls. Dyspnea was observed at 2500 and 3000ppm. Relative liver weight was increased in all groups exposed at 625ppm and higher (males 45-50%; females 17-54%). Relative lung weight was increased in females exposed to 100ppm and higher, and relative kidney weight was increased for females at 1250ppm and higher. There were no biologically meaningful changes in hematological or serum chemistry values. Centrilobular hepatocellular hypertrophy occurred in all males at 2500ppm and 4/6 males at 3000ppm. There were no exposure related effects on sperm motility or estrus cycle, and there were no notable histopathological findings.

Oral:

Rat: A 13-week oral gavage study was performed by the NTP (1990). Groups of 10 male and 10 female rats received 0, 312, 625, 1250, 2500, and 5000mg toluene/kg body wt. in corn oil. All rats in the 5000mg/kg group died within the first week, and at 2500mg/kg, 8 males and one female died before the end of the study. Clinical signs included prostration, hypoactivity, ataxia, piloerection, lacrimation, and excessive salivation in the 2500 and 5000mg/kg groups. Absolute and relative kidney and liver weight were increased in males at 625mg/kg and higher and in females at 1250mg/kg and higher. Absolute and relative heart weight were increased for both sexes at 2500mg/kg and at 1250mg/kg for females. Absolute brain weight was reduced in both sexes at 2500mg/kg. There were no meaningful changes in hematology or clinical chemistry findings (blood or urine) in any group. Males and females had neuropathological changes in the brain (neuronal cell necrosis in dentate gyrus and ammons horn of the hippocampus) at 1250 and 2500mg/kg, as well as necrosis or mineralization in the granular layer of the cerebral cortex. There was no evidence of hyaline droplet accumulation in kidney or of histopathological changes in the liver.

Mouse: A 13-week exposure study was performed by the NTP (1990). Groups of 10 male and 10 female mice received 0, 312, 625, 1250, 2500, and 5000mg toluene/kg body wt. in corn oil by gavage. In the 5000mg/kg group, all mice died during the first week, and 4 males and 4 females in the 2500mg/kg group died before study termination. Final body weight of males receiving 2500mg/kg was reduced by 16% but other groups were not affected. Clinical signs included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, hypoactivity, and ataxia in the 2500 and 5000mg/kg groups. Relative liver weight was increased in males at 2500 and 5000mg/kg (10-26%) and in females, absolute and relative liver weight were increased at 312mg/kg and higher. Relative brain and testes weight and absolute kidney weight were increased in males at 5000mg/kg, and several mice in this group showed myocardial degeneration. Except for the heart, no notable histopathological effects were observed.

Toluene was also evaluated by administration in drinking water for 28 days to male mice at concentrations of 0, 17, 80 and 405mg/l (estimated oral ingestion of 0, 5, 22, and 105mg/kg/day). At the highest dose, liver weight was significantly increased and thymus mass decreased. (Hsieh et al., 1989). The liver effects were likely reversible adaptations involving metabolism of toluene. It is not known whether the reduction in thymus weight was a toxic effect of toluene absorption or was caused by stress induced by the experimental procedure. Organ weight changes did not occur in a subsequent study by Hsieh et al (1990b) in which CD-1 male mice were exposed to toluene in drinking water at concentrations of 80 and 325mg/L (approximately 22 and 89.4mg/kg body wt) for 28days in a comparison with benzene immunotoxicity (see Section 6.8). No adverse effects were observed on body weight, organ weights (kidney, liver, spleen, thymus) or on red and white cell counts at either toluene dose.

The definitive LOAELs and NOAELs for all repeat dose (subchronic) studies are shown in Table 6.3.

Table 6.3: Hazard Assessment Studies for Toluene Toxicity: Repeat Dose (Tier 1 and 2)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Repeat Dose Toxicity Inhalation	Rats-male & female/	625 ppm	1250 ppm – inc relative. kidney wt (M&F); inc rel liver wt (M), dec leukocyte count (F); other effects at 2500 & 3000 ppm	6.5 hr/day, 5d/wk 15 weeks	NTP, 1990;
	Mice – male & female	None	100 ppm dec body wt, inc rel. organ wt. ≥625 ppm deaths, inc rel liver wt	6.5 hr/d, 5d/wk for 14 wk	NTP, 1990;
	Rat – male & female	100 ppm (2 doses only)	1500-2000 ppm – CNS depression, dec blood glucose (F)	6 hr/day, 5d/wk up to 26wks., 2 wk recovery	API, 1981b
	Rat – male	100 ppm for 6 mon	1000 ppm – at 3 mon, dec circulating lymphocytes, inc monocytes; dec rotarod, reduced general activity	1000 ppm, 6 hr/day, 5 d/wk for 3 mon; 100 ppm for 6 mon	Korsak et al., 1992
Oral gavage	Rat –male & female/	312 mg/kg	625 mg/kg - inc absol/rel kidney wt (M&F), deaths at 2500, 5000 mg/kg	5d/wk for 13 wks	NTP, 1990
	Mice – male & female	None	312 mg/kg inc absol/rel liver wt (F), clinical signs at 2500 ppm		
Oral drinking water	Mice-male	22 mg/kg (80 mg/l)	105 mg/kg (405 mg/l) – inc liver wt, dec thymus wt	28 days at 5, 22, 105 mg/l/day	Hsieh et al., 1989
	Mice-male	85.0 mg/kg (325 mg/l)	None	28 days at 22, 85.0 mg/kg/day	Hsieh et al., 1990b

6.4 Genetic Toxicity

The genetic toxicology of toluene has been evaluated in a range of *in vitro* and *in vivo* assays for gene mutation, DNA damage and cytogenetic effects. Table 6.4 lists key representative studies for each genetic endpoint.

In Vitro

Toluene did not induce reverse mutation in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 in, at least 7 plate incorporation assays with and without metabolic activation from rat liver homogenate. Representative dose ranges included 50-2000µg/plate (Conner et al., 1985), 100-2000µg/plate (Bos et al., 1981) and10-5000ug/plate (Spanggord et al., 1982). To accommodate the volatility of toluene (boiling point 110.6^{0}C), Haworth et al. (1983) tested toluene in the 5 *Salmonella* strains over a dose range of 10-1000µg/plate using a 20-minute preincubation with and without metabolic activation. Toluene did not induce mutation in any strain of *Salmonella* under these optimal exposure conditions. Reverse mutation in *E.coli* were also not induced by toluene exposure (Fluck et al., 1976). At very high doses, toluene did not induce differential killing of DNA repair deficient strains of *Bacillus subtilis* rec+/- (133,333-200,000µg/ml medium) or in *Escherichia coli* (400,000-600,000µg/ml medium) with or without metabolic activation (McCarroll et al., 1981a,b). Nakamura et al. (1987) demonstrated that 100µg/ml toluene (100% pure) did not cause SOS repair-inducing activity in *Salmonella typhimurium* TA1535/pSK1002 using the umu procedure. Considering these consistently negative results for mutation and DNA damage in bacterial assays, no additional testing for bacterial gene mutation is proposed.

Toluene has been tested in mammalian cells and human lymphocytes in culture for forward gene mutation, sister chromatid exchange, micronucleus formation and DNA damage. In the mouse lymphoma assay with and without metabolic activation from rat liver homogenate (S9), Jagannath et al. (API, 1978a) reported negative results at doses of 0.05-0.3ul/ml (44-260ug/ml) of medium, producing 90% toxicity at the highest dose and 50% toxicity at the next 2 lower doses. All mutant frequencies were within negative control range. In a similar study by McGregor et al. (1988), toluene induced total lethality at doses of 275-500µg/ml. Although mutagenic responses were observed at all cloned doses (6.26-250µg/ml), only slight increases (<1.5 times background) in colony counts were obtained. The investigators concluded it was not possible to predict toluene-induced mutagenicity in this assay.

Cytogenetic studies in human lymphocytes exposed *in vitro* were reported negative by Gerner-Smidt and Friedrich, 1978 (15.2-1520µg/ml, negative for chromosomes and SCE), Zarani et al., 1999 (0.1-2.0mM, negative for micronuclei in binucleate lymphocytes), and Richer et al., 1993 (50µm-1.0mM, negative for sister chromatid exchanges (SCE). Significant levels of toxicity were obtained with all *in vitro* exposures in the Richer et al. study. The Richer et al. study was particularly interesting because in addition to *in vitro* exposure, it included cultured lymphocytes from non-smoking male volunteers exposed to 50ppm toluene, 7 hr/day for 3 consecutive days.

NTP (1990) studies did not demonstrate increased sister chromatid exchanges or chromosome aberrations in Chinese hamster ovary (CHO) cells, as well as the absence of reverse mutations in *Salmonella*.

In Vivo

Toluene has been administered to laboratory rodents intraperitoneally (ip), orally and by inhalation to evaluate cytogenetic and DNA damage. Three early experiments performed in the

former USSR gave positive results for cytogenetic damage following subcutaneous injection of up to 1000mg/kg (2 studies) and inhalation exposure at 610mg/m^3 toluene (1 study). However, benzene contamination may have been responsible for these significant cytogenetic responses (IARC, 1989; McGregor, 1994). More recent studies have demonstrated an absence of toluene-induced biologically significant genetic damage.

Jagannath et al. (API, 1978a) following administration of a single ip dose of 22, 71, and 215mg/kg to rats reported no depression of mitotic index and the incidence of chromosome aberrations were within the range of spontaneous background. Roh et al. (1987) treated male Sprague Dawley rats with chromatographic grade toluene in a single ip dose of 108.75, 220, and 440mg/kg, producing a small but statistically significant increase in micronuclei at 220mg/kg but not at 440mg/kg, not considered biologically significant by the authors. Chromosome breaks, gaps and translocations were not significantly increased in any treatment group. Although the total number of abnormal cells were reported to be statistically significantly increased at 440mg/kg, the chromosome study was insufficiently described, making the biological significance of the findings questionable. Dobrokhotov and Einkeev (1977) reported a reversible increase in chromosome gaps and breaks in isolated bone marrow cells from male rats [strain not specified] exposed to 610mg/m^3 toluene for 4hr/day for 4 months.

In mice, two studies were performed with generally negative results. Gad-El-Karim et al. (1984) administered toluene (99% pure) by oral gavage at doses of 860 or 1720mg/kg body wt. and mice were sacrificed 30 hours after exposure; toluene did not induce micronuclei or chromosome aberrations. Mohtashamipur et al. (1985, 1987) administered toluene ip at doses of 104, 218, 322, and 435mg/kg body wt. twice, 24 hours apart, to NMRI and B6C3F1 mice, sacrificed 30 hours after the first injection. Small, statistically significant increases in micronuclei were observed which fell within the range of historical controls and were not considered biologically significant. Using the single cell starch gel electophoresis assay, Plappert et al. (1994) did not detect significant DNA damage in peripheral blood cells, bone marrow or liver of BDF1 mice exposed to 500ppm toluene by inhalation, 6hr/day, 5 days/ week for up to 8 weeks. However, Tokunaga et al. (2003) demonstrated an increase in 8-hydroxy-2'-deoxyguanosine immunoreactivity, a marker for oxidative DNA damage in lung, kidney and liver of rats exposed to 1500ppm toluene, 4hr/day over 7 days. Superoxide dismutase immunoreactivity also increased in these organs but the amount of lipid peroxidase did not change.

In a dominant lethal assay performed by Brusick and Mazursky for the American Petroleum Institute (1981a), male CD-1 mice were exposed to 100 and 400ppm toluene by inhalation, 6hrs/day, 5 days/wk for 8 weeks to encompass the entire spermatogenic cycle. Males were then mated to 2 untreated females/male each week for 2 weeks; females were killed 14 days after the midweek of mating and uteri were examined for living and dead implantations. Toluene exposure did not increase pre- or post-implantation embryo loss at any dose level and was not considered mutagenic to sperm in this assay.

Thus, in animal laboratory studies and one controlled human exposure study (Richer et al., 1993), toluene did not induce biologically significant cytogenetic effects *in vivo*. No significant DNA damage was observed in blood, bone marrow or liver of mice exposed to toluene by inhalation and toluene did not cause mutagenic events in sperm of inhalation-exposed mice.

Overall, toluene does not appear to be genotoxic in *in vitro* assays with bacteria or mammalian cells, or in controlled *in vivo* studies in animals and humans.

Table 6.4: Representative Hazard Assessment Studies for Toluene Toxicity: Genetic Toxicity (Tier 1 and 2)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Comments	Reference
Genetic Toxicology: Bacterial- reverse mutation	Sal. typhimurium TA98, 100, 1535, 1537, 1538: plate incorporation	Negative: 2000 µg/plate (doses 10 - 2000 µg/plate)	None	48 hrs. incubation with & without Rat S9	Conner et al., 1985 Bos et al., 1981
		Negative: 5000 µg/plate (doses 10 - 5000 µg/plate)	None		Spanggord et al. 1982
	Sal. typhimurium TA98, 100, 1535, 1537, 1538: pre-incubation	Negative: 1000 µg/plate (doses 10 - 1000 µg/plate)	None	48 hrs. incubation with & without Rat S9	Haworth et al., 1983
Mammalian Cells	Mouse lymphoma L5178Y forward mutation	Negative: 260 µg/ml (doses 44 - 260 µg/plate]	None	with & without Rat S9	API (Jagannath et al.) 1978a
		Negative: 250 µg/ml (doses cloned 6.25-250 µg/ml)	None	total lethality at 275-500 µg/ml	McGregor et al., 1988
Cytogenetics In vitro	Human lymphocytes	Negative: 2.0 mM (doses 0.1 –2.0 mM)	None	Negative for micro-nuclei	Zarani et al., 1999
		Negative: 1.0 mM (doses 50µM – 1.0 mM)	None	Negative for SCE	Richer et al., 1993
In vivo	Humans/ inhalation	50 ppm (only dose) – no SCE in peripheral lymphocytes	None	7 hr/day; 3 days	Richer et al., 1993
	CD-1 Mice: male & female/oral gavage, single dose	1720 mg/kg (max dose) – no micronuclei or chrom aberr. in bone marrow	None	30 hours	Gad-El-Karim et al., 1984
	NMRI & B6C3F1 mice/ ip: 2 doses, 24 hr apart	435 mg/kg (max dose) – small inc in micronuclei within historical control	None	30 hours	Mohtashamipur et al., 1985, 1987
DNA damage	BDF1 mice - males & females	500 ppm (only dose) – no DNA damage in peripheral blood, bone marrow or liver	None	6 hr/d, 5d/wk for up to 8 weeks. Gel electrophoresis	Plappert et al., 1994
Dominant lethal	CD-1 mice – males/ Inhalation	400 ppm (max dose) – no effect on sperm, reproduction, embryos	None	6h/d, 5d/wk for 8 wk; then mated for 2wk to untreated F.	API (Brusick and Mazurksy), 1981a

6.5 Reproductive Toxicity (see Table 6.5)

Animals: Several studies have been performed to evaluate effects of toluene on fertility in rodents. In a study performed by Ono et al. (1996), Sprague Dawley rats were exposed to 0, 600 and 2000ppm toluene; males for 90 days beginning 60 days prior to mating, and females 14 days prior to mating until day 7 of gestation and sacrificed on day 20 of gestation. At 2000ppm, fetal mortality and the number of dams with dead fetuses were higher than controls. Other reproductive parameters were unaffected. Among males, fertility was unaffected but sperm counts decreased 20-25% at 2000ppm and 10% at 600ppm; absolute and relative (to body wt.) epididymis weights were decreased at 2000ppm. No microscopic abnormalities of testes and epididymides were observed and the numbers of spermatogenic cells examined at three stages were not affected by toluene exposure. In a subsequent study in male Sprague Dawley rats, at high doses of 4000 or 6000ppm, 2hr/day for 5 weeks, Ono et al. (1999) reported a reduction in epididymal sperm count, sperm motility, sperm quality and *in vitro* penetrating ability in zona-free hamster eggs at 6000ppm only, while no exposure related changes were observed in testes weight or spermatogenesis within the testes. No significant changes in serum lutenizing hormone, follicle stimulating hormone or testosterone levels were observed. Authors concluded that high concentrations of toluene may directly target sperm in the epididymis and disrupt maturation.

In another male focused study, subcutaneous injection of toluene at 50 or 500mg/kg/day for 10 days decreased the epididymal sperm count and serum testosterone level (Nakai et al., 2003). The level of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxod G) formation, a biological marker for oxidative DNA damage, was increased in the testes, suggesting that oxidative DNA damage in the testes may play a role in male reproductive toxicity. Increase in this marker was also reported by Tokunaga et al. (2003), in lung, kidney and liver of rats exposed to 1500ppm inhaled, toluene 4hr/day for 7 days, so the effect may be a more generalized response to toluene exposure. Alternatively, inhalation of toluene at 1500ppm, 4hr/day, for 20 days did not have a clear influence on the division of spermatogonium and spermatocytes (Ishigami et al., 2005). Body weights were significantly decreased but testes and epididymal weights were unaffected. To examine changes in cell division and proliferation in spermatogenesis, proliferating cell nuclear antigen (PCNA) was stained immunochemically and apoptosis was also detected. To determine if toluene influenced testes and epididymides as a stress factor, anti-70KD heat-shock protein (HSP70) and c-Fos gene product were also observed. No positive immunoreactivity for HSP70 or c-Fos or differences in PCNA expression were observed compared to controls. Spermatogenesis appeared well maintained and not apparently damaged.

In a repeat dose NTP study (1990; Huff, 2003), no toluene treatment-related histopathological lesions were found in testes of Fischer 344/N rats or B6C3F1 mice exposed to up to 3000ppm toluene for 14-15 weeks or in ovaries or testes of rats and mice exposed to 1200ppm for 2 years. Similarly no lesions were seen in ovaries or testes of Fischer 344 rats exposed to 300ppm toluene for 24 months (CIIT, 1980), using standard histopathology techniques. Tap et al. (1996) reported that, with ultrastructure evaluation, exposure to toluene at 3000ppm for 7 days was associated with effects in rat ovaries, including vacuoles, lytic areas and mitochondrial degeneration in antral follicles. Because these findings derive from histopathology in systemic toxicity studies, which did not include breeding or reproductive endpoints, they are not listed in Table 6.5.

Female Wistar rats exposed to toluene at concentrations of 0, 300, 600, 1000 and 1200ppm, 6hr/day on gestation days (GD) 9-21 did not show adverse effects on pregnancy, parturition or lactation. Adult F1-generation animals were mated and no effects were seen on mating or fertility. Indeed, the fertility index of F1 rats prenatally exposed to toluene at 600ppm was significantly increased compared to negative controls; all other treatment groups were comparable to controls (Thiel and Chahoud, 1997).

In a combined 2-generation reproduction and teratogenicity study (API, 1985; Roberts, 2003), Sprague Dawley male and female rats, parental (F0) and first generation (F1), were exposed to 0, 100, 500 and 2000ppm toluene, 6hrs/day, 7 days/wk for 80 days premating and 15 days mating. Toluene was administered at 2000ppm to both sexes, or to females or males only to be mated with untreated partners. Pregnant females were exposed from GD1-20 and lactation day (LD) 5-21. At LD5, females were removed from their litters for daily exposure and returned when 6 hours of exposure was completed. F1 pups selected to produce the F2 generation were treated for 80 days beginning immediately after weaning (LD21) and initially mated at a minimum of 100 days of age. F2 pups were not directly exposed to toluene. Toluene exposure did not induce adverse effects on fertility, reproductive performance, or maternal/pup behaviors during the lactation period in males and females of F0 and F1 parents, but did inhibit growth in F1 and F2 offspring in the 2000ppm (both sexes treated) and 2000ppm (females only treated). Exposure to toluene caused decreased pup weights throughout lactation in F1 and F2 2000ppm (both sexes treated), and 2000ppm (females only treated) groups. Exposure at 2000ppm to male parents only did not induce similar weight inhibition in offspring. Microscopic evaluation of reproductive organs from parental, F1 and F2 generations did not indicate toluene-induced changes in any dose group up to 2000ppm. NOAEL was 500ppm in groups in which maternal animals were exposed, and 2000ppm for male only treated groups.

Exposure to toluene by inhalation at concentrations up to 2000ppm did not cause adverse effects on mating, fertility or gestation in rats or mice in several fertility studies and a 2-generation reproduction study. Significantly decreased sperm count and reduced epididymal weight were reported in rats exposed to 2000ppm for 90 days without affecting reproductive performance (Ono et al., 1996). Other effects on spermatogenesis have been reported at extremely high doses (Ono et al., 1999) or unusual routes of exposure (Nakai et al., 2003) but at levels as high as 1500ppm spermatogenesis appeared undamaged (Ishigami et al., 2005). In the 2-generation study (API, 1985; Roberts et al., 2003), in which males were comparably exposed, no pathological changes were seen in testes, epididymides or seminal vesicles of the parental, F1 or F2 generation. Testicular function –sperm counts, motility and morphology – were not evaluated. The absence of toluene-induced effects on observed male fertility, despite decreased sperm count seem to correlate with absence of effect on fecundity in human males reported by Plenge-Bönig and Karmaus (1999).

The 2-generation reproduction study and several fertility studies provide sufficient information to demonstrate that exposure to toluene at concentrations up to 2000ppm, does not produce adverse effects on fertility and reproductive performance.

6.6 Developmental Toxicity (see Table 6.5)

Numerous studies have been performed in a variety of species to address the developmental toxicity and developmental neurotoxicity of toluene. Studies focused on developmental neurotoxicity are outlined here but are discussed more fully in Section 6.8.

Rats - Inhalation: In an American Petroleum Institute study (1978b), toluene administered to pregnant Sprague Dawley rats at concentrations of 100ppm (375mg/m^3) and 400ppm (1500mg/m^3), 6 hrs/day, from days 6-15 of gestation (GD) did not induce adverse effects on reproductive parameters, fetal mortality, fetal body weight or teratogenic effects. In the developmental segment of the API 2-generation reproduction study (1985; Roberts et al., 2003), caesarean section of selected females from the group in which both male and female rats were exposed to 2000ppm toluene 80 days prior to and during mating, and during gestation was performed on GD20. No adverse effects on weekly maternal body weight were observed. Lower fetal body weights and increased incidence in skeletal variations, 14th rudimentary rib and unossified 5th and 6th sternebrae were reported.

A more extensive developmental toxicity study was performed at exposures of 0, 250, 750, 1500 and 3000ppm toluene (0, 938, 2812, 5625 and 11250mg/m^3), 6 hr/day, from GD6-15 (API, 1992). Toluene induced clinical signs of exposure (ataxia, hyper-responsivity, increased water intake and decreased food consumption) at 3000ppm, ataxia and hyper-responsivity at 1500ppm, and reduced maternal body weight gain at 1500 and 3000ppm. Absolute maternal body weights in all groups were comparable throughout gestation except for the adjusted final body weight (minus gravid uterus) of 3000ppm dams on GD20. The weight gain of 1500 ppm exposed dams became comparable to controls during the non-exposure period GD16-20. At caesarean section no adverse effects on implantation, number and viability of fetuses and fetal sex distribution were observed, however litter weight and mean fetal weight were reduced at 3000ppm, and mean fetal weight was reduced at 1500ppm ($p<0.01$) and slightly at 250ppm ($p<0.05$). Litter and fetal weights were comparable to controls at 750ppm. No treatment-related biologically significant malformations occurred but instances of reduced or unossified skeletal elements were seen at these doses. Lower maternal body weight gains in the 1500ppm group continued GD6-16 throughout the principal stages or organogenesis when impact on developing offspring could have been significant. The weight gains in the 1500ppm group did not become comparable to control values until exposure was completed. Lower maternal weight gain during organogenesis, occurrences of ataxia and hyper-responsivity at 1500ppm constitute clinical indicators of toluene effects.

Hudák and Ungváry (1978) exposed pregnant rats to 400ppm (1500mg/m^3) 24 hrs/day on days 1-8 or 9-14 of gestation, inducing death in 5/9 dams during the GD1-8 exposure and 2/19 during the GD9-14 exposure period with no effect on body weight gain in surviving dams. Fetuses from the GD1-8 group showed significant reduction in mean weight (46%) and ossification retardation; in the GD9-14 group, fetuses had significant increase in fused sternebrae and extra ribs. Rats exposed to 266ppm (1000mg/m^3) on GD1-21 showed no maternal toxicity but weight retarded fetuses and skeletal retardation was more common in litters from treated dams than controls. Similar effects were reported by Tátrai et al. (1980) when pregnant rats were exposed to 266ppm (1000mg/m^3) 24 hrs/day on GD7-14; no maternal toxicity but a significantly higher percentage of fetuses with skeletal effects was observed.

Other studies in which offspring of toluene-exposed dams showed effects in birth weight, survival and neurobehavioral responses at doses that were not or only slightly maternally toxic, have been reported. Da-Silva et al. (1990) demonstrated decreases in number of live pups at birth, increases in litters with low birth weight pups and behavioral impairment (t-maze performance) in male pups from Wistar dams exposed to 213ppm (800mg/m^3) toluene, 6 hrs/day from GD14-20; no maternal toxicity was observed.

Thiel and Chahoud (1997) examined developmental and behavioral endpoints in offspring of pregnant Wistar rats exposed to toluene over a concentration range of 0, 300-1200ppm (1125-4500mg/m^3), 6 hrs/day, from GD9-21; adult untreated F1 offspring were mated and their fertility evaluated. Decreases in body weight of parental dams were observed at 1000 and 1200ppm but were small with no clear dose response. Decreased maternal weight data was initially erroneously reported as statistically significant in the published paper; however, the authors corrected this in the European Union (2003) Toluene Risk Assessment and these results are no longer considered statistically significant. Increased mortality (postnatal days 2-21), lower body weight and slightly retarded development occurred in pups in the 1200ppm group and pup weight was lowered at 1000ppm. No significant effects on spontaneous activity, discrimination learning or fertility of F1 offspring were reported.

Hougaard et al. (1999) addressed developmental and neurobehavioral effects on offspring and toluene-induced auditory dysfunction, if any, in dams treated with 1800ppm (6750mg/m^3) from GD7-20, according to proposed OECD guideline 426. Maternal body weight was slightly suppressed during the exposure period but no effects were seen on reproductive parameters or maternal care during lactation. Reduced pup weight was significant until day 10 of lactation and impairment of learning (Morris water maze performance) was demonstrated at 2-3 months of age, especially in female pups, in the absence of significant maternal toxicity. Hass et al. (1999) produced similar results in Wistar dams exposed to 1200ppm (4500mg/m^3) toluene, 6 hrs/day from GD7, continuing exposure to dams and pups through lactation day 18. No maternal toxicity or decreased viability of pups was observed, but lower pup body weight until day 10 of lactation and delay of ontogeny of some reflexes occurred. Behavioral testing after weaning revealed significant increase in motor activity in both sexes and impaired performance in the Morris water maze by female offspring at 3 months of age.

Dalgaard et al. (2001) reported that pre- or post-natal exposure to 1200ppm (4500mg/m^3) toluene (Wistar dams exposed from GD7, continuing exposure of dams and pups to lactation 18) or prenatal exposure to 1800ppm (6750mg/m^3) toluene (GD7-20) did not induce significant effects in sperm analysis, histopathological evaluation of testes or vitmentin immunosuppression in Sertoli cells as markers of testes toxicity, despite reduction in absolute and relative testes weight at postnatal day 110. Prenatal exposure at 1800ppm (GD7 – 20) resulted in decreased body weight in pups at lactation day 11 but not at days 21 or 90. Testes weights were slightly decreased at all ages; values were not statistically significant and no histological changes in testes were observed.

Behavioral effects were also measured in offspring of 20 pregnant Sprague Dawley rats exposed to 0, 600 and 2000ppm (0, 2250 and 7500mg/m^3) toluene, 6 hr/day from GD7-17 (Ono et al., 1995). Decreased maternal body weight in the 2000ppm group occurred from GD14-20. Caesarean section on 13 rats/group at GD20, showed no significant effects in reproductive parameters including total fetal death, live fetuses, litter size or sex ratio. However, the number of dams with dead fetuses was slightly increased and fetuses had lower body weights at both dose levels. Remaining dams were allowed to deliver and untreated offspring were monitored for behavior (spontaneous activity, rotarod, and water maze) and development until postnatal week 7. Pup weights were lower in the 2000ppm group at birth and weaning (postnatal day 21). Spontaneous activity appeared normal, some slight effect in learning was observed in female offspring but the sample number was too small for results to be considered definitive.

Rats – Oral: Oral treatment by gavage of pregnant Sprague Dawley rats with 0 or 520mg/kg toluene in corn oil on GD6-19 resulted in 24% reduced maternal weight gain and a blood

toluene level of 7-61µg/ml, reduced fetal and placenta weights, reduced fetal liver and kidney absolute weights and increased fetal brain/fetal body weight ratio in offspring examined on gestational day 19 (Gospe et al., 1994). In a 1996 publication, Gospe et al. administered 650mg/kg in corn oil by oral gavage from GD6-19 and reported decreased fetal weight, decreased fetal organ weights (brain, liver, heart and kidney) and delayed skeletal ossification in fetuses delivered on gestation day 19. Gospe and Zhou (1998) again administered 650mg/kg toluene from GD6-19 with examination of offspring at GD19 and maintenance of pups for examination on postnatal days 10 and 21. This study demonstrated similar decreased fetal body weight and organ weights at GD19 and decreased body, heart and kidney weights at postnatal day 10. By postnatal day 21, body and organ weights in offspring of treated dams were comparable to controls. However, prenatal exposure to 650mg/kg toluene from GD 6-21 did demonstrate histological effects in the brain characterized by decreased neuronal packing and alterations in patterns of staining with bromodeoxyuridine, suggesting toluene - induced alterations in neurogenesis and neuronal migration (Gospe and Zhou, 2000).

Rabbits – Inhalation: Klimisch et al. (1992), performed two studies in Chbb HM rabbits using a method similar to OECD guideline 414. In the first study, rabbits were exposed to toluene 6hr/day from post-insemination day 6-18 at doses of 0, 30, 100 or 300ppm (0, 112, 375 or 1125mg/m^3), no maternal toxicity, no fetotoxicity or embryotoxicity was observed, except for slight delayed development of skeleton at 100 and 300ppm, statistically significant only when the fetus, not the litter, was the statistical unit. In a subsequent study reported in the same publication by Klimisch et al (1992) with a higher maximum dose of 500ppm (1875mg/m^3), performed according to OECD guideline 414, no maternal toxicity, no significant fetotoxicity, no soft tissue or skeletal developmental effects were observed. The NOAEL was considered to be 500ppm by the authors.

Ungváry and Tátrai (1985) exposed pregnant rabbits to toluene by inhalation 24hrs/day from post-insemination day 7-20 at concentrations of 133 or 266ppm (500 or 1000mg/m^3), resulting in substantial maternal toxicity and abortion at 266ppm and no maternal or fetal toxicity at 133ppm, except for slight, not statistically significant increase in percent of fetuses with skeletal growth retardation.

Hamsters – Inhalation: In the only study available, hamsters were exposed to 0 or 213ppm (800mg/m^3) toluene, 6hr/day from GD6-11. No adverse effects were observed on offspring growth and development. However rotarod performance was significantly worse than controls on postnatal day 25, the last of three test days. (DaSilva et al., 1990).

Mice – Inhalation: The profile of toluene developmental toxicity in mice appears similar to rats. Courtney et al. (1986) found some signs of fetotoxicity (increase in number of fetuses with 13 ribs) in offspring of CD-1 mice exposed to toluene at 400ppm (1500mg/m^3), 7 hrs/day from GD7-16. No effects were seen on maternal weight gain or other reproductive parameters. Jones and Balster (1997) reported lower birth weight, decreased postnatal weight gain and delayed reflex development at 2000ppm (7500mg/m^3) in the absence of maternal toxicity, in offspring of dams exposed to 200, 400 or -2000ppm toluene for 60 min., 3 times/day on GD12-17.

Ghantous and Danielson (1986) evaluated placental transfer of toluene after a 10 minute exposure of pregnant mice to 2000ppm ^{14}C-toluene on GD 11, 14, or 17 by measuring the distribution of radioactivity at time intervals of 0, 1, 4, and 24 hours. Measurements were made by autoradiography and by liquid scintillation counting. Sixty percent of the toluene was rapidly

absorbed by pregnant animals and concentrated in lipid-rich tissues [brain and fat] and well perfused organs [liver and kidney], then eliminated rapidly from maternal tissues except fat within 1 hour. Volatile toluene radioactivity was observed in the placenta and fetus/embryo within 1 hour of exposure at all stages of gestation but levels in fetal tissue were much lower than in maternal tissue. In early gestation fetuses, an even distribution pattern of was seen while more toluene accumulated in liver in later gestation fetuses. Non-volatile metabolites were unevenly distributed in fetal tissue. Both volatile and non-volatile metabolites were rapidly eliminated from the fetus. No firmly tissue-bound metabolites were observed in fetal tissue indicating no fetal capacity for formation of reactive metabolites.

Mice – Oral: Toluene was administered orally (no vehicle) by gavage at a dose of 2350mg/kg/day [identified as a maximum tolerated dose] form GD7-14 to 50 timed pregnant CD-1 mice (NIOSH, 1983). Females were weighed on GD18 and day 3 postpartum. A non-statistically significant trend in lower weight gain during pregnancy was observed. No adverse effects were seen in reproductive parameters or in number of living and dead pups within 12 and 48 hours post-delivery, in litter size or in litter weight.

Toluene has been demonstrated to induce developmental toxicity and behavioral effects in the presence and absence of maternal toxicity. Maternal toxicity as a contributing factor to developmental toxicity is not clearly defined. In some studies reduced maternal weight and effects in offspring occur at the same doses (API, 1992; Ono et al., 1995); in others developmental and behavioral effects occur in the absence of observed maternal toxicity (Da Silva et al., 1990; Hass et al, 1999). In studies at similar exposure concentrations, the presence or absence of maternal toxicity appeared to vary with duration of exposure (organogenesis, late trimester or entire gestation) and the time at which exposure was initiated (pre-pregnancy, or during gestation).

The studies summarized here demonstrate that sufficient data exists on the developmental toxicity potential of toluene. Toluene does not induce malformations in rats but has caused lower birth and postnatal weights, and postnatal developmental delays, primarily in skeletal parameters. Behavioral effects were also observed when toluene was administered to dams during periods of fetal brain development. In mice, radiolabeled toluene has been demonstrated to cross the placental barrier but accumulation of parent compound in the fetus is much lower than in maternal tissue and is rapidly eliminated. Generally, inhalation NOAEL for developmental effects ranged from 400-750ppm (1500-2812mg/m^3); LOAEL from 1000-2000ppm (3750-7500mg/m^3) when pregnant animals are exposed during periods of major organogenesis and growth. Two studies reported LOAEL below 300ppm (1123mg/m^3) but dosage regimens covered different gestational durations [Hudák and Ungváry, 1978: 266ppm (fetal wt and skeletal delay), 24hr/day, GD1-21; Da Silva et al., 1990: 213ppm (rotarod performance effects), 6hr/day, GD14-20].

Table 6.5: Hazard Assessment Studies for Toluene Toxicity: Reproductive and Developmental Toxicity [Tier 1 and 2]

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Reproductive toxicity: Fertility	SD rats/ inhalation male female	2000 ppm (max dose) no effect on fertility; 600 ppm	(2000 ppm- dec sperm ct., dec wt epididymis) 2000 ppm fetal mortality	M – 90 days F – 14 day prior to mating to GD 7, sacr. on GD20	Ono et al, 1996
	Wistar rat pregnant/ inhalation	1200 ppm (max dose) – no dam effects; no fetal effects	None	Dam exposed 6 hr/day GD9-21	Thiel and Chahoud, 1997
2-generation	Rats/ inhalation Parental F1 offspring	2000 ppm (max dose) – no effect on fertility, repro or lactation (LD) parameters 500 ppm	None 2000 ppm – dec fetal & pup wt F1 & F2, skeletal effects	6 hr/d, 7d/wk; Males 95 days Females 95 d + GD 1-20; LD5-21; F1 offspring same dosing regimen from weaning	API, 1985 Roberts et al., 2003
Developmental Toxicity Rat Inhalation	SD rat- pregnant/ inhalation	750 ppm (dam & fetus)	1500 ppm – dec maternal & fetal wt, ataxia in dams, skeletal effects in fetuses	6 hr/day, GD6-15	API, 1992
	Rat – pregnant/ inhalation	None	400 ppm (only dose) maternal death, dec fetal wt, skeletal effects	24 hr/day, GD1-8 or GD9-14	Hudák and Ungváry, 1978
	Rat – pregnant/ inhalation; fetus	No maternal effects	266 ppm (only dose) dec fetal wt, skeletal effects	24 hr/day, GD1-21	Hudák and Ungváry, 1978
	Wistar rat – pregnant/inhalation F1 offspring	No maternal effects 600 ppm	1000 ppm – dec pup wt; 1200 ppm inc pup death	7 hr/day, GD9-21	Thiel and Chahoud, 1997[a]

Table 6.5: Hazard Assessment Studies for Toluene Toxicity: Reproductive and Developmental Toxicity [Tier 1 and 2] (cont.)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Developmental Toxicity (cont.) Rat Inhalation	Wistar rat – pregnant/inhalation	None	1800 ppm (only dose) dec pup wt to lact day 10	6 hr/day, GD 7-20	Hougaard et al., 1999[a]
	Wistar rat – pregnant/inhalation	None	1200 ppm (only dose) dec pup wt to lact day 10	6 hr/day, GD 7-20	Hass et al., 1999[a]
	Wistar rat – pregnant/inhalation F1 offspring	1200ppm (only dose) reduced absol & rel testes wt in pups- no histologic changes 1800ppm (only dose) dec pup wt at d 11, normal at d 21, 90; testes wt dec at all ages, no histologic changes	Changes observed were not statistically significant [IRIS, 2005]	GD7-lactation day 18	Dalgaard et al. 2001[a]
	SD Rat –pregnant/ inhalation F1 offspring	600 ppm 600 ppm	2000 ppm – dec maternal body wt GD 14-20. 2000 ppm – dec fetal & pup wt.	6 hr/day, GD 7-17	Ono et al, 1995
Rat Oral	SD rat - pregnant/oral	None	520 mg/kg – dec. maternal, fetal and placenta wt., dec fetal organ wt.	Gavage, corn oil vehicle, GD 6-19	Gospe et al., 1994
	SD rat - pregnant/oral	None	650 mg/kg – dec fetal body wt, organ wts, delayed ossification. Similar to controls by postnatal day 21.	Gavage, corn oil vehicle, GD6-19	Gospe and Zhou, 1998
			650 mg/kg – abnormal neurogenesis	Gavage, corn oil vehicle, GD6-21	Gospe and Zhou, 2000

a- Developmental neurotoxic effects in Table 6.8

Table 6.5: Hazard Assessment Studies for Toluene Toxicity: Reproductive and Developmental Toxicity [Tier 1 and 2] (cont.)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Rabbit Inhalation	NZW Rabbit – pregnant/inhalation F1 offspring pregnant/inhalation F1 offspring	300 ppm (max dose) 30 ppm 500 ppm (only dose) 500 ppm	None 100 ppm skeletal effects None None	6 hr/day, GD 6-18 6 hr/day, GD 6-18	Klimisch et al., 1997
	Rabbit – pregnant/inhalation	133 ppm	266 ppm maternal death, abortion	24 hr/day, GD7-20	Ungváry and Tátrai, 1985
Hamster Inhalation	Hamster	213 ppm no maternal or fetal wt, soft tissue or skeletal changes	None	6 hr/day GD 6-11	DaSilva et al., 1990[a]
Mice Inhalation	CD-1 mice – pregnant/ inhalation F1 offspring	400 ppm (max dose) 200 ppm	None 400 ppm – abn. rib profile	7 hr/day, GD7-16	Courtney et al., 1986
	Mice – pregnant/ inhalation F1 offspring	2000 ppm 400 ppm	2000 ppm lower birth wt, dec pup wt gain, delayed reflex development	60 min, 3 times/day GD12-17	Jones and Balster, 1997
Mice Oral	CD-1 mice – pregnant/oral	2350 mg/kg (only dose) MTD	None	Gavage, no vehicle, GD7-14	NIOSH, 1983

6.7 Immunotoxicity (see Table 6.6)

In inhalation studies with Sprague Dawley rats, decreased thymus weight was observed in males exposed to 2000ppm for 90 days (Ono et al., 1996) and in dams exposed to 600ppm toluene during gestation days 7-17 (Ono et al, 1995). No adverse effects on thymus were reported in Fisher 344 rats or B6C3F1 mice exposed to 1200ppm toluene for 2 years or up to 3000ppm for 14-15 weeks (NTP, 1990), in Sprague Dawley CD rats exposed to 2000ppm toluene, 6hr/day, 7 days/week for 95 days (API, 1985), or in male rats exposed to 1000ppm, 6hr/day, for up to 7 days (API, 1997).

The impact of toluene on disease resistance was studied by Aranyi et al (1985). CD-1 mice exposed for 3 hrs/day at concentrations of 2.5-500ppm, exhibited increased but not dose-related susceptibility to respiratory infections when challenged with *Streptococcus zooepidemicus*. Pulmonary bactericidal activity was decreased at 2.5 and 100-500ppm but not at 5-50ppm. There was no effect on susceptibility to infection with toluene exposure of 1ppm for 3 hrs, 5 days (3hr/day) or 4 weeks (3hr/day), although measured pulmonary bactericidal activity decreased during the 5-day but not the 4-week treatment regimen. Authors theorized that toluene exerted an adverse effect on alveolar macrophages.

Hsieh et al (1989) exposed male CD-1 mice to 0, 17, 80 and 405mg toluene/L drinking water (approx. 0, 5, 22 and 105mg toluene/kg body wt-day) for 28 days. No changes in body weight, food or water consumption or absolute organ weights were induced by toluene exposure. Mice given 105mg/kg-day had increased relative liver weight, decreased relative thymus weight, decreased mixed lymphocyte culture responses, and decreased antibody plaque-forming cell (PFC) responses. Mitogen-stimulated lymphocyte proliferation and interleukin-2 immunity were depressed slightly at 22 and significantly at 105mg/kg-day. The biological significance of effects on proliferative response is unknown. The LOAEL = 105mg/kg/day and the NOAEL=22mg/kg/day.

In a subsequent study, Hsieh et al. (1990b) exposed CD-1 male mice to benzene (166mg/L; approx. 45.7mg/kg body wt/day), toluene (80 and 325mg/L; approx. 22 and 85mg/kg body wt/day), and benzene+toluene in drinking water for 28 days. Benzene-induced anemia and immune system depression were inhibited by simultaneous toluene administration at the highest dose (85mg/kg/day). Unlike the 1989 study, no effects of toluene exposure were observed on absolute or relative organ weights, lymphocyte response to mitogen stimulation or interleuken-2 immunity. The number of antibody plaque-forming cells (PFC) was reduced at 85mg/kg when expressed as number of antibody PFC/million splenocytes, but the effect was not apparent when expressed as PFC/spleen. Toluene exposure did not alter production of SRBC antibodies. Both 22 and 85mg/kg groups showed a significant decrease in incorporation of [^{3}H]TdR in mixed lymphocyte cultures stimulated with YAC-1 lymphoma cells but the authors were unclear about the significance of this effect. Although no other systemic or definitive immunotoxic effects were reported, a LOAEL=22mg/kg was identified based on the lymphocyte culture response to YAC-1 cells. In 1991, Hsieh et al again exposed CD-1 male mice to 0, 5, 22 or 105mg/kg/day toluene in drinking water for 28 days and demonstrated that, as in the 1989 study, treatment at 105mg/kg induced a decrease (25%) in IL-2 production in splenocytes stimulated with Con-A. Increases in biogenic amines were also reported in this study (see Section 6.8)

Results of Hsieh et al. (1989, 1990b, 1991) were not consistent with results of NTP immunotoxicity studies by Burns et al., 1994 in which toluene was used as a comparative control material. Oral doses of 600mg/kg/day toluene by gavage to female B6C3F1 mice for 14 days did not induce effects on absolute or relative thymus weight nor on the PFC assay. Delayed hypersensitivity responses, clearance of sheep erythrocyte by the reticuloendothelial system, or natural killer cell activity were not appreciably altered by toluene exposure. Host resistance to challenges with *Listeria monocyogenes, Streptococcus pneumoniae, Plasmodium yaelie,* or B16 F10 melanoma cells were

also not affected by toluene treatment. A reduced incidence of tumors was also observed in toluene-exposed mice when challenged with PYB6 fibrosarcoma. No effects on spleen or thymus weight or histopathology had been reported in Fischer 344 rats or B6C3F1 mice given gavage doses of up to 2500mg toluene/kg/day for 13 weeks (NTP, 1990).

Some immunosuppressive effects of toluene have been demonstrated. However, simultaneous administration of toluene acted to inhibit benzene induced anemia and immune system depression (Hsieh et al., 1990b). Also the absence of immunotoxic responses at a high oral exposure level of 600mg/kg, competent host resistance to infective agents and lower tumor incidence in fibrosarcoma-challenged animals (Burns et al.,1994) indicate that toluene does not significantly adversely affect the immune system.

There are several studies, discussed in Section 6.13.5, which evaluate the immunotoxicity endpoints in humans exposed to toluene.

Table 6.6: Representative Hazard Assessment Studies for Toluene Toxicity: Immunotoxicity [Tier 2]

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Immunotoxicity	Mice – Male CD-1/ drinking water	22 mg/kg/day	105 mg/kg-day- dec relative thymus and liver wt; dec antibody response (PFC responses decreased>40% to SRBC), decresed IL-2	28 days	Hsieh et al., 1989
	Mice –Male CD-1/ drinking water	85 mg/kg/day	No significant effect on organ wt, PFC, IL-2 immunity, SRBC antibody production; inhibited benzene-induced anemia/ immune depression.	28 days	Hsieh et al., 1990b
	Response to YAC-1 cells	None	22 mg/kg/day – decreased mixed lymphocyte culture response to YAC-1 cells		
	Mice –Male CD-1/ drinking water	22 mg/kg/day	105 mg/kg/day – decreased IL-2 production	28 days	Hsieh et al., 1991
	Mice – female B6C3F1 oral gavage	600 mg/kg/day	PFC assay unaffected. No changes in thymus wt; No effect on delayed hypersensitivity response, or host resistance	14 days used as comparative control for para-nitrotoluene	Burns et al., 1994
	Rats – Fisher 344 Mice B6C3F1 oral gavage	2500 mg/kg	No effects on spleen or thymus in either species.	13 weeks	NTP, 1990

6.8 Adult Neurotoxicity (see Table 6.7)

For animal adult neurotoxicity, the following discussion considers acute, subchronic or chronic experiments on adult animals (post-lactation, at least 42 days old at initiation of exposure for rats). Younger animals are considered under the developmental neurotoxicity section.

CNS effects
Inhalation:

Acute studies: Rebert et al. (1989a,b) reported abnormal flash-evoked potential in male Long Evans rats (1989a) and Fischer 344 rats (1989b) with singe exposures to toluene over a range of doses from 500-1600ppm. Wood et al (1983) demonstrated that toluene exposures up to 3000ppm for 4 hours induced reduced performance in behavioral test, particularly at 1780 and 3000ppm. In other studies by Wood and collaborators, biphasic responses characterized by increased activity at 1000ppm [mice and rats with 1hr exposure) and decreased activity at higher concentrations up to 3000ppm in rats were reported (Wood and Colotla, 1990; Wood and Cox, 1995, respectively).

Repeat dose studies: Several studies in the rat are available: 1) Groups of rats were exposed to 0 or 1500ppm toluene, 6 hr/day, 5/days/wk for 6 months followed by a 4 month recovery period prior to sacrifice [Korbo et al., 1996]; 2) Groups of 36 rats were exposed to 0, 500 or 1500ppm, 6hr/day, 5 days/wk for 6 months followed by a 2 month recovery period prior to sacrifice [Ladefoged et al., 1991]; 3) Groups of 8 Wistar male rats were exposed to 0, 100, 300 or 1000ppm, 8hr/day, 6 days/wk for 16 weeks (Huang et al., 1992); 4) Groups of 14 or 16 male rats were exposed to 0 or 80ppm, 6hr/day, 5 days/wk for 4 weeks, trained 3 days after final exposure and tested 7 days post exposure (Von Euler et al., 1993, 1994), and 30 rats exposed to 0 or 80ppm, 6hr/day, 4days/wk for 4 weeks, tested 4 weeks after final exposure (Von Euler et al., 2000).

In the Korbo et al. study (1996) total neuron count was measured in 5 subdivisions of the hippocampus and a statistically significant 16% neuron loss was found in the region inferior of the 1500ppm-exposed rats.

Ladefoged et al. (1991) evaluated learning and memory in several behavioral tests (water maze, radial arm maze, passive avoidance test). Diurnal motor activity was measured throughout the study. Organs were weighed and processed for histopathology. Brain was dissected into seven regions (cerebellum, hemisphere, hippocampus, hypothalamus, pons, thalamus, and medulla oblongata, and each region was analyzed for norepinephrine (NE), dopamine (D), and 5-hydroxytryptamine (5-HT). No neurobehavioral or gross changes were found except for a dose related reduction in hippocampus weight. NE, D and 5-HT levels were altered in various brain regions at 500 and 1500ppm. Effects were considered irreversible.

In the study by Huang et al. (1992), at sacrifice after 16 wk exposure, body weight, whole brain weight and cerebellum, and brain stem weight were determined. The brain regions were homogenized for determination of several neuronal and glial marker proteins. Body weight, whole brain weight, and brain region weight were unchanged by exposure. However, differential patterns of marker proteins were produced in the several brain regions at 100ppm and above, which were interpreted as possibly being indicative of early steps in development of toluene neurotoxicity.

Von Euler et al. (1993, 1994) exposed two groups of rats to 80ppm toluene for 4 weeks. Three days after the final exposure, rats were trained for 4 days in a water maze and 7 days later were

tested for retention of learning. Escape latency and swim length were increased for exposed rats during the third and fourth training days; escape latency during the retention test was also longer in the exposed rats. In addition, apmorphine-induced motor activity was enhanced in the treated rats, and dopamine receptor agonist binding was decreased, suggesting an increase in the number of receptors and decreased agonist affinity. The authors suggested that the findings indicated the possibility of altered cognitive function. In 2000, Von Euler et al. also exposed male SD rats to 80ppm toluene 4 d/wk for 4 weeks. Four weeks after the final exposure, animals were evaluated using the Morris water maze, open field tests, and beam walk performance. Brain morphology was examined *in vivo* using magnetic resonance imaging (MRI) and dopamine D3 receptor binding was measured postmortem by autoradiography. Toluene caused significant changes in water maze performance (increased time in correct quadrant) and reduced performance in beam walking but did not affect open field behavior. Whole brain volume was not affected, but a selective decrease of 6% in the parietal cortex was identified by MRI. Dopamine D3 receptor binding was not altered by toluene exposure but a 7-10% decrease in the cerebrocortical area was observed. LOAEL for neurobehavioral effects was 80ppm.

Oral:

Acute studies - rats: Mehta et al. (1998) treated SD rats with a single oral gavage dose of 0, 2600, 3900, or 5200mg/kg toluene and examined them after 2-3hr on day 1, day 7 and 14 post-dose for body weight and behavioral changes (functional observation battery). Dose-dependent decreases in male body weights were observed at day 7 in all groups; however slight changes in body weight gains seen in either sex on days 7 and 14 were not statistically significant. Behavioral changes [dose-dependent increases in abnormal gait and lower open field rearing scores] occurred at day 1 but were resolved by day 7 and 14. Horizontal motor activities were significantly lower in both sexes in all groups on day 1 and remained lower for all treated females on day 7 and 14 and on day 7 for males given 2600 or 3900mg/kg but not 5200mg/kg. Behavioral LOAEL appeared to be 2600mg/kg with no NOAEL

Transient effects on the ability of the brain to process visual information were reported by Dyer et al. (1988). Long Evans rats were given a single gavage dose of 0, 250, 500 or 1000mg/kg toluene in corn oil and flash evoked potential (FEP) tests were administered 45 minutes later. A significant but non-dose-related decrease in N3 peak was observed in all groups. Examination of another group of 500mg/kg-exposed rats at 4, 8, 16, and 30 hours post-dose demonstrated depression of the N3 peak at 4 and 8hr with complete recovery by 16hrs.

Repeat dose studies – mice, drinking water: Toluene was evaluated by administration in drinking water for 28 days to male mice at concentrations of 0, 17, 80 and 405mg/l (estimated oral ingestion of 0, 5, 22, and 105mg/kg/day. (Hsieh et al, 1990a). At the end of the exposure period, mice were evaluated for endogenous levels of the biogenic monoamines, norepinephrine (NE), dopamine (DA), and seratonin, and their respective metabolites, 3-methoxy-4-hydroxymandelic acid (VMA), 3,4-dihydroxyphenyl-acetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) in 6 brain regions. In hypothalamus NE concentration was significantly increased at all treatment levels (51, 63, 34%, respectively) and there were also significant increases in medulla oblongata and midbrain. Responses generally peaked at 22mg/kg and decreased at 105mg/kg. Concentrations of VMA and DA were increased in several brain regions. DA metabolite brain levels were not significantly altered. 5-HT and 5-HIAA levels were increased in several regions. Maximum effects were probably reversible and it is unknown whether they were adaptive changes, toxic effects or induced by stress.

In a later study, Hsieh et al. (1990c) exposed CD-1 mice to 0, 80 or 325mg/l (22 and 89.4mg/kg/day) for 28 days. No adverse effects were seen on tissue weight of whole brain or brain regions. Increased concentrations of biogenic amines and their metabolites were seen in several brain regions but responses were biphasic and not dose-responsive. In 1991, at exposure levels of 0, 5, 22 or 105mg/kg/day for 28 days increased concentrations of NE and its major metabolite VMA were observed at all dose levels with highest values at 22mg/kg. Increases (2.1 to 3.8 fold) in adrenocorticotrophic hormone (ACTH) were observed with increasing doses and corticosterone levels were elevated more than 100% in the highest doses at day 14 and 28. Statistically significant increases in brain neurotransmitter levels were observed at exposure levels as low as 5mg/kg-day in drinking water. In addition, production of IL-2, measured by uptake of [3H]TdR with Con-A stimulated T-lymphocytes in splenocytes, was decreased 25% at the 105mg/kg dose level in these mice [see Immunotoxicity section 6.7].

Neurotoxicity has been investigated in both the general toxicity studies in which neurological effects were described, and in mechanistic studies. These experimental findings, in concert with the human observations [see Section 6.13] indicate that toluene can produce neurotoxicity. The mechanistic research studies indicate that neurological effects can be observed at concentrations that are lower than the NOAELs established in the general toxicity studies.

6.9 Auditory Toxicity

Auditory impairment in rats induced by toluene has been described in numerous publications. Pryor et al. (1983a,b) induced the effect in weanling male Fisher344 rats exposed by inhalation to toluene at concentrations up to 1400ppm for 14wks, or 1200ppm for 5wks, employing multisensory conditioned avoidance response and/or tone-density discrimination tasks to measure impairment. At doses of 900 and 1400ppm for 14wk (1983a) deficiencies in learning were observed for both tasks. At 1200ppm for 5 wk (1983b), lack of response to sound (20kHz tone) was observed at 5 wks into exposure and 2 months post-exposure, but responses to other sensory stimuli in the conditioned avoidance task were comparable to controls. Tone-intensity discrimination at 4wk post-exposure was unaffected. Testing 2.5 months after the last exposure on a conditioned avoidance response showed normal hearing at 4kHz, slight impairment at 8kHz, and significant impairment at 12-20kHz, demonstrating that toluene induced long lasting hearing deficits to high frequency tones.

Electrophysiological studies in these same rats exposed to toluene at 1200ppm for 5 weeks (Rebert et al., 1983) measuring a click-evoked auditory brain stem response beginning at 2.5 months post-exposure, showed that auditory thresholds in exposed rats were elevated by 13-27dB, and other characteristics of the response were changed in a manner consistent with sensorineural hearing loss. Again, using exposure to 1200ppm toluene for 5wk, Pryor et al. (1984a) demonstrated that high frequency hearing loss was more severe when exposure was initiated in weanling rats than in young adults.

The relationship between toluene concentration, exposure pattern and hearing loss was further investigated by Pryor et al. (1984b). Exposure regimens which induced hearing loss were 1000ppm, 14hr/day, 7days/wk for 2wks; 1500ppm, 14 hr/day or 2000ppm, 8hr/day for 3 days. Intermittent exposure to 3000ppm, 30min/hr, 8hr/day, caused hearing loss within 2wk but similar exposure for 4hr/day was not ototoxic even after 9wks. Single exposure of 4000ppm for 4hr or 2000ppm for 8hr, and concentrations of 400-700ppm, 14hr/day for 2-16wk did not cause hearing loss. Hearing loss appeared irreversible because of failure to return to normal responses after 3

months recovery. Toluene ototoxicity apparently occurred only with relatively intense schedules of exposure. Concentrations of toluene and duration of exposure must be above a certain level before hearing loss takes place.

Subcutaneous administration of toluene at 1.5 or 1.7g/kg/day for 7 days (Pryor and Howd, 1986) to male rats housed in a quiet environment also caused hearing loss, measured more than 1 month post-exposure, demonstrating that direct introduction of toluene into the body can induce ototoxicity without direct contact with the ear or concurrent noise as necessary factors. Johnson et al. (1988, 1990) reported that toluene (1000ppm for 2wk), followed by noise (10hr/day for 4wk) produced a synergistic toxic effect on auditory function in rats, but when exposure to noise preceded toluene exposure, the hearing loss caused by the combined exposure did not exceed the sum of effects of equivalent individual exposure.

A synergistic loss of hearing sensitivity was also observed at 3 months post-exposure after toluene was combined with n-hexane (each at 1000ppm) and administered to male Sprague Dawley rats, 21 hr/day, for 28 days at a noise level of 76-78dB (Nylén et al., 1994). Exposure of male DA-HAN rats to 1000ppm toluene in air and 5.7-8.0% ethanol in drinking water for 8wk did not cause a synergistic enhancement of hearing loss (Nylén et al., 1995). Ethanol alone did not affect auditory function, and in combination with toluene, may have counteracted some toluene-induced effects on auditory sensitivity.

Only one study has been reported in female rats, exposed during gestation days 7-20 to 0 or 1600ppm toluene, 6hr/day (Hougaard et al., 1996). When examined 4-6wk after exposure, auditory brain stem responses to tone bursts of 4, 8, 16, 20, or 32kHz were elevated, significantly only at 16kHz. In a subsequent developmental study at 1800ppm (Hougaard et al., 1999), possible auditory damage to dams was not expressed by alteration of dam-offspring interactions during lactation or pup retrieval activity.

To evaluate the morphological correlate of toluene-induced functional hearing loss, Johnson and Canlon (1994a,b) investigated cochlear hair cell loss following 8 days of exposure to 1400ppm toluene, using light and scanning electron microscopy. Loss of hair cells were observed in middle and upper turn of cochlea at 4 days post-exposure, and progressed to the basal part by 6wk post-exposure, with 50-100% loss of outer hair cells. A good correlation was found between frequency regions showing loss of hair cells and shifts in auditory thresholds.

Similar results were reported by Lataye and Campo (1997) in Long Evans male rats, exposed to toluene (2000ppm), noise alone, and toluene + noise for 4 wk. Combined exposure produced enhanced auditory deficits. Noise alone caused injury to stereocilia of outer hair cells without cell loss; toluene caused massive loss of outer hair cells. Oral administration of 1.0ml toluene/kg/day for 8wk showed auditory deficits, maximal at 2-8kHz, at one-day post-exposure and hair cell loss in the region of the organ of Corti; outer hair cells were lost, inner hair cells were undamaged (Sullivan et al., 1989). Campo et al. (1997) also observed loss of outer hair cells and lack of intraganglionic bundles, indicative of primary cochlear damage in male Long Evans rats (7 months old) exposed over an inhalation concentration range of 1000-2000ppm, 5days/wk for 4 wk. Only toluene exposure at or above 1500ppm caused significant auditory shifts in a range of 8-24kHz, with no hearing loss at 32kHz. Brandt-Lassen et al. (2000) exposed male Wistar rats to toluene alone (500-2000ppm), 6hr/day or to toluene followed by noise (96dB) 6+2hr/day for 10 consecutive days. Rats exposed to toluene alone developed significant mid-frequency hearing loss at 1500 and 2000ppm but not at lower concentrations; toluene + noise caused slight effect at 500ppm, and statistically significant hearing loss at 1000-2000ppm. When rats kept for 36 days post-exposure

were subjected to noise (105dB) for a single 4hr interval, those animals previously treated with 500 or 1000ppm toluene responded similarly to control rats, while those treated with 1500ppm previously, had increased auditory threshold shifts, statistically significant at 4.0, 8.0 and 16.0kHz.

McWilliams et al. (2000) exposed guinea pigs (60 days old) to 0, 250, 500 or 1000ppm toluene, 8hr/day for 5 days and at 500ppm for 4 wks total. Hearing changes [distortion product otoacoustic emission; DPOAE] were assessed using the cubic distortion-product otoacoustic technique [CDP]. Statistically significantly reduced DPOAE (2F1-F2) was observed immediately following the final toluene exposure in all dose groups. DPOAE amplitude returned to control levels after 3 days post-exposure. Resumption of exposure in the 500ppm group animals for an additional 3 weeks produced a greater reduction in DPOAE amplitude but animals again recovered after 3 days without exposure. Histological evaluation of cochlea showed distinct reduction in enzyme activity (succinate dehydrogenase staining) in mid-frequency region of cochlea, but death of hair cells was not seen. A NOAEL of 250ppm and a LOAEL of 500ppm were identified for diminished startle response and histological alteration of cochlea in exposed guinea pigs. Whether this transient auditory system impairment suggests differential species sensitivity to toluene-induced ototoxicity or reflects effects of concentration and duration differences requires further investigation.

In the rat, functional and morphological auditory impairment has been induced by toluene alone, and enhanced by exposure to noise and n-hexane. Behavioral indices of effect were present 2.5 months after exposure was terminated, indicating long-lasting, irreversible ototoxic impairment. Estimate of threshold concentrations for hearing loss are LOAEL = 1000ppm and NOAEL = 700ppm (Johnson et al., 1988; Pryor et al., 1984).

Auditory decrement may be considered a form of neurotoxicity. Toluene has been clearly shown to induce hearing loss in laboratory animals at high exposure, due to damage to hair cells in the ear of rats (Campo et al., 1997; Sullivan et al., 1998) but not guinea pigs (McWilliams et al., 2000). There is some indication that very young animals are more sensitive to this effect than older animals (Pryor et al., 1984a,b). Occupational exposure to environments containing toluene (possibly with other solvents) have been reported to increase the risk of developing mild high frequency hearing loss in humans, possibly exacerbated in noisy environments (Morata et al., 1993, 1997).

Table 6.7: Representative Hazard Assessment Studies for Toluene Toxicity: Repeat Dose Adult Neurotoxicity and Auditory Toxicity [Tier 3]

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Adult Neurotoxicity	Rats/ Inhalation Brain physiology	None	1500 ppm (only dose) 16% neuron loss in hippocampus	6 hr/day, 5 days/wk; 6 mon with 4 mon recovery	Korbo et al., 1996
	Rats/ inhalation Behavioral tests Brain physiology	1500 ppm (max dose) <500 ppm	None 500 ppm – neurotransmitter changes	6 hr/day, 5d/wk, 6mon; 2 mon recovery	Ladefoged et al., 1991
	Wistar, male rats/ Inhalation	1000 ppm	No effect on body or brain wt at any dose	8 hr/day, 6 days/wk, 16 wks	Huang et al., 1992
	Brain physiology	None	100 ppm protein patterns changed		
	SD male rats Behavioral effects	None	80 ppm (only dose): MA enhanced, changes in water maze & beam walk performance	6 hr/day, 5 days/wk for 4 wks, tested 7 days post-exposure or tested 4 wks post-exposure	Von Euler et al., 1993, 1994
	Brain physiology		Dec. agonist affinity, dec parietal cortex		Von Euler et al., 2000
	CD-1 Male mice/ drinking water Brain physiology	None	5 mg/kg – inc. conc biogenic amines, no dose response, biphasic (high at mid dose; inc ACTH & corticosterone; no effect on brain wt	0, 5-105 mg/kg/day; 28 days	Hsieh et al., 1990a,c, 1991

Table 6.7: Representative Hazard Assessment Studies for Toluene Toxicity: Repeat Dose Adult Neurotoxicity and Auditory Toxicity (Tier 3) (cont.)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Auditory Toxicity	F344 rats- males (21 days old)/ inhalation	<900 ppm	900 ppm 1400 ppm – learning deficiencies	14 hr/d, 7d/wk, 14 wks	Pryor et al., 1983a
	F344 rats –male/ inhalation	<1200 ppm	1200 ppm (only dose) lack of response to sound at 5wk exp. and 2 mon post-exp	14 hr/d, 7d/wk, 5 wks	Pryor et al., 1983b
			1200 ppm (only dose) hearing loss more severe in weanling rats than young adults		Pryor et al., 1984a
	F344 rats –male/ inhalation	700 ppm - no hearing deficits after 16 wks exposure	1000 ppm – dec auditory sensitivity after 2 wk exposure	14 hr/d, 7d/wk, 2wk - 16 wks	Pryor et al., 1984b
	Long Evans rat- males (7 mon old)/ inhalation	1250 ppm	1500 ppm – auditory shifts 8-24kHz; cochlear damage- loss of hair cells	6 hr/d, 5d/wk, 4 wks	Campo et al., 1997
	Wistar rat – male/ inhalation: toluene	1000 ppm	1500 ppm mid freq loss	6 hr/day for 10 days	Brandt-Lassen et al., 2000
	toluene+noise	500 ppm (sl. effect)	1000 ppm	6 hr +2 hr noise/day for 10 days	
	Guinea Pigs/ Inhalation	250 ppm	500 ppm – transient diminished startle response (3 day recovery) dec. enzyme activity in cochlea; no loss of hair cells	0, 250, 500, 1000 ppm , 8 hr/day, 5 days; 500ppn for 4wks.	McWilliams et al., 2000

6.10 Developmental Neurotoxicity (see Table 6.8)

These studies often evaluate both developmental toxicity [see Section 6.6] as well as developmental neurotoxicity.

Rat – Inhalation: Da Silva et al. (1990) reported that male offspring of SD female rats exposed to 213ppm toluene during the final stage of gestation (GD14-20) displayed shorter latencies to choose one side of a T-maze than controls. Offspring of hamsters exposed to 213ppm toluene from GD6 –11 showed significantly poor rotarod performance at postnatal day 25, but no other effects were observed on growth or development (Da Silva et al., 1990). In the Ono et al. (1995) study, offspring of SD dams exposed to 600 and 2000ppm toluene, 6hrs/day from GD7-17, demonstrated normal spontaneous activity but female offspring showed slight increases in elapsed time and number of errors in learning (water maze) in both dose groups. However, only 5-6 dams/group were available for evaluation and effects on learning were not statistically significant. Offspring of Wistar rats exposed to toluene at concentrations of 300-1200ppm, 6hr/day, from GD9-12 did not demonstrate effects on spontaneous activity or visual discrimination learning (Thiel and Chahoud, 1997).

Hougaard et al. (1999) studied a range of developmental and neurobehavioral parameters in offspring of pregnant Wistar rats exposed to toluene 6hr/day, GD7-20, at only one dose, 1800ppm (6750mg/m^3). Neurobehavioral parameters were in accordance with proposed OECD guideline 426, and included neuromotor abilities (rotarod), open field activity, acoustical startle, sensory function (auditory brainstem response), and learning and memory ability (Morris water maze). Evaluation of auditory disfunction in dams by observation of dam/pup interactions and pup retrieval, demonstrated no adverse effects of toluene on auditory capabilities but small changes in hearing function were noted in older male pups. Significant behavioral effects were observed only in cognitive function tests performed at 2-3 months of age, primarily in female offspring who took longer to locate a hidden platform in the Morris water maze both initially and when the platform was moved to new locations in the pool (reversal and new learning measurements). Swim lengths were also increased in females by 50%.

A similar study by Hass et al. (1999) was performed in accordance with OECD guideline 426 in which pregnant Wistar rats were exposed to a single dose level of 1200ppm (4500mg/m^3) toluene, 6hr/day GD7 to postnatal day 18. Offspring stayed with dams and were thus also exposed postnatally. No maternal toxicity or decreased viability of offspring were observed but lower pup body weight gain until postnatal day 10 and delayed ontogeny of some reflexes were seen. Behavioral testing after weaning demonstrated significant increases in motor activity in both sexes. When tested in the Morris water maze at 3 months of age, female pups used significantly more time to locate a hidden platform after the platform had been moved to a new position. Swim length was increased by 50% but swim speed was comparable to controls. These results correspond to results reported by Hougaard et al. (1999) in female offspring exposed to 1800ppm toluene. This study demonstrated that pre- and post-natal exposure to toluene causes long lasting developmental neurotoxicity, particularly in female offspring. Decreased brain weight and effects on function in nerve cells of female littermates of offspring tested by Hougaard et al. (1999) and Hass (1999) were reported by Edelfors et al. (1999).

Dalgaard et al. (2001) found that prenatal exposure to 1800ppm toluene on GD7-20 increased neuronal apoptosis in cerebellum of weaned male rats on postnatal day 21, possibly resulting from delay of postnatal migration of granule cells to their final destination or as a results of generalized

fetal growth delay. No changes in apoptopic neuro-degeneration in the hippocampus were reported.

Exposure of male rat pups to 0, 100 or 500ppm toluene (0, 375 or 1875mg/m^3) 12hr/day on postnatal days 1-28, with sacrifice on day 28, resulted in volumetric changes in areas of the hippocampus in the 500ppm group.(Slomianka et al., 1990). When animals were allowed an exposure free period from postnatal day 28 to sacrifice on day 120, no differences in volume of dentate components of hippocampus were observed, suggesting compensation for changes caused earlier (Slomianka et al., 1992).

Mice – Oral: Exposure of pregnant Nya:NYLAR mice to 0, 16, 80 or 400ppm toluene in drinking water through pregnancy and lactation with maintenance of offspring on same regimen to weaning at 21 days, resulted in no adverse effects on maternal parameters, offspring body wt, mortality, eye and ear openings or surface righting reflex. Open field activity habituation was decreased in 400ppm exposed F1 mice at 35 days, and at 45-55 days, rotarod performance was impaired in all treatment groups but with an inverse dose response. To verify that open field decrements were not due to acute toluene exposure, 35 day old untreated male mice were given a single intraperitoneal injection of toluene 30 minutes prior to field testing at doses calculated to be comparable to the amounts ingested by chronically dosed mice; no adverse effects on habituation were seen. The results of this study suggest that perinatal dosing with toluene affects some behavioral parameters in the absence of maternal or general offspring toxicity (Kostas and Hotchin, 1981).

Several developmental neurotoxicity tests have demonstrated effects of toluene on cognitive function in rats at a prenatal inhalation exposure concentration of 1800ppm (Hougaard et al., 1999) and a pre- and post-natal concentration of 1200ppm (Hass et al., 1999). However, prenatal exposure to several different concentrations of toluene, overlapping those listed above, did not result in significant changes in spontaneous activity or visual discrimination learning (Thiel and Chahoud, 1997). Although it is possible to identify a LOAEL = 1200ppm, based on cognitive function changes, there is not sufficient data to establish a NOAEL.

Table 6.8: Hazard Assessment Studies for Toluene Toxicity: Developmental Neurotoxicity [Tier 3]

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Developmental Neurotoxicity Rat and Hamster	Wistar rat- pregnant/ inhalation F1 offspring	No maternal effects	213 ppm (only dose) – dec live pups/birth. Low birth wt, T-maze deficit (male pups)	6 hr/day, GD 14-20	Da Silva et al, 1990
	Hamster- pregnant/ inhalation F1 offspring		213 ppm (only dose) – dec rotarod on post natal day 25; no other effects		
	SD rat – pregnant/ inhalation F1 offspring	2000 ppm, sl. non-sign. Effect on water maze learning by female pups	None	600, 2000 ppm, 6 hr/day GD7-17	Ono et al., 1995
	Wistar rats/pregnant/ Inhalation F1 offspring	1200 ppm, no effect on activity or visual learning	None	300-1200 ppm, 6 hr/day, GD9-12	Thiel and Chahoud, 1997
	Wistar rat- pregnant/ inhalation	1800 ppm (only dose) no maternal effects	None	6 hr/day ,GD 7-20	Hougaard et al., 1999
	F1 offspring	None	1800 ppm - dec pup wt; impaired learning		
	Wistar rat- pregnant/ inhalation	1200 ppm (only dose) no maternal effects	None	6 hr/day, GD7-postnatal day 18	Hass et al., 1999
	F1 offspring	None	1200 ppm - dec pup wt; impaired learning, inc. motor activity		
	Wistar rat- pregnant/ inhalation F1 offspring	None	1200, 1800 ppm, dec brain wt, effects on nerve cell functions esp females	Hougaard and Hass pups	Edelfors et al., 1999
	Wistar rat- pregnant/ inhalation F1 offspring	None	1800 ppm, inc neuronal apoptosis in cerebellum of male pups	One dose only 6 hr/day, GD 7-20	Dalgaard et al., 2001

Table 6.8: Hazard Assessment Studies for Toluene Toxicity: Developmental Neurotoxicity [Tier 3] (cont)

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Developmental Neurotoxicity Mice	Nya:Nylar mice – pregnant & F1 offspring/ drinking water	400 ppm (max dose) no maternal effects None for behavioral	None 400 ppm – dec open field (35 d), dec rotarod (45-55 d) for all groups (incl 16, 80 ppm?- inverse response); no other offspring toxicity	GD1-20, and postnatal d1-21; dams and pups	Kostas and Hotchin, 1981
Rat Postnatal exposure only	Male rat pups/ Inhalation	100 ppm	500 ppm – volumetric changes in hippocampus at day 28 sacrifice. Recovery with exposure free period from day 28 to 120.	12 hr/day postnatal day 1-28	Slomianka et al., 1990, 1992

6.11 Chronic Toxicity and Carcinogenicity - (see Table 6.9)

6.11.1 Chronic Toxicity

Repeat dose chronic toxicity studies have been conducted by inhalation in both rats and mice. However, data for oral and dermal routes are not available.

Inhalation:
Rat: There are data for 2 chronic studies performed in the rat; 1) Exposure of groups of 120 male and 120 female rats to toluene for 6hr/day, 5d/wk, for up to 24 months at 0, 30, 100 and 300ppm (Gibson and Hardisty, 1983; CIIT, 1980), and 2) Exposure of groups of 60 male and 60 female rats to toluene for 6.5hr/day, 5 days/wk, for 15 and 24 months at doses of 0, 600 and 1200ppm (NTP, 1990; Huff, 2003).

The Gibson and Hardisty study (1983; CIIT, 1980) was performed at relatively low doses and no histopathological effects, gross lesions, or tumors were produced at any dose. Clinical observations did not reveal any toluene related effects. The body weight of treated males of all groups was higher than that of controls. Females exposed to 100 and 300ppm for 24 months had reduced hematocrit, and at 300ppm, there was increased hemoglobin concentration; however, these changes, although statistically significant, were small.

The NTP (1990; Huff, 2003) conducted a more comprehensive chronic inhalation study at higher concentrations than that of Gibson and Hardisty. At 15 months of exposure, 15 males and females at each dose level were sacrificed. With the exception of females at 600ppm where absolute liver weight was increased, there were no effects on body wt or absolute or relative weight of kidney, liver or brain. Slight nephropathy was observed in exposed females. There were no biologically significant toluene-related effects on hematological parameters or clinical chemistries. Mild/moderate degeneration of olfactory and respiratory epithelia, and slight goblet cell hyperplasia were seen in all treatment groups. No treatment related neoplastic lesions were found. After 2 years of exposure, mean body weight of treated male and female rats was slightly reduced (4-8%). No treatment related clinical signs were seen and there were no treatment related effects on survival of males or females. In the nose, treatment significantly increased the degeneration of olfactory and respiratory epithelia. Significantly increased incidence of mild inflammation of the nasal mucosa and metaplasia of the olfactory epithelium occurred in treated females. Ulcers of the forestomach were slightly increased in exposed males. Nephropathy was increased in severity in a dose responsive manner in both sexes. There were no treatment-related increases in tumor types.

Mouse: The NTP (1990; Huff, 2003) conducted a comprehensive chronic inhalation study in which groups of 60 mice/sex/group were exposed to 0, 120, 600 and 1200ppm toluene, 6hr/day, 5 days/wk, for two years. After 15 months, an interim sacrifice of 10mice/group was conducted. After 15 months, there were no toluene-induced effects on body weight, absolute or relative organ weight of brain, liver or kidney and hematologic parameters were not altered. Slight hyperplasia of the epithelium was observed in female mice at 1200ppm. After 2 years, female body weight was somewhat reduced at 1200ppm but there were no differences in survival between female dose groups. In the male groups, survival was poor although this did not differ between any of the male groups.

6.11.2 Carcinogenicity

Toluene has been studied for carcinogenic effects by inhalation exposure or oral gavage in the rat and by dermal exposure in the mouse.

Dermal administration:
Mouse: In mouse dermal carcinogenicity studies, toluene has been used as a vehicle and diluent for applying solids and viscous liquids to the skin surface. In one such study, directed to the testing of refinery streams, two control groups (50 mice/group) were included. One group was untreated and the other received 50µl of neat toluene (vehicle control) twice per week. In this lifetime study mice were sacrificed only when moribund (Broddle et al., 1996). Toluene caused a reduction in survival (86% vs. 76% at 18 months, 62% vs. 52% at 24 months) and induced skin tumors in 4 mice. There were no tumors in untreated mice. Skin tumors are rare in untreated mice in this type of study and a common criterion for a positive tumorigenic response is the finding of two tumors in a 50-mouse treatment group. Skin irritation was also produced by toluene and skin irritation has been implicated as a causative factor in a mouse dermal cancer study from non-mutagenic, but irritating, refinery streams that are known to contain alkyl benzene components; dermal carcinogenic effects were found to require the presence of skin irritation (Nessel et al., 1999) suggesting that the mode of action of toluene toxicity was by cancer promotion caused by chronic skin inflammation.

Inhalation:
Two inhalation studies have been conducted in rats and mice. Gibson and Hardisty (1983; CIIT, 1980) administered toluene for 6.5hr/day, 5 days/week for up to 24 months at concentrations of 0, 30, 100 and 300ppm (0, 112, 375, and 1125mg/m^3) toluene to groups of 120 male and female animals. Body weight of all treated rats was increased during the study but no gross pathological or histopathological effects of toluene were observed, and there was no increase in tumor frequency. The upper dose of 300ppm was, however, below the maximum tolerated dose (MTD).

In a thorough NTP study (1990; Huff, 2003) toluene was administered for 6.5hr/day, 5 days/week to male and female rats and mice for two years. Rats were exposed to 0, 600 or 1200ppm, and mice received 0, 120, 600 or 1200ppm toluene. In rats, there were no toluene-related increases in any tumor type and there were no differences in survival. In female mice, there was a significant increase in number of adenomas of the pituitary gland at 600ppm only, but this effect was considered not to be biologically meaningful in the absence of supporting hyperplasia and dose response. These adenomas are benign tumors not known to become malignant.

Oral:
In two studies toluene was administered to male and female Sprague Dawley rats at 0, 500mg/kg body wt/day or 0, 800mg/kg body wt/day, 4-5 days/week for 2 years followed by observation until death (Maltoni et al., 1983, Maltoni et al., 1997). Slightly reduced survival was observed in 800mg/kg/day animals compared to concurrent controls. An increase in “total” tumor-bearing rats was greater in the 500mg/kg study (69%) than in the 800mg/kg (44%) study. Overall control tumor incidence was 24%. Mammary tumors and lymphomas/leukemias were elevated in 500mg/kg but not in 800mg/kg females. These values were derived by adding neoplasias (e.g., hemolymphoreticular) and malignant tumors together to show an increase in total “malignant” tumors. This method of estimating tumor incidence is open to question, leaving the significance of these results inconclusive.

The most appropriate and complete cancer study of toluene using current experimental methods was that of NTP (1990; Huff, 2003) in which there was no indication of a carcinogenic response by inhalation at doses up to 1200ppm for 2 years.

Table 6.9: Hazard Assessment Studies for Toluene Toxicity: Chronic and Carcinogenesis [Tier 3]

Study Type	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Chronic Toxicity and Carcinogenesis	Fischer rat – male & female/ inhalation		300 ppm – sl. increase in hemaglobin	6 hr/d; 5d/wk for 106 wks	Gibson and Hardisty, 1983; CIIT, 1980
	Tumors	300 ppm (max dose) – no tumors			
	SD rat- male & female/ inhalation	<600 ppm	600 ppm – pathology of nasal cavity, forestomach ulcers	6.5 hr/d, 5d/wk; 24 mon; interim sacr. at 15 mon	NTP, 1990; Huff, 2003
	Tumors	1200 ppm (max dose) –no tumors			
	Mice – males & females/ inhalation	600 ppm	1200 ppm – sl dec body wt (females)	6.5 hr/d, 5d/wk; 24 mon; interim sacr. at 15 mon	
	Tumors	1200 ppm (max dose) –no tumors			
dermal	Mouse skin painting – CD males		50µl – dec survival; skin irritation; skin tumors in 4 mice	Applied neat 2x/wk lifetime	Broddle et al., 1996
oral	SD rat – male & female/ oral 2 studies	None	500 ppm & 800 ppm (only doses) inc in "total malignant tumors", 500 ppm incidence > 800 ppm	4-5 days/wk 2 yrs	Maltoni et al., 1983, 1997

6.12 Toxicokinetics and Metabolism

In general, the metabolism and pharmacokinetic/toxicokinetic findings in rodents compare favorably with those from human studies.

Absorption:
In rats, toluene was rapidly absorbed through the lungs (Benignus et al., 1984) and absorbed less rapidly by the oral route (Ameno et al., 1992). In rats receiving toluene by gavage, maximum blood level was reached 1.5-3hr after dosing. Blood levels rise more slowly after oral dosing but oral administration can produce blood levels similar to those after inhalation (Gorpe and Al-Bayati, 1994). Turkall et al (1991) reported that >99% of a single gavage dose of radiolabelled toluene in rats was eliminated in urine or expelled in air, indicating near-total absorption of the ingested dose. Absorption of toluene in the mouth and gastrointestinal tract is through the lipophilic matrix of the membrane, and lipid content, not membrane structure, is critical for absorption (Alcorn et al., 1991). Dermal absorption can occur from exposure to liquid or vapors of toluene but takes place more slowly than other routes (Tsuruta, 1989; Morgan et al., 1991).

In humans experimentally exposed to toluene (80 ppm), uptake was rapid and toluene appeared in blood within 15 minutes of exposure (Hjelm et al., 1988), and there was a high correlation between arterial and alveolar concentrations of toluene during and after exposure in volunteers breathing 53 ppm for 2 hours during light exercise (Lof et al., 1993). Human volunteers have been exposed to toluene via a nasal-gastric tube with controlled drip rate (Baelum et al. 1993). Toluene in the expired air indicated rapid absorption via the oral route.

Toluene is slowly absorbed through human skin (Dutkiewicz and Tyras, 1968). Absorption through forearm skin ranged between 14 and 23 mg/cm^3/hr. Soaking the skin of 2 volunteers for 5 min produced a maximum blood concentration of 5.4 µmol/l (Aitio et al., 1984) but there were marked variations between individuals and large blood concentration changes occurred over short periods of time; Sato and Nakajima (1978) also reported highly variable results. Toluene uptake through skin was also measured in printing workers who washed their hands with toluene for 5 min and had alveolar samples collected periodically over the following 24 hr. Exhaled toluene concentrations were between 0.5 and 10 mg/m^3 (Monster et al., 1993).

Samples of human tissue collected after death from individuals who were breathing solvents containing toluene showed preferential distribution to highly vascularized lipid-rich tissues/organs, such as brain (Takeichi et al., 1986) and to the brain areas with the greater amounts of lipid, such as white matter. Brain to blood ratios were higher in midbrain, medulla oblongata, pons and spinal cord than in hippocampus and cerebellum (Ameno et al., 1992).

Subcutaneous concentrations of toluene in adipose tissue of male volunteers exposed to 300 mg/m^3 were measured during rest, and during exercise (Carlsson and Ljungquist, 1982). At rest, concentration after 2 hr was 0.7 mg/kg and after 2 hr of exercise was 9.9 mg/kg; tissue concentrations (but not total amounts) were inversely related to total body fat, indicating a dilution effect.

Dermal absorption factors (i.e. the proportion of a chemical which is absorbed) vary by orders of magnitude depending on the toluene solution or vehicle tested, as shown in Table 6.10.

Table 6.10: Dermal Toluene Absorption Factors

% Dose Absorbed	Exposure	Species	Reference
0.07%	Neat Toluene	Human	Maibach 1980
0.08%	Toluene in solvent (0.36%)	Rhesus Monkey	Maibach and Anjo 1981
0.2%	Toluene in toluene (0.5%)	Human	Franz 1984
6.2%	Toluene in water (0.5%)	Human	Franz 1984

Absorption factors for volatile chemicals are available from EPA Region III for dermal contact with soil. These values are also appropriate estimates for products such as lacquer adhering to the skin because their magnitude is based on the chemical's volatility and the permeability of human skin to volatile organic chemicals. Recommended absorption factors are also available from EPA Region IV. However, Region IV's absorption factors do not take into account the volatility of the chemical. Absorption factors proposed by the EPA are summarized below in Table 6.11. The absorption factors in Table 6.11 and absorption data in Table 6.10 indicate that a very low proportion of the applied volatile chemical is actually absorbed by the skin.

Table 6.11: EPA Absorption Factors

Chemical Type	(EPA 1995c) Region III	(EPA 1995d) Region IV
Semivolatile Chemicals	10%	1%
Volatile Chemicals (moderate vapor pressure chemicals including toluene and mixed xylene isomers)	3%	1%
Volatile Chemicals (high vapor pressure chemicals including toluene)	0.05%	1%

Distribution:
In humans and in experimental animals, toluene is distributed between plasma and blood cells, and toluene accumulation in blood and transfer to tissues is enhanced by the presence of hydrophobic centers in the cells (Lam et al., 1990).

In experimental animals, as with humans, toluene is preferentially accumulated in tissues with high lipid levels (Bergman, 1979). A one-compartment model has been successfully developed for blood and whole-brain toluene levels covering absorption, saturation, distribution, half-life, etc. (Benignus et al., 1981). Many studies have evaluated toluene distribution in animals after administration by different routes (Armeno et al., 1992; Zahlsen et al., 1992; Bergman, 1979; Ikeda et al., 1990).

Body distribution of toluene was measured in a single individual who died 30 min after ingesting about 625 mg/kg. Toluene levels in organ were liver > pancreas > brain > heart > blood > body fat

> cerebrospinal fluid, but distribution was restricted by the short time period prior to death (Ameno et al., 1992).

Metabolism:
Metabolism in animals and humans occurs via similar pathways, the initial step is either conversion to benzyl alcohol or cresol. Benzyl alcohol is oxidized sequentially to benzaldehyde and benzoic acid, which is, in turn, conjugated with either glycine to hippuric acid (60-70%), or with glucuronic acid to benzoyl glucuronide (10-20%). Alternatively, small amounts of toluene can be hydroxylated to cresol and subsequently to sulfate, glucuronide, glutathione or cysteine conjugates. Initial hydroxylations of toluene are carried out predominantly by CYP2E1 in the liver.

Sex, age, pregnancy, nutrition, circadian rhythm and a variety of other extrinsic factors including co-administration of solvents can alter enzyme activities and metabolic rates. All of the oxygenated metabolites can be excreted in urine; p-totlylmercaptic acid and s-benzylmercapturic acid have also been found in human urine (ATSDR, 1998). Experiments in rats pretreated with toluene showed induction of hepatic cyp-P450 and GSHG-transferase, suggesting that toluene might be converted to an epoxide intermediate in the synthesis of cresol. This epoxide might contribute to macromolecular binding observed during metabolism of radiolabeled toluene by human and rat liver slices (Chapman, 1990). Initial hydroxylation of the methyl group of toluene may be the rate limiting step in toluene metabolism (Ling and Hanzlik, 1989).

Elimination:
Toluene can be eliminated by exhalation after exposure. In humans, this route of removal appears to be triphasic and pharmacokinetic modeling yields ½-lives of 1.5, 2.6, and 22min (Leung and Paustenbach, 1988). The blood half-life is also fit by a triphasic model with half-lives of 3, 40 and 738min after 8 hr exposure (Lof et al., 1993); the different half-lives represent mobilization from compartments of different lipid content (Carlsson and Ljungquist, 1982).

Only metabolites appear in the urine and the urinary elimination is fit by a biphasic model with mean elimination half-life = 34min in the rat (Rees et al., 1985). Hippuric acid accounts for 65-75% of absorbed toluene in both rats and humans (Ogata et al., 1970) although there is some variation in cresol/hippuric acid ratios between rat strains (Inoue et al., 1984).

Physiologically based pharmacokinetic (PBPK models):
Physiologically based pharmacokinetic (PBPK) models are now being employed to quantitatively and dynamically describe changes in test article derived components in defined compartments. Thus these models can be used for interval determinations of dosimetry and to describe the relationship between dose in target tissue and toxic effect. Since the models are biologically based, they allow improved projections of effects at different doses, between species, and between routes of exposure. A discussion of the available PBPK models for toluene is provided in Appendix C.

6.13 Human Experience

Human exposure occurs primarily during toluene production and use as a chemical intermediate, during coke production, and in spraying applications of materials containing toluene as a solvent or by intentional abuse (sniffing). Most of the human data is derived from short duration, laboratory controlled studies with volunteers, from cases of solvent abuse (Fornazzani et al., 1983; Lazar, 1983), and from occupational studies where the actual exposures were often to mixtures of compounds rather than to pure toluene, so that results are perhaps indicative of solvent exposure in general. Workplace studies are also complicated by smoking, alcohol use and other lifestyle factors.

6.13.1 Acute toxicity (see Table 6.12)

In acute experimental studies, volunteers exposed to a range of concentrations of toluene showed transient upper respiratory tract irritation (200 ppm); eye irritation, exhilaration (400 ppm); lassitude and nausea (600 ppm); nasal irritation and mucous secretion, drowsiness and poor balance (800 ppm) (Henderson, 2001). In studies at lower doses, acute inhalation exposure to toluene produced symptoms of headache, dizziness, intoxication, irritation, and sleepiness from 75-150 ppm (281-562 mg/m^3 ; Iregren et al., 1986). At 40 ppm (150 mg/m^3) and below, no significant effects were reported. The LOAEC was 75 ppm (Echeverria et al., 1989), and NOAEC was 40 ppm (Andersen et al., 1983).

Dermal contact with toluene may cause skin damage by removing skin lipids (EPA, 1983). Studies from inhalation exposure of human volunteers to toluene for 6-7 hours, demonstrated that exposure to 75-150 ppm caused increases in number of subjects experiencing eye irritation (Anderson et al., 1983; Echeverria et al., 1989), while exposure to 40 ppm and less did not induce irritation (Anderson et al., 1983).

6.13.2 Repeated Dose Toxicity

Repeated exposure to moderate/high airborne concentrations of toluene may alter neuromuscular development and cause central nervous system (CNS) effects. At very high concentrations, tremors, speech impairment and ataxia can develop, associated with defects in vision, speech and hearing that may become permanent (Henderson, 2001). The preponderance of information on human exposure indicates that repeated, high-level exposure to toluene can produce long lasting CNS dysfunction, including abnormal electroencephalograms, ataxia, tremors, cerebral atrophy, and impaired speech, vision and hearing.

Toluene Abuse: Fornazzani et al. (1983) studies 24 hospitalized solvent abusers with an average history of 6.3 years toluene sniffing and current exposure of 160-425 mg toluene/day. Forty-six percent of subjects suffered from tremors and ataxia, and 21% demonstrated memory impairment. Other symptoms included decreased sense of smell, optic atrophy, hearing impairment, spasticity and peripheral neuropathy. Abnormal results were demonstrated in psychological tests for all subjects and significant brain atrophy was revealed in CT-scans from 14 scanned subjects compared to controls. Lazar et al. (1983) studied 4 toluene-sniffing patients who exhibited similar neurological symptoms. Brain stem auditory evoked potential was severely affected and oculomotor abnormalities were found in 3 of 4 subjects.

The recently updated U.S. EPA IRIS database summarizes a number of occupational studies in workers addressing neurotoxicity, and other endpoints (ATSDR IRIS, 2005). These repeat exposure studies and the work of other investigators are discussed in the following sections

organized by VCCEP toxicology endpoints. Results of occupational studies and animal research indicate that neurological effects are the most sensitive endpoints for toluene exposure.

6.13.3 Genetic Toxicity (See Table 6.12)

Results from occupational studies in which cytogenetic damage (chromosome breakage, micronucleus formation or SCE) was measured in peripheral blood lymphocytes from workers exposed to toluene in rotogravure printing plants, shoe factories, filling stations, or the paint industry, vary. Results were confounded by co-exposure to other solvents (eg. benzene), printing inks, smoking and other lifestyle factors. For example, Forni et al. (1971) did not find any significant increases in structural chromosome aberrations in peripheral blood lymphocytes of rotogravure workers (age 29-60 yrs) at average exposure of 200 ppm toluene for 3-15 years. Mäki-Paakkanen et al. (1980) also did not identify significant increases in structural chromosome aberrations or sister chromatid exchanges (SCE) in peripheral blood lymphocytes from rotogravure workers (age 21-50 yrs) with occupational exposure of 7-112 ppm toluene for 3-35 years. Benzene contamination was below 0.05%. Interestingly smokers whether exposed to toluene or not, showed significant increases in SCE compared to non-smokers. Haglund et al. (1980) did not find significant increases in SCE in paint industry workers exposed to toluene at an average exposure level of 11 mg/m^3 (2.9 ppm) toluene. No significant increases in structural chromosome aberrations were found in the 5 most-exposed workers at levels >100 mg/m^3 (27 ppm) toluene.

Occasional high excursion levels of toluene may have induced the positive clastogenicity results reported by Pelclová et al. (1990) in rotogravure workers exposed over a range of 104-1170 ppm toluene for 12 years. Bauchinger et al. (1982) reported significant increases in structural chromosome aberrations (chromatid-type) and SCE in male rotogravure workers (age 30-60 yrs) with average toluene exposures of 200-300 ppm for >16 years. Smokers showed increases in SCE compared to non-smokers and among toluene exposed workers compared to controls matched for smoking habits, suggesting a synergistic effect between toluene exposure and smoking. An enhanced incidence of chromatid-type aberrations was also reported at similar levels of toluene exposure (200-300 ppm) by Schmid et al. (1985).

However in a controlled study, sister chromatid exchanges were not induced in peripheral blood lymphocytes from human volunteers exposed to 50 ppm toluene by inhalation for 3 consecutive days (Richer et al., 1993). Pitarque et al (1999) using the sensitive Comet assay did not detect DNA damage in female shoe workers (age 38 yrs) exposed to concentrations of toluene from 96 mg/m^3 (26 ppm) to 412.3 mg/m^3 (110 ppm) over 12 years.

Overall, results of cytogenetic studies indicate that toluene alone does not induce significant chromosomal damage in workers under normal low exposure conditions.

Table 6.12: Human Experience - Exposure to Toluene

Study Type	Route of Exposure	LD50/LC50	Comments	Reference
Acute Toxicity:	Humans/Inhalation	No LC50 NOEC 40 ppm (150 mg/m^3) 6 hr	100 ppm (375 mg/m^3) headache, dizziness, intoxication; no effects on performance tests	Andersen et al., 1983
	Humans/ Inhalation	No LC50 One dose only, 4.5 hr exposure	80 ppm (300 mg/m^3) headache, irritation; no effect on performance tests	Iregren et al., 1986
	Human/Inhalation	No LC50 One dose only, 6.5 hr exposure; Printers with 9-25 yr work vs controls	100 ppm (375 mg/m^3) results similar in both groups: dec. manual dexterity, visual & color perception, fatigue, sleepiness, intoxication, irritation of eyes, nose, throat.	Bælum et al., 1985
	Human/Inhalation	No LC50 One dose only, 7 hr exposure or 30 min episodes (300 ppm-50 ppm in each) =100 ppm TWA	100 ppm (375 mg/m^3) no effect on performance tests by either regimen; throat and respiratory irritation, headache , dizziness	Bælum et al., 1990
	Human/Inhalation	No LC50 75 or 150 ppm, 7 hr/day exp for 3 days	LOAC = 75 ppm (281 mg/m^3) increased headache, mucosal irrit; increasingly poorer results on performance tests with increasing exposure days .	Echeverria et al., 1989
	Human/Eye irritation/Inhalation	Slight irritant to eye and skin at 100 ppm	Exposed to 10, 40 or 100 ppm , 6 hr	Andersen et al., 1983
	Human/Eye Irritation/Inhalation	Slight irritant at 75 ppm	Inhalation at 75, 150 ppm, 7 hr 50% subjects affected at 150 ppm	Echeverria et al., 1989

Table 6.12: Human Experience - Exposure to Toluene (cont.)

Study Type	Sex/ Route of Exposure	NOAEL	LOAEL	Comments	Reference
Genetic Toxicity - Cytogenetics	Male - Rotogravure/ Inhalation	200 ppm	Negative – chrom. aberrations	3-15 year exposure	Forni et al., 1971
	Male - Rotogravure/ Inhalation	7 – 112p mM	Negative – SCE & chrom aberrations	3-35 year exposure	Mäki-Paakkanen et al., 1980
	Male – Paint industry/ Inhalation	>100 mg/m3 (27 ppm) 11 mg/m3 (2.9 ppm)	Negative - chrom aberr. Negative – SCE	Not specified	Haglund et al., 1980
	Male - Rotogravure/ Inhalation	None	104 – 1170 ppm – positive chromo aberr.	12 year exposure	Peleclová et al., 1990
	Male - Rotogravure/ Inhalation	None	200 – 300 ppm – positive chrom aberr & SCE	> 16 year exposure	Bauchinger et al., 1982; Schmid et al., 1985
	Male/ inhalation	50 ppm (only dose)	Negative for SCE in peripheral lymphocytes	7 hr/day; 3 days	Richer et al., 1993
DNA damage: Comet assay	Female - Shoe workers/ Inhalation	96-412.3 mg/m3 (26-110 ppm)	Negative for DNA damage	12 year exposure	Pitarque et al., 1999

6.13.4 Reproductive and Developmental Toxicity

Case reports suggest that toluene abuse during pregnancy may cause congenital malformations similar to those described for fetal alcohol syndrome, including microcephaly, deep-set eyes, low-set prominent ears, micrognathia, spatulae fingertips, hypotonia, and hyperreflexia (Arnold et al., 1994; Pearson et al., 1994). However, the limitations and potential for bias within such case reports preclude definitive conclusions (Bukowski, 2001). The literature also contains reports of reproductive or developmental problems associated with toluene exposure in the workplace: primarily spontaneous abortion, congenital malformations, or reduced fertility.

Spontaneous abortion

Spontaneous abortion (SA) is the most common reproductive endpoint associated with occupational toluene exposure, with several epidemiological studies presenting toluene-specific results. Most of these involved Scandinavian workers exposed to toluene and other solvents. Axelsson and Rylander (1984) reported SA rates among toluene-exposed Swedish laboratory workers that were similar to rates for non-exposed women. An additional four case-control studies examined the risk of SA from occupational exposure to toluene in Finland. All four of these latter studies reported elevated risk ratios (RR), ranging from 1.5 to 4.8 (Lindbohm et al., 1990; Taskinen et al., 1986; 1989; 1994). Two of these studies found statistically significant associations, which were confined to those with the highest levels or frequency of exposure (Taskinen et al., 1989; 1994). Airborne levels are not listed for most studies. Lindbohm et al. (1990) reported limited IH measurements of up to 40 ppm, but exposures may have been higher in the past or during peak periods.

Several factors detract from the strength of the Scandinavian studies and limit the conclusions that can be drawn from them:

- Workers were generally exposed to mixed solvents, so that associations cannot be linked directly to toluene.
- Four of these five studies were performed by the same group of investigators on the same or overlapping populations of Finnish workers. Findings from such homogenous data do not carry as much causal significance as consistent results reported across many different populations by many different investigators (Bradford-Hill, 1965).
- Results within this body of literature were somewhat inconsistent.
    - Axelsson and Ryland (1984) found no elevated SA rates from toluene exposure, while other studies reported elevated RR.
    - Lindbohm et al. reported RRs that were higher among those with low toluene exposure (1.8) than those with high exposure (1.4).
    - Taskinen et al. (1989) reported a significantly increased RR among the wives of men occupationally exposed to solvents, but not women exposed to solvents directly. This finding is unusual, given that paternal exposures are not generally thought to measurably influence fetal loss (Kline, 1989).

A study by Ng et al. (1992a) provides the most specific evidence for an association between toluene and SA. This study evaluated 55 exposed workers, 31 low-exposure (0-25 ppm toluene) factory controls, and 190 unexposed women who visited a community pre/postnatal clinic. The exposed group worked with toluene-based glues in the bond assembly department of a speaker assembly plant, where toluene levels averaged 88 ppm (with peak levels up to 150 ppm). The SA rate was significantly elevated among the bond assembly workers compared to either the community (RR 2.8, 95% CI 1.3-5.9) or factory (RR 4.8, 95% CI 1.0-22.9) controls.

The Ng et al. (1992a) study provides perhaps the best evidence of an association between occupational exposure and SA. Toluene was the predominant exposure, with only minimal confounding coexposure to other solvents. Participants were of similar socio-economic working

class backgrounds and were all non-smokers and non-drinkers. Only physician-diagnosed SAs that resulted in curettage between 12-28 weeks of gestation were included, reducing the potential for recall bias. However, these findings should still be treated cautiously, because of several factors that may have artificially elevated the RR:

- Ng et al. (1992a) reported that SA within the high-exposure group were clustered around four women that accounted for 9 (70%) of the 13 SA. The authors acknowledged that inclusion of women with multiple SA may have artificially elevated the SA rate among this high-exposure group.
- Only two SA occurred among the 68 births in the factory controls, leading to statistical instability, potential underestimation of the SA rate among this reference group, and potential overestimation of the RR. The two SA within 68 births suggests a baseline prevalence rate of only 3%, which is considerably less than the 10%-15% reported for the US (Kline, 1989).
- The SA rate among the community reference group may also have been underestimated, because of biased selection based on recruitment of women at a pre/postnatal clinic. Such a selection process captures women who have had (or will have) a live birth, which underestimates the SA rate in earlier pregnancies, given that SA tends to recur among affected women.

Congenital malformations

McDonald et al. (1987) reported a significantly increased risk of aromatic solvent exposure among the mothers of 300 congenital malformation cases in the Montreal area. This exposure was dominated by toluene. However, these malformations were primarily renal-urinary and gastrointestinal defects, not the microcephaly and craniofacial defects noted among the offspring of toluene abusers. Taskinen et al. (1989) investigated 25 congenital malformation cases, but found no increased risk from paternal organic solvent exposure (RR 0.6).

Infertility

Several cross-sectional studies have investigated the potential for infertility among women occupationally exposed to toluene. Sallmen et al. (1995; 1998) asked the controls and SA cases from earlier studies (Taskinen et al, 1989; Lindbohm et al, 1990) to recall the number of menstrual cycles during past periods of unprotected intercourse. There was some suggestion of an increased number of cycles prior to pregnancy for women exposed to high levels of toluene and for the wives of men exposed to low-moderate levels (RR 0.71 and 0.76, respectively). However, neither of these findings was statistically significant.

Plenge-Bönig and Karmaus (1999) performed a cross-section survey of men and women currently employed in the German printing industry. A total of 300 men and 231 women were selected, but only 150 men (50%) and 90 women (39%) participated. The outcome of interest was “time of unprotected intercourse,” which was used to generate “fecundability ratios” (FR). No association between fecundity and occupational exposure to toluene at concentrations up to 200 ppm was found for men and their partners (FR 1.05). However, maternal employment in the printing industry was associated with a greater than 50% reduction in fecundity (FR 0.47, 95% CI 0.29-0.77), even though most women were exposed to low levels (<10 ppm) of toluene.

The sparse data on fertility following toluene exposure suggest cautious interpretation. Furthermore, there are substantial limitations in the available studies that suggest further caution. Outcomes in these studies are subjective measures (i.e., number of menstrual cycles or time of unprotected intercourse) that are subject to recall bias. That is to say, women who were worried about occupational exposure might tend to overestimate time to pregnancy or might recall this time more accurately than those without exposure. This could explain why even low levels of maternal exposure appear to produce an association, while high levels of paternal exposure do not.

Selection bias is another potential limitation in these data. It is unclear if the unconventional use of SA cases from an earlier study as controls in Sallmen et al. (1995; 1998) led to selection bias. However, selection bias is probable for Plenge-Bonig and Karmaus (1999), where maternal participation was only 39%. The authors of this study noted that poor participation was likely to bias selection "toward less fertile people with a higher interest in participation." Indeed, participants were in fact younger and less fertile than non-participants, confirming selection bias.

There is also the potential for confounding in the fertility literature. Participants in the Finnish studies were exposed to multiple solvents, so associations could not be linked directly to toluene. Plenge-Bonig and Karmaus (1999) noted that known risk factors for infertility (e.g., shift work, noise, and stress) were not examined and "cannot therefore be excluded as having produced part of the findings or the overall results."

Other reproductive endpoints

Various other reproductive endpoints have also been explored. Ng et al. (1992b) reported no menstrual disorders among 231 workers exposed to 88 ppm toluene at the same speaker factory mentioned previously. Cho et al. (2001) reported a significantly increased risk of oligomenorrhea among 440 women coexposed to a mixture of solvents (including toluene), after adjustment for potentially confounding factors. Toluene-specific risk was moderately increased (RR 1.43), but not statistically significant. All workers were exposed to multiple solvents.

Xiao et al. (1999) reported sperm abnormalities among 24 married workers exposed to multiple organic solvents, including toluene. Liquefaction time was significantly correlated to semen level of toluene, but these workers were simultaneously exposed to other organic solvents as well. Furthermore, participation was substantially poorer among the exposed (42%) compared to the unexposed (93%), raising the question of selection bias.

To evaluate the effects of toluene on serum gonoadotrophin production, both female volunteers (in the follicular and luteal phases of the menstrual cycle) and men inhaled 50 ppm toluene (19% of PEL) through a mouthpiece for 3 hours (Luderer et al., 1999). Blood was sampled by intravenous catheter at 20-minute intervals for 3 hours before, during and after exposure. Three-hour exposure to 50 ppm toluene did not result in abnormal episodic serum gonadotropins (luteinising hormone [LH] or follicle stimulating hormone [FSH]) secretion profiles. Subtle effects on LH secretion in men and women (in the luteal phase) were reported, but the clinical relevance of these effects are unclear

Conclusions for reproductive and developmental toxicity

The SA studies provide the most suggestive evidence of an association with occupational toluene exposure. However, the limitations of this database make definitive conclusions impossible. Most workers experienced mixed solvent exposure, making it impossible to draw causal conclusions for toluene. Selection and recall bias may have also impacted this body of literature. Ng et al. (1992a) provides the most specific evidence for an association with toluene, with a LOAEL of 88 ppm mean exposure. This exposure level is well above the current 50 ppm occupation threshold and generally higher than the effect levels reported for some neurotoxic endpoints.

It should also be noted that SA have not generally been noted as a common problem among women who abuse toluene during pregnancy. Wilkins-Haug and Gabow (1991) observed an SA rate of only 10% for 30 pregnancies among 10 mothers who abused toluene, which is similar to the 10%-15% SA rate among all clinically recognized pregnancies in the US (Kline, 1989). However, it should be noted that Wilkins-Haug and Gabow (1991) represents a small case series, not a powerful epidemiologic study.

The literature for other reproductive endpoints is sparse and provides no consistent evidence of an association with toluene. There is considerable potential for bias in the fertility studies, which detracts from any causal interpretation. In fact, it has been suggested that potential for bias precludes causal judgments about infertility decline (Sallmen, et al. 2005). The birth defect, hormone, semen quality, and menstrual data are similarly sparse and difficult to interpret, often with coexposure by other solvents.

6.13.5 Immunotoxicity

Limited data are available on immunological effects of inhalation exposure to toluene in humans. Studies of workers usually involve exposure to toluene in mixtures with benzene, xylenes and other solvents. Despite their limitations, possible slight effects of toluene on immunoglobulins, leukocytes and lymphocytes have been indicated but there is no evidence that these effects are clinically significant. Lange et al (1973) reported that workers exposed to a mixture of toluene (0.003–0.16 mg/L; 0.80-42.7 ppm), benzene (0.18–3.0 mg/L; 56.3-939 ppm) and xylene (0.18-3.0 mg/L; 41.4-690 ppm) had significantly lower serum IgG and IgA levels than unexposed controls. Leukocyte agglutinins for autologous leukocytes and increased leuko-agglutination titer in human sera after incubation with the solvents were also observed.

However, no differences were observed in serum IgG, IgA and IgM values in rotogravure printers exposed to 104-1170 ppm (0.39-4.38 mg/L) for an average of 13 years compared to office workers at the same facility (ATSDR, 1998; Pelclova et al., 1990). A decrease in T lymphocyte count in workers exposed to a mixture of benzene (0-116 ppm), toluene (0-160 ppm) and xylene (0-85 ppm) may have resulted from the known depressive effect of benzene on the lymphocyte system. No signs of diminished immunological function or disturbances in immune skin reactions to tuberculin or distreptase antigens were observed (Moszczynski and Lisiewicz, 1984). At mean toluene exposures of 41 ppm (females) and 46 ppm (males), Yin et al. (1987) reported increased prevalence of headache, dizziness and significant decreases in total lymphocytes in workers involved in shoemaking, printing and audio equipment production.

Stengel et al. (1998) assessed immunologic and early renal toxicity from chronic toluene exposure in printers. Exposure concentration from 8-hour personal monitors was 50 ppm (187 mg/m^3) (range of 26-62 ppm) with mean duration of exposure of 16.3 years. Dose-effect relationships were adjusted for age and smoking. Pre- and post-study samples of blood and urine were measured for IgE, antiglomerular basement membrane and antilaminin antibodies in blood, creatinine and beta2-microglobulin in blood and urine, and microalbumin, N-acetyl-b-D-glucosaminidase (NAG), and alanine-aminopeptidone in urine.No significant effects were demonstrated for these marker enzymes except for some increase in creatinine clearance and a dose response relationship between cumulative toluene exposure and IgE and NAG levels. The NAG relationship did not persist when hypertensive subjects were excluded. The authors considered NOAEL=50 ppm and that toluene was not related to detectable renal dysfunction or significant impact on the immune system.

No immunotoxicology studies by oral exposure in humans are available.

6.13.6 Adult Neurotoxicity

Studies of acute and chronic exposures have reported subtle neurological deficits and CNS depression in humans. These health effects have been investigated using both clinical experiments and epidemiological studies of toluene exposure in the workplace.

6.13.6.1 Clinical experiments

Clinical experiments with acute toluene exposures were performed by Bælum et al. (1985,1990) and Echeverria et al. (1989). Bælum et al. (1985) reported decreases in manual dexterity, color discrimination, and accuracy of visual perception in printers (9-25yr occupational exposure) and in previously non-exposed controls, given exposure conditions of 100 ppm toluene for 6.5 hours. Effects were observed in both groups with equal frequency, suggesting an absence of a developed tolerance to acute irritation and CNS effects, and also the absence of cumulative sensitivity from long-term toluene exposure. However, Bælum et al. (1990) did not observe significant performance decrements in most dexterity tests (with the exception of a slight tendency toward a lower score in the vigilance test) or in a color vision test during a second experiment with exposure of 100 ppm toluene. Similar findings were obtained when subjects in this second study were exposed to either 100 ppm toluene for 7 hours straight or to 14 half-hour episodes with concentrations reaching 300 ppm after 5 min, then decreasing to 50 ppm over 15 min (time weighted average (TWA)=100 ppm for the entire 7 hour period). The results of this second study suggest only a minimal, if any effect, on psychomotor or visual performance. There were no differences in effect between exposures at peak concentrations and constant exposure.

College students exposed to 75 or 150 ppm toluene, 7 hr/day for 3 days demonstrated significantly worse results in digit span, pattern memory, pattern recognition, symbol digit and one-hole test with each day of exposure (Echeverria et al., 1989). Thus, the LOAEC was 75 ppm (281 mg/m^3) for performance effects, but no NOAEC was established. Longer-term occupational exposure studies evaluating neurotoxicity are discussed below.

Conclusions about clinical experiments

The results of clinical experiments suggest that slight neurological or psychometric changes may be associated with toluene exposures above the TLV, although the negative findings by Bælum et al. (1990) detract from this conclusion. Observed changes could be due to subtle neurological impairment, to secondary sensory irritation, or to a psychogenic affect from exposure to odors. These acute data cannot be used to determine the reversibility of the observed changes or whether there are additional cumulative or long-term effects.

6.13.6.2 Epidemiologic investigations of neurobehavioral associations with occupational exposure

A fairly large body of literature has investigated the neurobehavioral effects of chronic occupational exposure to toluene. Some have investigated only subjective symptoms; others have evaluated neurological, neurobehavioral, or psychomotor tests; while others have investigated a combination of endpoints. Several studies have explored organ function through standard serological tests, but these results will not be discussed, given that toluene is not known to have significant effects on organ systems (e.g., liver, kidneys, etc.) other than the CNS at typical workplace exposure levels.

Symptom surveys

Several published studies have relied solely or primarily on cross-sectional evaluation of subjective symptoms among workers with toluene exposure (Yin et al., 1987; Morck, et al., 1988; Lee et al., 1988; Tanaka et al., 2003). These studies generally reported significantly greater subjective complaints among exposed compared to unexposed workers. Common complaints included irritation and CNS symptoms, including headache, dizziness, decreased concentration, and reduced memory. Average exposures ranged from 15-30 ppm (Tanaka et al, 2003) up to 200 ppm, with peak levels often much higher (e.g., 30-minute exposure in excess of 3000 ppm) (Morck et al, 1988).

Symptoms were also evaluated as one component in studies primarily interested in neurological, neurobehavioral, or psychometric deficits (Cherry et al., 1984; Antti-Poika et al, 1985; Juntunen et al. 1985; Chia et al., 1987; Larsen and Leira, 1988; Orbaek and Nise, 1989; Foo et al., 1990; Boey et al., 1997; Eller et al., 1999; Neubert et al., 2001; Gericke et al., 2001; Chouaniere et al., 2002; Zupanic et al., 2002). Results for these studies were mixed. Some authors reported significantly increased symptom prevalence among exposed workers compared to referents (Larsen and Leira, 1988; Orbaeck and Nise, 1989; Foo et al, 1990; Boey et al., 1997; Eller et al., 1999), but many found no significant or meaningful increase in symptoms associated with toluene exposure (Antti-Poika et al., 1985; Jutunen, 1985; Chia et al., 1987; Gericke et al., 2001; Neubert et al., 2001; Chouaniere et al., 2002; Zupanic et al., 2002). Most exposures were near or above the TLV of 50 ppm, but magnitude of exposure did not seem to predict symptoms. Exposure ranges were generally similar between positive and negative studies, with toluene levels ranging from approximately 25-100 ppm or higher. Long-term or peak exposures ranged as high as 500-1000 ppm.

The lack of a consistent association between symptoms and exposure, even for toluene levels above the TLV, suggests cautious interpretation of these data. Furthermore, data on symptoms should generally be regarded suspiciously, for a variety of reasons:

- Symptoms are subjective outcomes that are subject to bias, especially "recall bias" (Rathman and Greenland, 1998). That is to say, exposed subjects are often concerned about potential for harm, so they recall (or imagine) symptoms more readily. Referents tend to report fewer symptoms, because they lack the exposure and therefore have no such recall stimulus. The potential for recall bias is greater when exposed subjects are aware that the study is investigating workplace health effects, as is often the case.

- Many of the studies used volunteer samples, which creates the potential for selection bias. Exposed subjects who are concerned about symptoms would be more likely to volunteer, leading to an exposure subgroup with artificially raised symptom prevalence. This would not necessarily be true for referents, creating the potential for differential participation and results that are biased in a positive direction.

- Symptoms are not specific markers of exposure to toluene, or any workplace chemical.
  - Symptoms often have a psychological or emotional component, making them poor markers of somatic effect. For example, stress, job dissatisfaction, poor working conditions, management-union conflict, and even dissatisfaction at home can all increase symptom reports in the workplace.

  - The odor of solvents can have a psychological impact that leads to subjective complaints, without producing somatic effects (Knasko, 1992; 1993; Shusterman, 1992; Bell et al., 1993).

  - The stress and fatigue related to increased production/productivity can cause subjective complaints. Furthermore, such complaints might be expected to increase with increasing toluene exposure, given that increased rates of printing, gluing, etc. could increase airborne levels.
    - The results from Lee et al. (1988) seem to support a stress- or job-related effect. These authors found a significantly increased linear association between toluene exposure and joint pain, which is a subjective complaint more related to job stress than to toluene exposure.

  - Exposed and referent subjects are never fully comparable on the above nebulous factors. In fact, referent populations often include workers with different social or

socioeconomic status (SES) characteristics than printers (e.g., clerks, salesmen, drivers, etc.), increasing the potential for bias.

- The relatively small sample sizes in most of the cited studies would tend to exacerbate this problem.

- Several studies found that exposed workers had greater alcohol intake and/or lower education than referents, confirming differences in SES.

- Many workers in the cited studies were coexposed to solvents other than toluene, albeit at lower levels. Therefore, there is no way to confirm that symptoms are related to toluene, rather than solvents in general.

- Most symptoms are mild and may represent only transient effects, rather than serious or permanent impairment. In fact, some studies have reported that symptoms do not seem to be associated with duration of exposure, suggesting a temporary or at least non-cumulative effect (Juntunen et al., 1985; Foo et al., 1990).

Neurobehavioral/Psychometric tests

Approximately a dozen studies compared results of neurobehavioral/psychometric test batteries between exposed and unexposed (or less exposed) workers. Key characteristics of these studies are summarized in Table 6.13. Investigators primarily evaluated the psychometric domains of short-term memory, perception, attention/concentration, and psychomotor function.

Table 6.13. Studies assessing neurobehavioral effects in workers with chronic or subchronic toluene exposure.

Reference	Design	Number of workers (exposed / referent)	Mean exposure duration (yrs.)	Recent / Past exposure (ppm) (mean or range)	Comment
Cherry et al., 1984	X-sectional	59 / 59	9	100 / 200	Reading skill (intelligence) significantly worse among exposed.
Antti-Poika[1] et al., 1985 Juntunen et al., 1985 Hanninen et al., 1987	X-sectional	43 / 31	22	83 / 117	Much heavier alcohol intake among exposed. Abnormalities during birth or childhood (e.g., school problems) more common in exposed. Slight head trauma less common among exposed. Exposed and referents with similar job function.
Chia et al., 1987	X-sectional	54 / 54	--	83[2]	Referents matched on age, sex, race, and occupational class.
Orbaek and Nise, 1989	X-sectional	30 / 72	29	17-41[3] / 150-400+	Higher verbal ability (intelligence) among referents (adjusted in analysis). Printers fully aware of study purpose. Testing after 48 hours without exposure.

Reference	Design	Number of workers (exposed / referent)	Mean exposure duration (yrs.)	Recent / Past exposure (ppm) (mean or range)	Comment
Foo et al., 1990	X-sectional	30 / 30	6	88 (exposed) 13 (referents)	Referents with significantly better education. All workers were non-drinkers and non-smokers.
Boey et al., 1997	X-sectional	29 / 29	5	91 (exposed) 12 (referents)	Higher education among the referents
Eller et al., 1999	X-sectional	79[4] / 19	>12 (high) <13 (low)	<20 / 100+	Exposed (printers) likely to be different SES than referents (executives, foremen, electricians, etc.)
Deschamps et al., 2001	X-sectional	72 / 61 (36 factory 36 laboratory)	20	9-83 (factory) 184-467 (lab)	Testing after 48 hours without exposure. Exposed with significantly better vocabulary (intelligence).
Geriecke et al, 2001	X-sectional	1077 / 109	15-17	4-24[5]	Primarily a dose-response analysis over range of toluene exposures.
Chouaniere et al., 2002	X-sectional	128 (no reference group)	14	0-27 / 0-179	Nonparticipation varied from 15%-57%. Testing after 48 hours without exposure. Good control for confounding.
Zupanic et al., 2002	X-sectional	154 / 124	15	2 / 6 (low) 25 / 45 (high)	Volunteer sample of about 20% of total workforce
Seeber et al., 2004	X-sectional and longitudinal	181 / 152 X-sectional 106 / 86 longitudinal (high/low exposure)	21-22 yrs. (long exposure)	3 / 9 (low) 26 / 45 (high)	Volunteer sample of about 5% of total workforce. Drop out rates similar among low and high exposed.

1 All three studies investigated same group of workers
2 Estimated from urinary level
3 Recent means at two plants / long-term range
4 49 with high LWAE and 30 with low LWAE
5 Range of area means

The results of these studies (Table 6.14) suggest that higher exposures (>50 ppm) may produce a measurable neurobehavioral effect, especially on short-term memory. The LOAEL in these studies was approximately 90-100 ppm (Foo et al., 1990; Boey et al., 1997; Eller et al., 1999). However, such findings were not universal. Several high-exposure studies reported totally or largely negative findings (Cherry et al., 1984; Chia et al., 1987; Deschamps et al., 2001), even with recent exposures near 100 ppm and past/peak exposures often greatly exceeding this level (Cherry et al, 1984; Deschamps et al., 2001). Studies with average (current) exposure levels below 50 ppm were largely negative (Table 6.15), with NOAELs in the range of 25 ppm (or higher) for recent exposure and 45-100+ ppm for long-term (past) exposure. The LOAELs and NOAELs suggested by the above studies

overlap considerably in many instances, with LOAELs for short-term memory loss as low as 0-27 ppm recent exposure (Chouaniere et al., 2002) and NOAELs as high as 100 ppm (Cherry et al., 1984).

Table 6.14. Results of neurobehavioral/psychometric tests among toluene exposed workers

	< 50 ppm[1]				>50 ppm			
Study	**M[2]**	**A/C**	**P**	**PM**	**M**	**A/C**	**P**	**PM**
Cherry et al., 1984					-[3]	-	-	+
Chia et al, 1987					-	-	NA[4]	-
Hanninen et al., 1987					-	NA[5]	-	-
Orbaek & Nise, 1989[6]	-	-	-	-				
Foo et al., 1990					+	-	+	+/-
Boey et al, 1997					+	+	+	+
Eller et al, 1999[7]	-	-	-	-	+	-	+	-
Gericke et al., 2001	+	-	-	NA				
Deschamps et al, 2001					-	-	-	-
Seeber et al, 2004 & Zupanic et al., 2002[8]	-	-	-	-				
Chouaniere et al, 2002	+	-	-	NA				

1 Results for recent exposure estimates are used, unless otherwise indicated
2 M= memory, A/C= attention/concentration, P= perception, PM= psychomotor
3 + = significant association with exposure, - = no significant association with exposure
4 Not Applicable (psychometric domain not evaluated in study)
5 No test of attention/concentration, but a significant crude association between exposure and visual intelligence
6 Results adjusted for higher innate intelligence among referents
7 Results are presented separately for those with or without long-term exposure
8 Both studies evaluated the same worker population

A common feature among many of the studies investigating neurobehavioral effects is lack of comparability between exposed and referent subjects, which suggests substantial potential for selection bias in this body of literature. Many authors reported substantial differences between exposed and reference groups on key demographic or lifestyle variables (see table 6.13), including major differences on alcohol intake (Antti-Poika et al., 1985; Hanninen et al., 1987), education (Foo et al., 1990; Boey et al., 1997), intelligence (Cherry et al., 1984; Orbaek and Nise, 1989; Deschamps et al, 2001), and occupational class (Eller et al, 1999). Comparability on such factors is crucial to detecting neurobehavioral differences that are due to exposure, rather than differential selection.

In some instances the authors adjusted for innate differences in the analysis. For example, Orbaek and Nise (1989) adjusted for higher innate intelligence among the referents, which removed any significant associations with toluene exposure. Foo et al. (1990) reported significant exposure-related differences after adjustment for education. However, it is important to remember that problems of selection bias represent basic differences in comparability that are not necessarily confined to one or two key variables. Major differences on one or two demographic factors may signal less obvious (but important) differences on other factors that could influence neurobehavioral performance. For example, differences on education might suggest differences in intelligence, concentration, problem solving, test-taking ability, motivation, and other important factors that may not be completely controlled by adjustment for education alone.

The apparent selection bias in this body of literature is understandable, given that most of the studies represent relatively small, volunteer samples, with no real attempt at randomization or complete participation. In many instances, referents were matched to exposed subjects on age or one or two

other factors (e.g., sex and ethnicity), or were assumed to be similar if there were no statistically significant a priori differences. However, such procedures do not ensure comparability in small samples, which is why randomization is such a vital part of experimental design. Most authors failed to provide information on the sampling frame (i.e., total number asked to participate), refusal among the referents, or other factors that would help the reader determine the potential for selection bias.

In general, there were no associations between neurobehavioral tests and duration of exposure (Cherry et al., 1984; Foo et al., 1990), suggesting that any neurological effects were not cumulative and were potentially reversible. Those studies that had tested workers after 48 hours without exposure were largely negative (Orbaek and Nise, 1989; Deschamps et al, 2001; Chouaniere et al., 2002), which supports this conclusion.

Other neurological endpoints

"Organic brain syndrome" is thought by some to be induced by long-term exposure to organic solvents. Larsen and Leira (1988) reported a higher frequency of slight to moderate organic brain syndrome in subjects exposed to toluene for more than 12 years at average concentrations of at least 50-80 ppm. Long-term exposure to concentrations exceeding 1000 ppm had been incurred 5 years earlier.

Antti-Poika et al. (1985) examined male rotogravure workers (average age 41 yrs) exposed to 68-185 ppm toluene over an average of approximately 22 years (range 11-40yrs). No clinically important abnormalities were detected using neurologic examination, tests of autonomic nervous function, EEG, psychological tests, or brain topographical analysis. However, the authors correlated results for total symptoms or total abnormalities with exposure, which may have obscured subtle effects on individual domains. On the other hand, exposed workers drank substantially greater quantities of alcohol than referents, which could have biased results in a positive direction.

Juntunen et al. (1985) also reported on the same groups investigated by Antti-Poika et al. (1985). Juntunen et al. (1985) reported that all results were within the clinically normal range and that alcohol consumption seemed to be correlated with toluene exposure, so that the heavier drinkers also had heavier exposure. Hanninen et al. (1987) reported more detail on the neurobehavioral tests in this study, noting a significant association on visual intelligence between the exposed and referent groups. However, this finding was unadjusted for confounding and might have been a preexisting difference, considering the cross-sectional nature of the study and the other preexisting differences already noted (Table 6.13). Hanninen et al. (1987) also reported that heavy drinkers tended to perform better than moderate drinkers, which is an anomalous finding that detracts from confidence in the overall results.

Murata et al. (1993) examined electrocardiographic intervals and nerve conduction velocities in 10 rotogravure printers exposed to 83 ppm (313 mg/m^3) toluene for a mean duration of 11 years (range 1-36yrs). These printers were compared to a reference group of 10 age-matched, healthy workers (skilled tradesmen, salesmen, clerks, etc.). Blood and urine samples were also collected. Some electrophysiological responses were significantly reduced in toluene exposed workers, but these data did not correlate with blood toluene levels, urinary hippuric acid levels, or exposure duration. These findings suggest differences between exposed and reference groups that are unrelated to toluene exposure. Such differences may be the result of selection bias, given the small sample size and the fact that a reference group of skilled workers, clerks, and salesmen might be expected to differ from printers. The authors provide no information on how the 20 subjects were selected, which adds to reader concerns about selection bias.

6.13.6.3 Overall conclusions about neurobehavioral effects

The above results suggest that subjective complaints are more common among those with higher-level toluene exposure. However, such data should be interpreted with extreme caution, because of the considerable potential for both recall and selection biases.

The results of clinical experiments suggest that slight neurological or psychometric changes may be associated with toluene exposures above the TLV of 50 ppm, although the data are limited and somewhat inconsistent. Findings from occupational epidemiology studies also suggest that there may be subtle neurobehavioral differences associated with toluene exposures above the current TLV, although such findings are not universally reported. The most consistent association is with short-term memory.

Minimal associations were reported for occupational exposures below the TLV, even when long-term or peak exposures were considerably higher. A NOAEL for LWAE might be estimated at approximately 45 ppm, based on the study by Seeber et al. (2004), which is the only longitudinal study available. However, it should be noted that several studies reported negative results for past or cumulative exposures well above this level. It should further be noted that the heterogeneity of these neurobehavioral findings detracts from confident conclusions about subtle neurological effects from toluene exposure.

The potential for serious selection bias further detracts from conclusions about neurological effects and suggests cautious interpretation of these findings. Subjects were largely volunteers from larger worker populations. "Volunteer bias" can result in selection of individuals who are different than the population as a whole (Rothman and Greenland, 1998). For example, one would expect exposed workers with noticeable neuropsychological symptoms or impairment to volunteer more readily, suggesting a positive bias. Most studies provided insufficient information on the level of participation among the exposed and unexposed, so one cannot tell if differential participation (and a greater potential for selection bias) occurred. However, many studies noted obvious preexisting differences between these two groups, supporting a conclusion of selection bias.

Almost all studies were cross-sectional in nature, essentially taking a snap shot of workers employed at a point in time. Therefore, one cannot tell if the differences among groups existed before exposure. The cross-sectional nature of these studies also raises the possibility of "survivorship bias," where those with neurobehavioral decrements leave the workforce, while others remain or transfer to other jobs (aka transfer bias). However, it should be noted that the longitudinal analysis by Seeber et al. (2004) found no impact on neurobehavior over 5 years, with similar dropout rates among the four exposure groups. This does not support a survivorship bias that is associated with exposure.

Overall, the findings from this body of literature are reassuring that any impact from toluene exposure is mild and potentially reversible. The above neurologic findings generally represent only subtle effects, rather than clinically important abnormalities. Exposed workers did not report noticeable impairment or inability to perform their jobs, although neurobehavioral results sometimes correlated with symptom scores (Orbaek and Nise, 1989). Neurological exams were generally normal, with no signs of peripheral neuropathy or psychopathology. Larsen and Leira (1988) diagnosed significantly more mild-moderate "organic brain syndrome" among toluene exposed workers, but reported that workers had no clinically significant psychopathology and had not sought medical help. These workers had been exposed to average toluene levels exceeding 1000 ppm only 5 years earlier, suggesting a potentially long-lasting effect from past exposure to extremely high solvent levels. Effects from lower levels generally appeared to be reversible, having no significant association after 48-withdrawl or when correlated with duration of exposure.

6.13.7 Sensory Effects

Some epidemiologic studies have evaluated the potential effect of occupation toluene exposure on sensory impairment. These range from subtle changes in sensory evoked potentials or color discrimination, to more gross effects on overall hearing (Table 6.16).

Table 6.16 Studies assessing sensory effects in workers with chronic or subchronic toluene exposure.

Reference	Design	Number of workers (exposed / referent)	Mean exposure duration (yrs.)	Toluene exposure (ppm) (mean or range)	Comment
Sensory Evoked Potentials					
Abbate et al., 1993	X-sectional	40 / 40 (out of 600)	12-14	97	No information regarding how original group of 600 workers selected. Study subset of 80 chosen randomly. All workers had normal hearing. Referents matched on age and sex.
Vrca et al., 1995-1997b	X-sectional	49 / 59	21	40-60	No information on selection or participation among referents. Higher prevalence of head injuries and past anesthesia among exposed. No adjustment for confounding
Color Discrimination					
Muttray et al., 1995	Repeated measures across the work week	59	10	0.22 - 7.4 mg/l (blood)	98% participation Provides no information on chronic effects.
Muttray et al., 1999	Repeated measure before/after cleaning	8 / 8[1]	10	300-400	Provides no solid information on chronic effects.
Zavalic et al., 1998a	X-sectional	32 / 41 / 83[2]	18 (print) 16 (shoe)	132 (print) 32 (shoe)	Analyses adjusted for age and alcohol. Women much more common in unexposed than exposed.
Zavalic et al., 1998b	X-sectional	45 / 53	17	120	Participation rates high and similar between exposed and referents. 2-3-fold more drinking and smoking among referents.
Cavalleri et al., 2000	X-sectional	33 /16	10	42	Exposure estimated from current urinary hippuric acid levels. Volunteer subjects. Exposed fully aware of study goals. Exposed slightly older and significantly more drinking.
Campagna et al., 2001	X-sectional	72 / 34 / 19[3]	18-19	36 (printers) 9 (ambient)	The process by which participants selected is not clearly stated. Unexposed group significantly younger, drank more alcohol, and shorter employment than either of the two exposure groups. Confounding by past exposure to mixed organic solvents.
Nakatsuka et al., 1992	X-sectional	174 / 120	Not reported	44 (men) 48 (women)	Young workers. Lanthony's new color test (less sensitive than Lanthony D-15). Lack of adjustment for confounding. Factory workers compared to clerical workers (referents).

Table 6.16 - Continued

Reference	Design	Number of workers (exposed / referent)	Mean exposure duration (yrs.)	Toluene exposure (ppm) (mean or range)	Comment
Schaper et al., 2004	X-sectional and longitudinal	154 / 124 X-sectional 104 / 85 longitudinal (high / low exposure)	21 (long) 7-8 (short)	26 (recent hi) 43 (LWAE hi) 3 (recent low) 9 (LWAE low)	Volunteer subjects. Workers divided into hi/low exposure and short/long duration Dropout rate slightly higher among those with longer exposure, but similar between high and low exposed. Good control of confounding in models.
Hearing Impairment					
Morata et al., 1993	X-sectional	51 / 50	8	75-365 (recent) up to 600 (past)	Confounding by noise. Unexposed with greatest length of employment, chemical exposure, and participation in noisy activities.
Morata et al., 1997	X-sectional	124	8	0-244	No unexposed referents. Coexposure to solvents up to and exceeding the TLV. Coexposure to high levels of noise. Few workers used hearing protection.
Schaper et al., 2003	X-sectional and longitudinal	181 / 152 X-sectional 106 / 86 longitudinal (high / low exposure)	21-22 (long) 6 (short)	26 (recent hi) 45 (LWAE hi) 3 (recent low) 10 (LWAE low)	Volunteer subjects. Workers divided into hi/low exposure and short/long duration Dropout rate similar across four exposure groups. Good control of confounding in models.

1 8 historical controls used as referents
2 printers / shoe workers / unexposed
3 printers / ambient (low) exposed / unexposed

6.13.7.1 Sensory Evoked Potentials

Sensory evoked potentials are electrophysiological tests for dysfunction of sensory nerve pathways and CNS function. Somatosensory evoked potentials measure nervous response to tactile stimulation, while brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) measure nerve conduction along the auditory and visual nerve pathways, respectively. Several studies have used BAEP and/or VEP tests to evaluate toluene exposure.

Abbate et al. (1993) identified 300 rotogravure printing workers exposed to an average of 97 ppm (366 mg/m^3) toluene for 12-14 years. These workers were compared to 300 age-sex matched workers without toluene exposure. No information is given as to how workers were selected. Exclusion criteria removed all workers with abnormal hearing, serious neurological or metabolic illness, or previous exposure to excess noise or ototoxic chemicals. This left 80 exposed and 90 comparison subjects, from which 40 of each type were randomly selected. Measurement of BAEP indicated significantly increased wave latencies for exposed workers, although all workers demonstrated normal hearing capacity.

Vrca et al. (1995-1997a,b) also examined alterations in BAEP and visual evoked potential (VEP) in 49 Croation rotogravure printing workers with an average work service of 21.4 years (range 4-30 yrs). This printing group was compared to 59 electronics workers with no toluene exposure and similar average work service (20.6 years, range 4-32 yrs). Toluene exposure measurements in the workplace were not reported, but average exposure was estimated to range from 40-60 ppm (151-226 mg/m^3). Exposed workers had statistically significant increases in VEP wave amplitude (Vrca et al., 1995), as well as significantly deceased BAEP wave amplitude, prolonged P1 wave latency, and increased intervals of interpeak BAEP latencies (Vrca et al., 1996, 1997a,b).

Several potential limitations of the above studies deserve mentioning:

- Vrca et al. (1995-1997a,b) recruited 49 out of a total of 51 printers, resulting in 96% participation and little potential for biased selection among the exposed. However, no information is given regarding participation among the comparison group of electronics workers. Substantial refusal to participate (or "volunteerism") among the unexposed could result in selection of an atypical comparison group and spurious study findings. Information on selection of participants in Abbate et al. (1993) is similarly lacking.
- Vrca et al. (1995-1997a,b) performed no adjustment for confounding, because the exposed and reference groups appeared to be similar on several risk factors (e.g., age, alcohol intake, smoking). However, several important (albeit non-significant) differences appear to have been overlooked. The exposed had a higher historical prevalence of serious head injuries (18%) compared to the referents (7%), as well as a higher prevalence of past anesthesia (35% vs. 24%). Considerable confounding can result from differences on major risk factors, even when such differences are not statistically significant. Potential confounding would be expected to skew results in a positive direction, although it is impossible to say to what extent this occurred.
- The four studies by Vrca et al. (1995-1997a,b) evaluated the same groups of exposed and unexposed workers. Therefore, they should be viewed as only a single set of positive results, rather than a consistent body of literature.

Conclusions about evoked potentials

The findings of Vrca et al. (1995-1997a,b) suggest a toluene LOAEL of 40-60 ppm for changes in evoked potentials. There is some potential for selection bias and uncontrolled confounding in this study, although it is impossible to determine the impact from the information provided. All research was conducted on the same exposed and unexposed workers, which detracts from a causal determination. Findings from such homogenous data do not carry as much causal significance as consistent results reported across many different populations by many different investigators (Bradford-Hill, 1965).

Evoked potentials outside of the reference range are useful clinical markers of CNS disease, such as cranial nerve tumors or early demyelinating illness (Huszar, 2002). However, it is not clear that the slight differences reported in the toluene literature have clinical importance or predictive value. For example, Vrca et al. (1995) reported peak mean P100 values that were significantly different between exposed and unexposed workers, but clinically quite similar (111.3 ms vs. 109.0 ms). There is no indication that the exposed had a greater prevalence of values outside the normal range or that they suffered from vision, hearing, or CNS disorders. There is also no indication from these data that changes in evoked potential were permanent or that they led to later illness. Overall, the findings from this body of literature are reassuring that any impact from toluene exposure is subclincial, without apparent effects on quality of life.

6.13.7.2 Color Discrimination

Color discrimination has been shown to be an especially sensitive indicator of chemical exposure. Many drugs have been shown to impact color vision, including alcohol; digitalis; and various anti-malaria, anti-tuberculosis, or anti-epileptic agents. Color vision dysfunction has also been investigated as a possible subtle effect of organic solvent exposure. The most commonly used test in industrial studies has been the Lanthony D-15 desaturated assay, which is a simple and sensitive test that is well suited to surveillance of occupational populations (Irgren et al., 2002). The most commonly used metric is the color confusion index (CCI), which compares an individual's Lanthony score to the ideal value (Paramei, 2004).

Muttray et al. (1995) used a repeated-measures design to examine 59 rotogravure printers with relatively high toluene exposure (blood levels up to 7.3 mg/L). No subacute effect on color vision was noted across the work week. A later study by Muttray et al. (1999) failed to find any acute effect from rotogravure cleaning operations that produced 300-400 ppm toluene exposure. Neither of these studies provides much insight into chronic exposure, although the median CCI of the 8 rotogravure cleaners (1.18) was poorer than in a group of 8 historical controls (1.05, p=0.06).

Zavalic et al. (1998a,b) explored color vision impairment in several groups of Croatian workers exposed to toluene. In one study (Zavalic et al. 1998a), 41 shoe workers had an average exposure of 32 ppm (11.3-49.3 ppm) for an average of 16.2yr, while 32 rotogravure printers were exposed to an average of 132 ppm (66-250 ppm) toluene for an average of 18.3yr. Both groups were compared to 83 unexposed electronics workers. There was significantly higher CCI at 132 ppm exposure (1.30) compared to either 32 ppm (1.18) or no exposure (1.14). A second study by Zvalic et al. (1998b) compared 45 printing press workers exposed to 120 ppm toluene for an average of 16.8yr. to a similar unexposed population of 53 electronics workers. There were significant correlations between color discrimination score (CDS) and multiple indices of toluene exposure.

The results from Zavalic et al. (1998a,b) suggest an effect on color vision from average exposures above 100 ppm , with a LOAEL of 120 ppm and a NOAEL of 32 ppm. However, alcohol consumption was substantially greater among the printers in one of the studies (Zavalic et al., 1998a) and substantially greater (along with smoking) among the referents in the other study (Zavalic et al., 1998b). These differences in smoking or drinking were adjusted for in the analysis. However, such differences in major lifestyle variables between groups suggest SES differences related to exposure, which raises the possibility of selection bias. It is uncertain to what extent this may have influenced these results.

Thirty three rubber workers with average exposure duration of 117 months were examined by Cavalleri et al. (2000). Toluene levels in urine averaged 63 µg/l, which extrapolated (based on previous experience) to an estimated environmental level of 42 ppm. Exposed workers had significantly increased mean CCI (1.29) and total CCI (1.49) values, compared to 16 unexposed workers from another factory (1.10 and 1.16, respectively). There was a significant dose-response correlation with estimated cumulative exposure (urinary toluene X months of exposure), but not current exposure.

The results from Cavalleri et al. (2000) suggest an effect on color vision from exposures near the 50 ppm TLV for toluene, with a LOAEL of 42 ppm. However, cautious interpretation is warranted, for several reasons:

- Toluene air levels were estimated based on current urinary values, which is a crude approach. The method for this estimation and its accuracy were not stated, so that the reader cannot judge the validity of the approach. Toluene metabolism and excretion is likely to vary

among individuals, so experience with previous populations may not provide reproducible results.

- Urinary values measure only current toluene exposure, not exposures 10 or more years earlier. Past exposure were likely to be higher than the 42 ppm estimate.

- All subjects were volunteers from larger worker populations, raising the issue of selection bias. "Volunteer bias" can result in selection of individuals who are different than the population as a whole (Rothman and Greenland, 1998). No information was provided on the level of participation among the exposed and unexposed, so one cannot tell if differential participation (and a greater potential for selection bias) occurred.

- All exposed subjects were fully briefed before hand on the aims of the study. This may have influenced volunteerism, with those with poorer color vision being more likely to participate.

- The unexposed (comparison) group had significantly lower alcohol consumption and was slightly younger (average 34 yrs) than those exposed (average 37 yrs). Differences on such basic demographic characteristics suggests possible selection bias, especially given that the exposed and comparison group consist of only small subsets (33 and 16, respectively) of volunteers from a larger population of factory workers.

- The authors reported that there was no significant correlation (in multiple regression analyses) with the known risk factors of age and alcohol consumption. Lack of correlation with the well-established risk factor of age is puzzling and raises questions about the accuracy of the overall analysis.

Campagna et al. (2001) reported acquired color vision loss in 72 French photogravure workers exposed to toluene and total hydrocarbons. Current (1991-1992) toluene exposure levels were 36 ppm (136 mg/m^3) among exposed workers and approximately 9 ppm (32 mg/m^3) for a comparison group of workers from the same plant with ambient (i.e., incidental) toluene exposure. Past exposures were higher than current values and included exposure to mixed aromatic solvents at levels up to 900 mg/m^3. A second comparison group consisted of 19 unexposed workers from a bookbinding plant in the same community. Statistically significantly higher proportions of workers with acquired dyschromatopsia were seen in both toluene exposure (52%) and ambient exposure (56%) groups, compared to the unexposed bookbinders (21%). Logistic regression models adjusted for age and alcohol intake produced statistically significant, RR for dyschromatopsia at current toluene exposure (1.26, 95% CI 1.00-1.57), cumulative toluene exposure (1.22 95% CI 1.04-1.43), and cumulative total hydrocarbon exposure (1.16 95% CI 1.01-1.34).

As with Cavalleri et al. (2000), the results from Campagna et al. (2001) suggest an effect on color vision from exposures near the TLV for toluene, with a LOAEL of 36 ppm. However, as with Cavalleri et al. (2000), cautious interpretation is warranted:

- The process by which participants were selected is not clearly stated, raising the possibility of "volunteer selection bias."

- The unexposed group was significantly younger (mean 37 yr.) and drank more alcohol (mean 17 g/d) than either of the two exposure groups (40-43 yr. and 10-14 g/d, respectively). The unexposed group also had an average duration of employment that was much shorter (8 yr.) than among the exposed (18-19 years). These demographic differences suggest differential participation and selection bias.

- Results could not be definitely linked to toluene, because of confounding by past exposure to mixed organic solvents. Results were similar for either cumulative toluene exposure (RR 1.22) or cumulative total hydrocarbon exposure (RR 1.16). Furthermore, the exposure metrics were correlated with each other, making it difficult/impossible to identify a toluene-specific effect.

- Inconsistencies in the presented results detract from reader confidence. For example, levels of dyschromatopsia are similar among the high and ambient exposure groups (52% abd 56%, respectively), even though high exposure is approximately 4 times greater than ambient. This suggests no dose-response relationship with toluene. However, all metrics of toluene exposure are said to significantly correlate with both CCI and dyschromatopsia, with no apparent threshold. This suggests a dose-response relationship that is contrary to the earlier finding. On a similar vein, current (1990) average exposure levels are reported as 24 ppm (89 mg/m^3) in the methods, but 36 ppm (136 mg/m^3) in the results.

Other studies found no effect on color vision from toluene exposure near the TLV. Nakatsuka et al. (1992) compared 63 men and 111 women employed in paint production and application plants to 120 clerical workers (48 men and 72 women) with no known occupational exposure to solvents. Toluene made up over 90% of solvent exposure, with mean levels ranging from 44 ppm (men) to 48 ppm (women). Average worker age was 31-33 years, but exposure durations were not reported. No statistically significant effects on color vision were observed in exposed workers compared to referents using Lanthony's new color test and Ishihara's color vision test. The NOAEL of 44-48 ppm is similar to the NOAEL of 32 ppm reported by Zavalic et al. (1998a). Limitations of this study include lack of adjustment for confounding and use of the Lanthony new test, which is less sensitive than the Lanthony D-15 desaturated test. There was also a suggestion of selection bias, given that the unexposed group had the highest prevalence of color vision problems (36% for men and 26% for women). Selection bias is also suggested by the design, which compared factory workers to clerical workers.

Schaper et al. (2004) performed a repeated measures longitudinal analysis, following rotogravure print workers for 5 years. A total of 278 participants volunteered from among all workers at the 14 German rotogravure printing plants, although only 162 completed all three repeated tests. Participants were categorized into four groups based on duration and magnitude of toluene exposure: short-low, short-high, long-low, long-high. Current average exposure ranged up to approximately 30 ppm, while average lifetime TWA toluene exposure ranged up to 56 ppm (in the long-high group). Color vision was assessed using the Lanthony D-15 panel. Based on cross-sectional analysis of the initial 278 participants, mean CCI values were very similar among those with low vs. high exposure (1.10 vs. 1.07) or short versus long duration (1.07 vs. 1.10). Those in the long-high group (lifetime TWA 56 ppm) had very similar CCI values to those in the short-low group (lifetime TWA 5.7 ppm). Neither toluene intensity nor duration of exposure were significant in a repeated-measures analysis of covariance (ANCOVA) adjusted for age, alcohol intake, occupational qualification, and smoking. Both age and occupational qualification were significantly associated with log CCI in the ANCOVA.

The results from Schaper et al. (2004) suggest that long-term toluene exposure near the TLV has no effect on color discrimination, and that no measurable color vision problems developed over the 5-year follow-up. However, there are limitations that deserve mention:

- This is a volunteer sample, so potential for selection bias is high. Drop-out rates were similar among the high and low exposure groups, suggesting that selection bias would not have substantially affected the repeated measures portion of the study.

- This study compares only high exposure with low exposure, not with no exposure. This lack of an unexposed reference group detracts somewhat from the cross sectional interpretation of the study, but less from the repeated-measures analyses.

Conclusions about color discrimination

This body of literature suggests that chronic, high-level exposure above 100 ppm appears to be associated with decreased color discrimination. Results near the TLV are inconsistent, with both positive and negative findings. The LOAEL of 32-42 ppm suggested by Cavalleri et al. (2000) and Campagna et al. (2001) runs contrary to the NOAEL of 30-56 ppm reported by Nakatsuka et al. (1992) and Schaper et al. (2004). The substantial potential for bias (especially selection bias) in these four studies precludes any firm or definitive conclusions about lower-level exposures. It is difficult to judge the impact of selection bias with any certainty. Those who feel that solvents may have affected their vision might be more likely to participate (especially if they have been briefed about the purposes of the study), which could bias the data toward a positive result. On the other hand, those who have noted a worsening of color vision may fail to participate because of concerns about administrative action (e.g., job loss or transfer), which could bias results in a negative direction. The direction and magnitude of bias is likely to depend on corporate culture, level of worker satisfaction, and the degree of nonparticipation.

Most studies were cross-sectional in nature, essentially taking a snap shot of workers employed at a point in time. For this reason, there may be a "survivorship bias," where those with better color discrimination remain in the workforce, while others leave for jobs that do not require this skill. However, it should be noted that the longitudinal analysis by Schaper et al. (2004) found no impact on color vision over 5 years, with relatively similar dropout rates among the four exposure groups, which does not support a survivorship bias.

Color vision changes were subtle and of no real clinical significance. Exposed workers did not report any visual impairment or inability to perform their jobs. Furthermore, a study in workers exposed to styrene suggests that solvent-induced impairment of color vision is reversible after approximately four weeks (Triebig et al, 2001). Overall, the findings from this body of literature are reassuring that any impact from toluene exposure is mild and potentially reversible.

6.13.7.3 Hearing loss

Epidemiological studies have also explored associations between toluene exposure and hearing loss. Morata et al. (1993) evaluated Brazilian print and paint manufacturers exposed to either noise (n=50), noise and toluene (n=51), or mixed solvents (n=39). Workers from the preparation division were selected as an unexposed reference group (n=50). All exposures were quite high, with current toluene exposures ranging from 75-365 ppm (past TWA exposure up to 600 ppm), mixed solvent exposure near the TLV for the summed concentration, and noise levels ranging from 88-97 dB(A). All subjects were randomly selected to participate, but non-participation rates were not discussed.

Morata et al. (1993) reported significantly higher prevalence of mild (type I) high frequency hearing loss (30-40dB) among workers exposed to toluene and noise (mean 8yr employment), compared to any other group. No substantial differences were noted for more serious hearing loss. Multiple regression analyses adjusted for duration of employment yielded significant RR of 10.9 for toluene and noise, 5.0 for mixed solvent exposure, and 4.1 for noise. These findings suggest an additive interaction between noise and solvent exposure, but specific interactions associated with toluene exposure could not be determined from these data. Due to wide variations in toluene air concentration measurements, setting of a LOAEC/NOAEC is not considered possible.

There was some evidence of selection bias in Morata et al. (1993), given that the unexposed population had the longest length of employment (13 yrs vs. 6-12 yrs) and the longest years of previous chemical exposure (1.6 vs. 0.9-1.4), as well as the highest participation in most noise-related activities (e.g., motor sports, power tools, and military service). There was also a suggestion of high unilateral hearing loss among the unexposed (approximately 15%-20%). It is possible that the unexposed group had been excluded from work involving noise or solvent exposure (i.e., transfer bias), because of an increased risk for serious hearing loss. However, such bias would probably not have significantly influenced the prevalence of mild hearing loss among the various groups.

A later study by Morata et al. (1997) examined the combined effect of solvent and noise exposures. They monitored 124 male printing workers (min. 1yr employment) exposed to as much as 244 ppm (919 mg/m^3) airborne toluene, or to ethanol and ethyl acetate. It is also likely that individual toluene exposures were much higher than suggested by the IH measurements, given the admission that toluene was used carelessly and haphazardly (e.g., mopping and cleaning). All groups were exposed to noise levels of 71-93dB, with approximately 84% exposed above 80 Db(A) and 60% above 85 Db(A). No unexposed subjects were examined. A biological exposure index (BEI) for total toluene exposure (inhalation + dermal) was measured using urinary hippuric acid levels. Only age and hippuric acid levels in urine correlated with hearing loss in stepwise multiple logistic regression models. There was no significant association with airborne toluene levels, interaction terms (e.g., toluene + noise), or noise.

The findings of Morata et al. (1997) should be interpreted with caution, because of serious inconsistencies in the results. For example, noise levels were quite high and 49% of workers had bilateral, high-frequency hearing loss. Furthermore, only 11% of workers claimed to use hearing protection consistently. Yet, noise was not associated with hearing loss in the logistic models (RR 1.00, 95% CI 1.00-1.01). There was similarly no association with airborne toluene (RR 0.99, 95% CI 0.98-1.01) or with the other solvents (RR 0.97-1.01). These incongruous results suggest that many (all) of these variables are highly correlated, so that it is impossible to distinguish individual or even composite effects. In such cases of multiple collinearity, one variable (in this case toluene BEI) can become a surrogate for multiple exposures. Furthermore, these results are probably at least partly due to the low p-value (0.05) used for entering or keeping variables in the stepwise model. Less stringent criteria (p= 0.10-0.25) are generally recommended (especially for keeping variables), in order to create a final model that controls for all potentially important risk factors. In the current model, it is likely that one of the other variables would become significant if toluene BEI were excluded, or if it were entered later in the regression. The authors do not mention the results of regression diagnostics, which can be used to highlight problems of multicollinearity.

Morata et al. (1993, 1997) performed cross-sectional studies dealing with relatively high-level exposures. Schaper et al. (2003) pursued a longitudinal hearing study with toluene exposures near the TLV. This study was a 5-year repeated-measures design very similar to the studies by Seeber et al. (2004) and Schaper et al. (2004). Schaper et al. (2003) recruited a total of 333 volunteers for the study (5% of all workers in the 14 German rotogravure plants), but only 192 completed all four hearing evaluations over the five years (1996-2001). Individual exposures were measured 10 times during the study, and lifetime weighted average exposures (LWAE) to toluene and to noise were determined from individual work histories. Mean LWAE and recent exposures were 45 ppm and 26 ppm for printers (high exposure), and 10 ppm and 3 ppm for end-processors (low exposure), respectively. Participants were categorized as short- or long-term, and low- or high-level exposure.

Repeated measurement analysis of variance did not demonstrate significant effects for toluene concentration, exposure duration, or interaction between toluene and noise intensity. A subsample (n=80) of participants were evaluated with BEI for toluene exposure. Multiple logistic regression analyses of these data did not detect an increased risk of high-frequency hearing loss associated

with toluene exposure (RR 1.00). Noise exposure was associated with a significant hearing reduction in the ANOVA. Long-term workers had somewhat poorer hearing at the start of the study, but this could be explained by lack of hearing protection. Almost half of long-term workers never wore hearing protection, versus only 9%-23% of short-term workers.

The findings of Schaper et al. (2003) suggest that no hearing loss developed over 5 years of exposure to toluene, with a NOAEL of approximately 26 ppm. The hearing thresholds for the low- and high-toluene exposure groups were quite similar at the start of the study, suggesting no substantive effect of chronic exposure and a chronic NOAEL of 45 ppm. However, several limitations of this study need to be considered.

- This is a volunteer sample, so potential for selection bias is high. However, drop-out rates were similar among the four exposure groups, suggesting that selection bias would not have substantially affected the repeated-measures analyses.

- This study compares only high exposure with low exposure, not with no exposure. This lack of an unexposed reference group detracts somewhat from the cross-sectional interpretation of the study, but less from the repeated-measures analyses.

- All printers have some degree of coexposure to noise, which is a known risk factor that might confound the relationship between hearing loss and toluene.

Conclusions about hearing loss

There are concerns about the above studies, including potential for selection bias, confounding from noise and mixed solvent coexposure, uncertain exposure metrics, and inconsistent results. The most that can be said from the reviewed literature is that high-level toluene exposure (i.e., much higher than the TLV) appears to be associated with mild hearing loss. The findings from Schaper et al. (2003) suggest that toluene levels below the TLV are not associated with significant hearing loss, at least over 5 years of exposure, but that these findings should be interpreted with caution. No reliable NOAEL or LOAEL can be determined from these data.

6.13.7.4 Overall conclusions about sensory impairment

This body of literature suggests that high-level toluene exposures (often more than 100 ppm) are probably associated with a variety of sensory effects, including changes in brain evoked potentials, color discrimination, and hearing. Data for exposures near or below the TLV of 50 ppm are much more difficult to interpret. The most sensitive marker of lower-level exposure appears to be color discrimination, with LOAELs as low as 32-42 ppm. However, it is important to note that these LOAELs overlap with NOAELs from other studies. Furthermore, the overall impact on color discrimination was mild, with no apparent vision problems, loss of job skills, or decreased quality of life. It should also be noted that research suggests that such impairment is reversible after approximately one month without exposure.

6.13.8 Summary of human experience and overall conclusions

Existing evidence suggests that toluene is not genotoxic and that toluene exposure alone does not induce significant chromosomal damage in workers under normal exposure conditions. Data on immunotoxicity are limited. Slight effects on immunoglobulins and leukocytes have been reported, but there is no evidence that these effects are clinically significant.

Reproductive studies have reported suggestive evidence of an association between spontaneous abortion and occupational toluene exposure, although the limitations of this database make definitive

conclusions impossible. Most workers experienced mixed solvent exposure, making it impossible to draw causal conclusions for toluene. The literature for other reproductive endpoints is sparse, has a high potential for bias, and provides no consistent evidence of an association with toluene.

Results from clinical experiments and human epidemiological studies suggest that high-level toluene exposure may be associated with subjective complaints and subtle neurobehavioral effects. Common symptoms include mucosal irritation, headache, dizziness, and lapses in short-term memory or concentration. The most common neurobehavioral association was for short-term memory, although associations with perception, attention, concentration, visual intelligence, and psychomotor function were also reported. These findings agree fairly well with the results of laboratory experiments, where high-level exposures can induce CNS effects, sensory impairment, mucosal irritation, and acute intoxication.

Sensory changes appear to be the most sensitive endpoints associated with toluene exposure. This body of literature suggests that high-level toluene exposures (often more than 100 ppm) are probably associated with a variety of sensory effects, including changes in brain evoked potentials, color discrimination, and hearing. Data for exposures near or below the TLV of 50 ppm are much more difficult to interpret. The most sensitive marker of lower-level exposure appears to be color discrimination, with LOAELs as low as 32-42 ppm. However, it is important to note that these LOAELs overlap with NOAELs from other studies.

Potential impact of uncontrolled bias

It is important to remember that epidemiological studies are observational, not experimental, in nature, so that bias is always a potential explanation for the results. Potential for bias limits the conclusions that can be drawn from the occupational epidemiology on toluene.

Some authors recognized the potential for confounding bias in their study, using matching or limited statistical adjustment in an attempt to control this bias. However, this control was often limited to 1-2 key factors (e.g., age and alcohol), without considering the myriad other variables that might impact subtle neurosensory effects. Furthermore, potential confounders were often determined by statistical significance, which leaves considerable room for uncontrolled confounding, especially given the relatively small sample sizes. That is to say, substantive differences between small groups of subjects can substantially bias an association, even if these differences do not reach statistical significance.

The issue of confounding examines only whether the true exposure-disease relationship is reflected within the population of interest, not whether this unknown relationship is reflected in the selected sample and/or the generated data. These latter concerns relate to the potential for selection bias and misclassification, including differential misclassifications such as recall bias (Phillips, 2003). Such biases are potentially more serious than confounding, because they must be removed during study design and execution. Most of the above studies have relatively weak designs, leaving considerable room for bias that could lead to spurious results.

Almost all the cited studies selected relatively small (8-100 subject), cross-sectional samples of volunteers, without any real attempt to assure high participation or non-differential selection. Selection bias is a potentially very real problem in these studies. In fact, many of the authors reported substantial or even statistically significant differences on key demographic variables between exposure and reference groups, confirming differential (i.e., biased) selection. Furthermore, the cross-sectional nature of these studies does not permit a clear temporal relationship between exposure and health effects. That is to say, one cannot be certain that exposure precedes disease. It is interesting to note that the one available longitudinal study reported overwhelmingly negative

results for multiple endpoints, including hearing (Schaper et al, 2003), color vision (Schaper et al., 2004), and nurobehavior (Zupanic et al., 2002; Seeber et al., 2004).

Publication bias is another potential problem that has been noted in both the clinical and epidemiological literature (Dickersin, 1990; Easterbrook et al., 1991; Dickersin et al., 1992). This is more than just the traditional "file-drawer" effect, where investigators file away negative studies. A more pernicious problem is the tendency for epidemiologic investigators to mine data for positive findings and to preferentially present such results, while ignoring or downplaying negative findings. This latter tendency, which has been termed "selective reporting" (Hahn et al., 2000; 2002) or "publication bias in situ," (Phillips, 2004) is driven by the fact that analytical choices are often driven by the natural human tendency to pursue results that lead to a preconceived, expected, or desired effect.

Publication bias in situ is an insidious problem that is not easy to detect within published literature, because authors choose what to present and are typically limited in the space that can be devoted to discussion of methods and results. However, it is interesting to note that a hint of publication bias can be detected within the reviewed studies. Boey et al. (1997) report in their discussion that

> "subjects in this study were also assessed on neuropsychological measures of conduction velocities and somato-sensory evoked potentials. However, no significant differences were found in these neuropsychological parameters between the toluene exposed workers and their controls."

This means that a negative (i.e., uninteresting) result on the sensitive marker of evoked potentials was not published as such, representing publication bias in-situ. This negative result probably would not have been mentioned at all if it had not provided suggestive evidence in support of another positive finding (i.e., that "neuropsychological tests were more sensitive than biological measures") (Boey et al., 1997).

Publication bias in situ is exacerbated and abetted by the issue of multiple comparisons (Phillips, 2004). Multiple statistical comparisons impact the interpretation of statistical significance, given that the probability of observing extreme events by chance increases as the number of attempts (i.e., statistical tests) increases. Therefore, some statistically significant associations are likely by chance alone, given a large enough (i.e., 20 or more) number of comparisons. This is especially an issue in studies where there are multiple outcome-exposure combinations, such as symptom surveys and neurobehavioral test batteries.

It is also important to remember that the NOAELs and LOAELs derived from occupational epidemiology are imprecise and somewhat uncertain. Exposures in observational studies are not delivered in the steady, predictable patterns seen in controlled experiments. Rather, there is typically exposure heterogeneity, with average exposure estimates obscuring peak values. Exposure is also impacted by personal behaviors (e.g., hygiene, use of personal protective equipment, etc.) and other factors that are difficult to quantify. Furthermore, exposures in years past are often much higher than current average (or even peak) exposures. Therefore, the toluene literature does not allow a clear differentiation between the effects of current average exposures, past average exposures, and shorter-term peak exposures.

Human Health Conclusions

The above literature provides evidence that high-level toluene exposures is associated with a variety of sensory and neurological endpoints, including subjective complaints; hearing impairment; and subtle effects on evoked potentials, color vision, and neurobehavior. The literature on lower-level occupational exposures is less consistent and more difficult to interpret. The most sensitive marker of lower-level exposure appears to be color discrimination, with LOAELs as low as 32-42 ppm. However, it is important to note that these LOAELs overlap with NOAELs from other studies.

Overall, the findings from this body of literature strongly suggest that the neurosensory impact from toluene exposure is generally mild and reversible. The color vision, evoked potential, and neurobehavioral changes that were reported were generally subtle and within the range of clinically normal values. It is important to remember that such tests are used in the diagnosis of clinical illness among people exhibiting signs and symptoms of illness. It is not clear that they have clinical significance as markers of early pathology or future illness in normal, health workers. The reviewed studies provide no evidence of lost job skills or clinically important neuropathy or psychopathology in any of the exposed workers, even those with high-level exposures. Furthermore, most effects appeared to be temporary, with a return to normal in 2-30 days without exposure.

7. Exposure Assessment

This section summarizes the methodology, results and conclusions of the exposure assessment for toluene under VCCEP. As part of this pilot program, EPA has requested that exposure information be submitted to determine the extent of children's exposure to toluene. The types of exposure information needed for the assessment includes the identification and characterization of the population groups exposed, sources of the exposure, as well as frequencies, levels, and routes of exposure. The methodology employed in this assessment provides a comprehensive analysis of childhood exposures to toluene and uses the available data to focus on those sources of exposure that are likely to have the most significant impact on children's total toluene exposures.

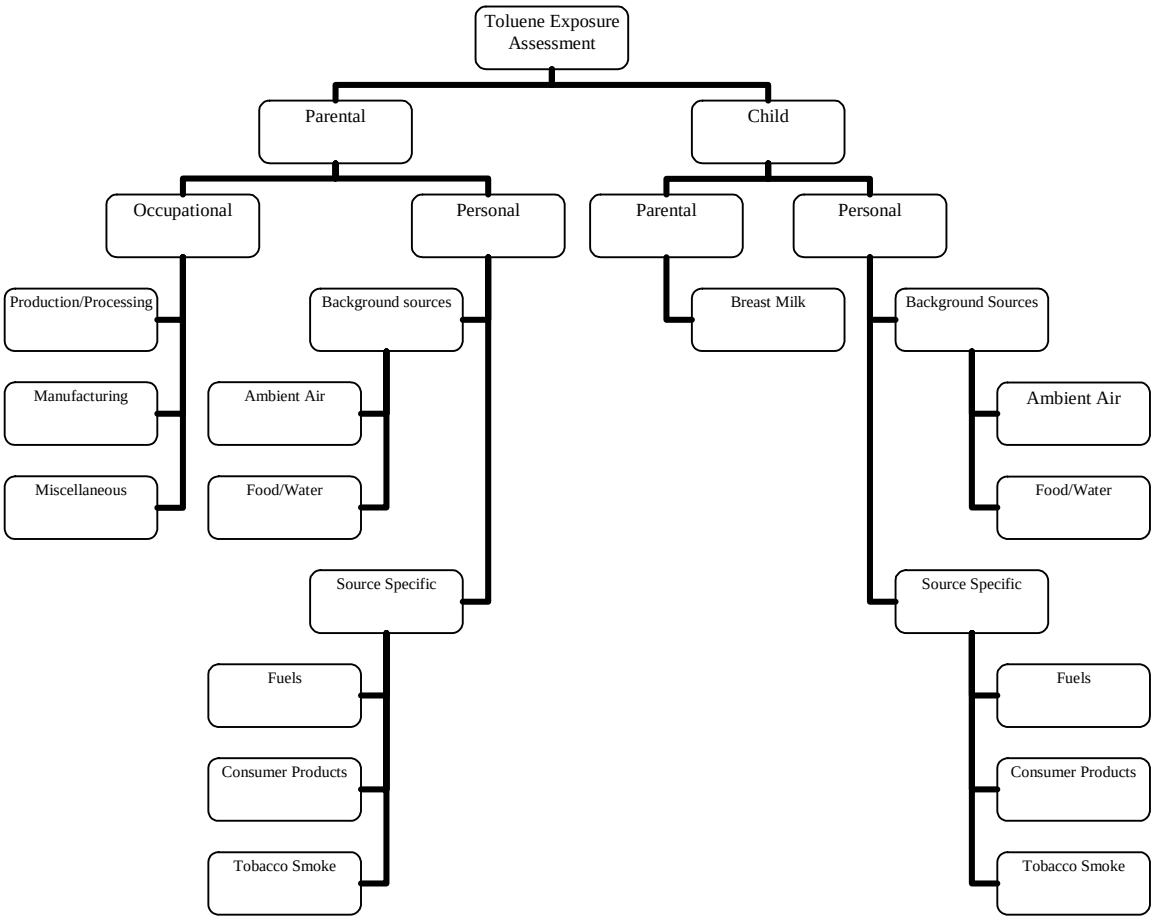
7.1 Methodology/ Scope of Assessment

As suggested by EPA, exposure assessments for both children and prospective parents were conducted. Sources of exposure to toluene in the ambient environment can come from both chain-of-commerce and non-chain-of-commerce sources and in many environments it is impossible to quantify the exposure contribution from each type of source. In accordance with the notice of the program published in the Federal Register (2000), exposures for the chain-of-commerce sources were assessed and quantified. Contribution to toluene exposure from non-chain of commerce sources such as automobile exhaust, cigarettes, and other sources of combustion are frequently captured in the exposure data presented (e.g. indoor air monitoring data, in-vehicle monitoring data),and where possible, exposures from these sources were quantified. Additionally, the exposure assessment does not include exposures from accidents or intentional misuse of toluene containing products.

A child-centered approach was used to define realistic exposure scenarios for children's interaction with toluene sources including environmental (ambient) sources, and use of consumer products. Figure 7-1 shows the relevant sources of toluene exposure for children and prospective parents. For most people, exposure to toluene is a daily occurrence. Toluene exposures to children and prospective parents have been quantified by evaluating the ambient or background toluene levels in a child's/parent's air (indoor and outdoor), diet, and water as well as specific sources and microenvironments to which subpopulations of children may be exposed. Available data indicate that all children are exposed to background levels of toluene in the ambient air, water, and food supply as a result of releases from natural sources, mobile sources, and the chain of commerce sources described in Section 3. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to toluene in microenvironments depending on specific activities such as transportation via gasoline powered vehicles, use of toluene-containing consumer products, or living in a home where tobacco smoking occurs (either used by parents or teenage children).

Toluene exposures vary by age. This age variation occurs because individuals interact with different sources in different ways at different ages. Thus, an older child (teenager) or an adult may receive an exposure when using certain consumer products, whereas a small child may only be passively exposed to toluene because of his or her presence in the home while the product is used. Age variation also occurs because exposure related characteristics such as body weight, breathing rate, and diet vary with age. Because of this, exposure scenarios have been developed for different age groups. Seven (7) age groups have been chosen based on relevant activities upon which children spend substantial amounts of time throughout childhood, as well as differences in infant metabolism (see Table 7.1).

Figure 7.1



In evaluating prospective parents, only prospective mothers have been included in the exposure assessment. The rationale for this is that toluene is not associated with male reproductive health effects. Thus, a prospective father's exposure to toluene does not impact his children. Consideration of prospective mothers' exposures provides a picture of potential fetal exposures as well as consideration of the breast milk pathway. As discussed in Section 6, toluene is not a mutagen or teratogen, and only toxic to the fetus at levels associated with maternal toxicity. Therefore, fetal exposures have not been quantified separately.

Table 7.1: Age Groups for the Toluene Exposure Assessment

Age Group	Category	Subcategory
0-6 weeks old	Children	Infant
7-12 weeks old		
13 weeks – 12 months old		
1-5 year old		Toddler
6-13 year old		Child
14-18 year old		Teenager
Female 19-35 * year old	Adult	Prospective Mother

*It is acknowledged that some women conceive children later in life, however, the largest percentage of pregnancies occur in women between the ages of 19 and 35.

Exposures from each source of toluene are characterized using exposure scenarios. The exposure scenarios define the population, source of exposure, the routes of exposure, and the values for the exposure factors that determine the dose and dose rate received from the source. A summary of ambient and the source-specific exposure scenarios for specific age groups is provided in Table 7.2.

A child's exposure to toluene depends upon a number of variables, or exposure factors. These exposure factors include the activities of the child that bring the child into contact with the source of exposure and which determines the dose resulting from the interaction and the physiology of the child. The relevant exposure parameters associated with each exposure scenario are presented in Appendix A-1.

For the various types of exposure, efforts were made to characterize both typical exposures and high-end exposures. In general, typical exposures were calculated using the average of the reported values of exposure concentrations, and exposure parameters (i.e., exposure frequency, body weight, inhalation rate, etc.) that reflect the central tendency values in the exposed populations. High-end exposures for sources of toluene other then consumer products were calculated using exposure concentrations representative of a 90 - 95th percentile of the range of values in a dataset (where data were sufficient to allow the determination of a range). In defining high-end exposure scenarios for the consumer product scenarios, 90th percentile product usage amounts were used to estimate airborne concentrations. It should be noted that the high-end scenario is meant to represent a reasonable, higher than average exposure, but not a "worst case" estimate for exposure.

The issue of defining the high-end scenarios raises a number of challenges in the assessment of toluene exposure from consumer products. In this assessment the following decisions were made on the characterization of consumer exposure. First, the assessment does not consider exposures that occur from the intentional misuse of the products (solvent abuse). Second, the product uses that are considered in this assessment are those that are consistent with label directions. Thus, toluene containing products with label directions instructing the user to avoid skin contact and use with adequate ventilation were not assumed to be used in a manner that contradicts these instructions (extensive dermal contact or use in small unventilated spaces). Third, exposures from use of consumer products occur in a wide range of situations where various amounts are used, under varying conditions (frequencies of use, room sizes, and ventilation rates), and in the presence or exclusion of children. Scenarios based on conservative (exposure enhancing) values for all possible exposure factors will result in situation that contradict the label directions (i.e., use with adequate ventilation).

Table 7.2: Summary of Toluene Exposure Scenarios

Exposure Scenarios	Age Group 0-6 weeks	7-12 weeks	13 weeks-12 months	1-5 years	6-13 years	14-18 years	Female 19-35 years
Ambient Exposures							
Outdoor Air							
Urban	✓	✓	✓	✓	✓	✓	✓
Rural	✓	✓	✓	✓	✓	✓	✓
Indoor Air							
In-home	✓	✓	✓	✓	✓	✓	✓
In-School				✓	✓	✓	
Food			✓	✓	✓	✓	✓
Water	✓	✓	✓	✓	✓	✓	✓
Human Milk	✓	✓	✓				
Source-Specific Exposures							
Tobacco Smoke							
ETS	✓	✓	✓	✓	✓	✓	✓
Mainstream						✓	✓
Consumer Products							
Users						✓	✓
Non-users	✓	✓	✓	✓	✓		
Gasoline Sources							
In-Vehicle	✓	✓	✓	✓	✓	✓	✓
Refueling						✓	✓
Occupational							
Production/Processing							✓
Non-Production							✓

✓ = Included in evaluation.

Therefore, the exposure scenarios considered in this assessment are based on above average but not the maximum values of all exposure related factors.

7.2 Sources of Toluene Exposure

This section provides a summary of sources of toluene to which children and prospective parents may be exposed. Toluene exposure has been quantified based on information provided in the scientific peer-reviewed literature or through exposure modeling using various EPA exposure models. The sources of toluene are defined in terms of two general source categories: ambient sources of exposures, and exposures resulting from the use of consumer products.

7.2.1 Ambient Environmental Exposures

Ambient childhood exposures to toluene could occur from four general sources: 1) ambient air, 2) food, 3) drinking water, and 4) human milk. Potential exposures to each source are described further below.

7.2.1.1 Ambient Air

During the 1980s and early 1990s the EPA funded and provided oversight for human exposure research with the objective of directly measuring exposure using personal air samplers. The conclusion of this extensive research project, known as the EPA Total Exposure Assessment Methodology (TEAM) Studies, was that the most important sources of exposure are small and originate close to the person (Wallace, 2001). The presence of major point sources, such as refineries, was not correlated with increased personal exposure to organic chemicals. This was also found by Phillips et al. (2004) who evaluated personal exposures to toluene in cities with and without refineries. In this study, the authors found that outdoor air concentrations of toluene were not correlated with indoor concentrations or personal concentrations regardless of the presence of a refinery. As with the TEAM studies, it was concluded that indoor exposures were dominated by indoor sources.

The Clean Air Act Amendments of 1990 provided for creation of the National Urban Air Toxics Research Center (NUATRC). The goal of this organization is to promote, develop and support research related to human health risks from air toxics. As part of the NUATRC mission, several studies have been conducted where VOC exposures to children have been evaluated. The Health Effects Institute (HEI) and the Mickey Leland National Urban Air Toxics Research Center (NUATRC) are jointly funding a project called the Relationship between Indoor, Outdoor and Personal Air (RIOPA); a large urban air toxics project that is comprised of three studies. The RIOPA project tests the hypothesis that personal exposure to air toxics is influenced by outdoor sources of these air toxics. It involves 3 cities with different air pollution source profiles: Los Angeles, California is dominated by mobile sources; Houston, Texas is dominated by industrial point sources; and Elizabeth, New Jersey includes a mixture of mobile and point sources. In each city, 100 homes were monitored for 48 hours in each of 2 seasons. The homes were monitored indoors and outdoors for $PM_{2.5}$ VOCs, and aldehydes. In addition, personal exposure to $PM_{2.5}$, VOCs, and aldehydes, and in-vehicle exposure to aldehydes were measured for residents of these homes. In general it was found that

indoor air toluene concentrations were higher than outdoor air, but lower than the personal toluene concentrations.

A community based study conducted by Buckley et al.,(2005) in Baltimore evaluated the impact of industry on community air quality and individual resident exposure to 15 VOCs. The study was designed to examine the potential industry effect by comparing indoor, outdoor, and personal air concentrations in South Baltimore to those in Hampden, an urban Baltimore community with a less intense industrial presence. Buckely et al. concluded that except for ethylbenzene and m,p-xylene, the VOC concentrations at all three levels of monitoring (outdoor, indoor, and personal) were comparable in the two communities, suggesting no industrial impact or an impact smaller than that detectable with the sample size of the study.

Inhalation of toluene from ambient air (both outdoor and indoor air) was evaluated for each childhood age grouping and the prospective mother. For ambient air, both urban and rural settings were considered, as toluene concentrations are highly dependent on mobile source emissions. For indoor air, exposures from both in-home and in-school environments were considered.

Ambient Outdoor Air

Urban and rural ambient air concentrations of toluene were obtained from EPA's AirData database (http://www.epa.gov/aqspubl1/annual_summary.html; accessed 8/20/03). This database contains annual summaries from air monitoring stations, pulling data from three EPA databases: 1) Air Quality System, 2) National Emissions Trends and 3) National Toxics Inventory. Collectively, these databases represent measured data from air monitoring stations, as well as estimated air data from point, area and mobile source emission measurements. As compared to random measured concentrations that may be provided in some literature studies, the AirData database represents a more comprehensive source of ambient air data that covers numerous counties throughout the U.S.

At the time of this assessment, the most recent year for which data was available was 2004. The 2004 data for two geographical setting categories, rural and urban were evaluated. A summary of the geographical diversity of the AirData for toluene is provided in Table 7.3 below, and the 2004 AirData data for toluene are presented in Table 7.4.

Table 7.3: Summary Description of the AirData Database for Toluene

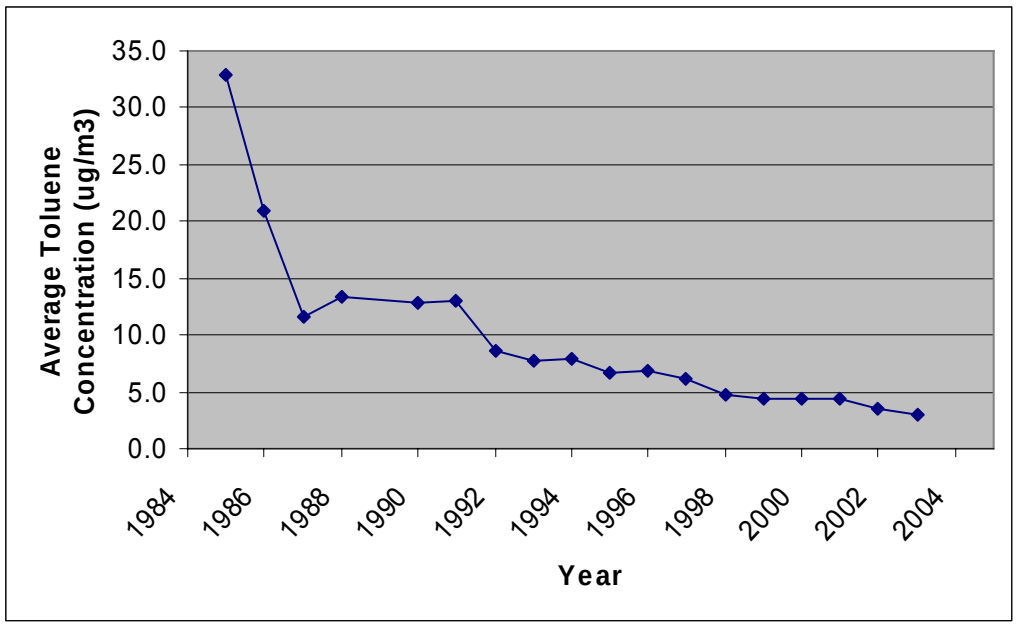
Setting	States	Number of Counties	Number of Monitoring Stations
Rural	AZ, CA, DE, FL, GA, LA, ME, MI, MN, MO, MS, NC, ND, NJ, NM, NY, PA, TX, WI	31	42
Urban	AZ, CA, CO, DC, DE, FL, IA, IL, IN, LA, MA, MD, MI, MN, MO, MS, NC, NH, NM, NY, OH, OK, OR, PA, RI, SD, TN, TX, WA, WI	72	132

Table 7.4: 2004 Ambient Air Toluene Concentrations from EPA's AirData Database

Setting	Median ($\mu g/m^3$)	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)
Rural	0.9	1.4	2.9
Urban	2.6	3.6	9.2

Ambient outdoor air concentrations have been steadily declining over time. The average toluene ambient air concentrations across the US, as measured at the Photochemical Assessment Monitoring Stations (PAMS) stations since 1985 are shown on Figure 7.2.

Figure 7.2 Trend in Toluene Ambient Air Concentrations in the U.S. (1985 – 2005)



*Note the data in Figure 7.2 were converted from the units of ppbC in the AirData database. The 1989 average of 263 µg/m3 was omitted from the graph; it was skewed by two averages of approximately 12,500 and 13,800 µg/m3 in suburban New York state.

As shown on this graph, significant decreases in toluene concentrations have occurred since the mid-1980s. Therefore, use of the most recent air monitoring data (as shown on Table 7.4) to characterize typical and high-end exposure concentrations is appropriate (http://www.epa.gov/aqspubl1/annual_summary.html; accessed 6/14/05). As such, the mean rural concentration of 1.4 µg/m^3 and the mean urban concentration of 3.6 µg/m^3 have been selected as representative of typical exposure concentrations for the child and prospective mothers in the rural and urban settings, respectively. The 95th percentile concentrations of 2.9 µg/m^3 and 9.2 µg/m^3 have been selected as representative of high-end exposure concentrations for rural and urban settings, respectively.

Analysis of Ambient Toluene Concentrations in Industrial Source Areas

A common misconception regarding individuals' exposures to toluene and other volatile compounds is that those living near industrial air emitters (stationary sources) have higher exposures than those who live elsewhere. This assumption is the basis for the air toxic regulations under the Clean Air Act. For many chemicals this has been shown not to be true (Ott and Roberts, Phillips et al. 20041998; Wallace, 1996;1989). In this assessment, an analysis of exposure from stationary sources was conducted to determine the potential contribution from this source.

The approach used was to develop a reasonable high-end estimate of the long-term average ambient air concentration for an individual living near a facility. At the time of this assessment, the most recent TRI release data were those reported for the year 2003. In 2003, 2,968 facilities reported toluene air emissions. The top 5 urban and top 5 rural facilities based on total pounds released to the air are listed on Table 7.8 below.

Table 7.8: Top Five Sources of Toluene in Rural and Urban Settings

Urban Facilities (location)	Total Air Releases (lbs)	Rural Facilities (location)	Total Air Releases (lbs)
Intertape Polymer Group (*Columbia, SC*)	1,966,208	Quebecor World KRI Inc. (*Corinth, MS*)	982,270
Quebecor World Memphis Corp. (*Dickson, TN*)	1,558,361	Quebecor World Franklin (*Franklin, KY*)	973,253
Quebecor World Richmond Inc. (*Richmond, VA*)	1,321,736	R.R. Donnelley & Sons Co. (*Warsaw, IN*)	643,193
Shurtape Technologies LLC (*Hickory, NC*)	1,318,616	Syngenta Crop Protection, Inc. (*Saint Gabriel, LA*)	448,919
Quebecor World Inc. (*Memphis, TN*)	1,169,825	Day International Inc. (*Arden, NC*)	432,786

Of the 2,968 reporting facilities, 5, or approximately 0.2% reported emissions exceeding 1 million pounds, with the top emitting facility being located in urban South Carolina with emissions of just under 2 million pounds of toluene.

To determine a reasonable high-end for air concentrations surrounding the second highest TRI facility, air emissions for the Quebecor World Memphis Corp., Dickson, TN facility were estimated using an air dispersion model and site specific data on the location of the exposed population. The second highest TRI emitter was used because site specific data was not available for the top TRI emitter. EPA's SCREEN3 model was used in this analysis. Details of the modeling are presented in Appendix A2. Results of this model run predicted long-term off-site toluene concentration would be 9.2 $\mu g/m^3$.

The SCREEN3 model prediction for the top TRI emitting facility is consistent with the 95% value from EPA's AirData database for urban areas. This indicates that the vast majority of individuals living near facilities would not experience air concentrations that differ from the range of background concentrations in the rural or urban environments. As such, the high-end for the majority of the U.S population is believed to be reasonably characterized by the measured toluene data presented in Table 7.4.

Ambient Indoor Air

The indoor environment in which children and prospective mothers spend most of their time is the home. Indoor air concentrations of toluene were obtained from the summary of the measurements of residential indoor air concentrations presented in the ATSDR Toxicological Profiles for Toluene (ATSDR, 2000), various residential indoor air studies, and indoor air quality studies of schools. The available data indicate that indoor air generally has higher concentrations of toluene than the outdoor ambient air.

Toluene in the indoor air environment occurs as a result of a variety of indoor sources, including the use of common household products, smoking tobacco products, wood stoves, cooking, and infiltration from attached garages. Toluene levels in the home may also be influenced by outdoor air levels and the whole house air exchange rates (ACH), which vary with the season and are lower in cold weather (Murray and Burmaster, 1995). Within the home, the two most common sources of toluene are household products and cigarette smoke (ATSDR, 2000). Source specific exposures to toluene from use of consumer products and exposure to tobacco smoke and are addressed separately in Sections 7.2.2.2 and 7.2.2.3, respectively.

The ATSDR review of toluene presents measurement data on indoor levels (home or office) of toluene that range of 2.64 $\mu g/m^3$ to 91.23 $\mu g/m^3$, with a mean indoor toluene concentration of 31.5 $\mu g/m^3$ (ATSDR, 2000). The studies from which the ATSDR has determined this range and mean were conducted in the late 1980s. A review of the recent peer-reviewed literature of indoor air studies was conducted focusing on residential studies. Several studies from the mid-1990s to the present were identified although those conducted in the US are limited (Adgate et al., 2004b; Bozzelli, et al. 1995; Hodgson et al. 2000; Isbell, 1999; Mann et al., 2001; Phillips et al., 2004; and Van Winkle and Scheff, 2001). Table 7.5 summarizes the data from these studies.

Table 7.5

Summary of Recent Published Indoor Air Studies of Toluene

Study	Location	Indoor Concentration ($\mu g/m^3$)	Outdoor Concentration ($\mu g/m^3$)	Notes
Adgate et al., 2004b	Minneapolis, MN, St. Paul, MN, Rice County MN, and Goodhue County MN	24.3 (mean) 14.3 (25^{th} percentile) 18.2 (50^{th} percentile) 66.5 (95^{th} percentile)	9.7 (mean) 7.6 (25^{th} percentile) 8.8 (50^{th} percentile) 15.6 (95^{th} percentile	Evaluated 101 private residences for indoor air, outdoor air and personal air concentrations of VOCs. Examined both urban and nonurban households and included smoking and non-smoking households and those with and without attached garages
Bozzelli, et al, 1995	Elizabeth, NJ	40 – 45	16	Evaluated indoor air impacts during use of kerosene heaters. Data on this table is without the heaters in use.
Gordon et al., 1999	Arizona 1995 - 1998	10 (50^{th} percentile) 22 (75^{th} percentile) 49 (90^{th} percentile)	2.2 (50^{th} percentile) 5.1 (75^{th} percentile) 11 (90^{th} percentile)	This is a report of the National Human Exposure Assessment Survey (NHEXAS) Phase I conducted in Arizona. 185 households were included in the study including those with attached garages.
Hodgson et al., 2000	East and Southeast US	5.7 – 19	5.7	Measured values in newly constructed homes prior to occupancy. Both manufactured and site-built homes included
Isbell, 1999	Fairbanks, AK	0.38 – 419 55 (study mean when max is excluded)	NR	Study of Alaskan homes with attached garages. Highest value associated with vehicle and 4 small engine sources.

Study	Location	Indoor Concentration ($\mu g/m^3$)	Outdoor Concentration ($\mu g/m^3$)	Notes
Kinney et al, 2002	New York City, NY	16.3 (mean, range not reported)	6.99 (mean, range not reported)	Study of 8 homes to characterize personal exposures to urban air toxics in inner city neighborhoods.
Mann et al., 2001	United Kingdom	36.8	NR	UK study of homes with attached garages. Only one measurement of toluene
Phillips et al., 2004	Oklahoma City, OK; Tulsa, OK; Ponca City, OK; Stillwater, OK	12 (median, day) 22 (median, night) 120 (max day) 140 (max night)	0.4 (median day) 1.9 (median night) 73 (max day) 26 (max night)	Study of 37 U.S. homes in urban and rural Oklahoma to characterize indoor, outdoor and personal air concentrations of various VOCs. Presence of refinery was a primary factor investigated.
Van Winkle and Scheff, 2001	Chicago, IL	2.37 – 44.7 12 (median)	2.7 (median)	Study of 10 homes in 1994 –1995
Weisel et al. 2005	Elizabeth, NJ; Houston, TX; Los Angeles, CA Summer 1999 through Spring 2001	15.4 (mean) 3.02 (5^{th} percentile) 10.1 (50^{th} percentile) 39.8 (95^{th} percentile)	7.09 (mean) 2.82 (5^{th} percentile) 5.42 (50^{th} percentile) 19.6 (95^{th} percentile)	Study of 306 homes in three urban centers including Elizabeth, NJ, Houston, TX and Los Angeles, CA. Purpose of study was to characterize the relationship between indoor, outdoor and personal air concentrations of various air toxics. Non-smoking homes near stationary sources were preferentially sampled.

In each study where outdoor air measurements were made, it can be seen that indoor air concentrations are higher than outdoor air concentrations. This is consistent with the older TEAM studies where they found levels of nearly a dozen common organic pollutants to be 2 to 5 times higher inside homes than outside, regardless of whether the homes were located in rural or highly industrial areas (Wallace, 1991; Wallace, 2001).

None of the recent studies are necessarily representative of the current overall U.S. demographic because of differences in home construction, presence of an attached garage, and outdoor ambient air concentrations. As indicated previously, because the outdoor air concentrations of toluene have declined over time and the outdoor air concentrations have some influence on the indoor air concentrations, the usefulness of the indoor:outdoor (I/O) ratio was evaluated for use in predicting indoor air concentrations based on current outdoor air levels. It was found, however, that the application of the I/O ratio implies that the outdoor air is the predominant factor influencing indoor air, irrespective of indoor sources. Phillips et al., (2004) found that for toluene, there was no significant correlation between the indoor and outdoor air concentrations. Also, recent studies in Germany have shown that for toluene, outdoor air is not the predominant source of toluene in the indoor air (Ilgen et al., 2001a,b). Therefore, it was determined that the difference (i.e., I-O delta) between the indoor and outdoor values might be more useful in estimating indoor air concentrations, as it represents the incremental toluene concentration attributable to indoor sources.

Of the studies listed on Table 7.5, only Adgate et al. (2004b) had paired indoor and outdoor data for individual homes. Therefore, this study was used to derive typical and high-end I-O deltas. These are presented on Table 7.6. It should be noted that this data was not published. However, the Minnesota Department of Health provided the raw air sampling data (personal communication with J. Panko, 2004).

Table 7.6 I-O Deltas from Adgate et al. (2004b)

Study	Typical I-O Delta (µg/m^3)	High-End I-O Delta (µg/m^3)
Adgate et al., 2004b	20	74

As such because of the limited data from recent representative studies of toluene in the indoor air, typical and high-end indoor air concentrations have been estimated by applying the I-O delta as follows:

$$C_{indoor} = C_{outdoor} + C_{\Delta indoor\,source}$$

The results are summarized on Tables 7.7 and 7.8 below.

Table 7.7: Typical Representative Indoor Air Toluene Concentrations in Rural and Urban Areas

Setting	Typical Outside Exposure Concentration (µg/m^3)	Typical Indoor Exposure Concentration (µg/m^3)
Rural	1.4	21
Urban	3.6	24

Table 7.8: High-end Representative Indoor Air Toluene Concentrations in Rural and Urban Areas

Setting	High-End Outside Exposure Concentration (µg/m^3)	High-End Indoor Exposure Concentration (µg/m^3)
Rural	2.9	77
Urban	9.2	83

The estimated typical and high-end indoor air exposure concentrations are consistent with the mean or median and high-end values presented in the recent literature (Table 7.5).

In-School Air

There is no systematic program in the United States requiring the collection of indoor air samples for VOC analyses in schools. In cases were data is collected, the data is usually collected by a private consultant in response to an indoor air quality complaint. Results from these studies are not usually published; rather, they are typically presented as a private report to the school administration. Thus, database searches of the scientific published literature did not identify a large number of studies of schools and indoor concentrations of toluene that would be representative of schools nationwide.

EPA conducted indoor air studies of schools from 1995-1998 (EH&E, 2000). The purpose of these studies was to determine whether intervention actions could improve indoor air quality and other endpoints. The detection frequency of toluene in the schools was 94%, and the mean and high-end (95th percentile) concentrations were 23 µg/m^3 and 65 µg/m^3, respectively.

This study did not include information regarding the setting of the schools (i.e., urban, suburban, or rural). The representativeness of the data is questionable for schools nationwide, because the schools that were studied were those for which complaints about the air quality had been made and the air samples were collected prior to implementation of any interventions in any given building. Additionally, no data regarding the outdoor toluene concentrations were presented.

Two other studies of indoor air at public schools indicate that the in-school levels of toluene are likely more comparable to concentrations found in the outside ambient air. This was most evident in a nine-school study conducted in the Saugus Union School District in Santa Clarita, California (Spielman, 2000). In-school concentrations ranged from 1.2 to 15 µg/m^3 and had an average of 6.3 µg/m^3, and outdoor concentrations ranged from 2.9 to 22 µg/m^3, and had an average of 8.2 µg/m^3. The study was initiated under the EPA's Tools for Schools Program, which was developed to evaluate and ensure healthy indoor air quality for students and staff at U.S. schools. Indoor levels of total VOCs were measured concurrently with outdoor levels in each of the schools, and

the researchers found that the indoor school concentrations were similar to the outdoor ambient concentrations. An additional study for a portable school building in the Saugus District (Spielman, 1999) indicated similar results, with in-school concentrations ranging from 2.5 to 5.4 μg/m^3 with an average of 3.3 μg/m^3, and outdoor concentrations ranging from 2.0 to 3.8 μg/m^3, with an average of 2.4 μg/m^3.

In addition to the Spielman studies, an investigation by Brown et al. (1994) provides summary indoor air concentration data from numerous U.S. and overseas sources. The total VOC concentrations measured in this study indicated that the concentrations in school were on average 6 times lower than those measured in homes.

Because none of the published studies are necessarily representative of in-school air quality nationwide, exposures have been estimated using both the findings of the Spielman and the EPA studies. The typical exposure is represented by the urban outdoor ambient concentration and the high-end exposure is represented by the high-end concentration from EPA's 10-school study (EH&E, 2000). These values are presented in Table 7.9.

Table 7.9: Typical and High-end In-School Toluene Exposures

Exposure	Toluene Concentration (μg/m^3)
Typical	3.9
High-End	65

7.2.1.2 Food and Tap Water

Toluene occurs in both food and water; therefore exposure to toluene can occur as a result of diet and tap water consumption. Toluene in tap water can also result in exposure by inhalation and dermal routes during showering. Toluene exposures from these sources and routes are evaluated using LifeLine™ Version 2.0, a publicly available software program for the simulation of aggregate exposures to chemicals. This software allows the determination of the total concurrent dose from the oral exposures, ingestion of food and tap water, from dermal exposure to toluene in shower water, and inhalation exposures to toluene that is released from shower water. Infant exposure to toluene in breast milk was determined separately as described in Section 7.2.1.3.

Exposure concentrations for food were derived from FDA's Total Diet Survey (FDA, 2003). In the Total Diet Survey, FDA personnel purchase foods from supermarkets or grocery stores four times per year from each of the four U.S. geographic regions. Each collection, referred to as a Market Basket, is a composite of similar foods purchased in three cities in each of the four regions (12 cities). Foods are prepared for consumption (i.e., as they will be eaten), and analyzed.

One Market Basket per quarter from the third quarter of 1995 through the fourth quarter of 2001 was available for analysis (totaling 24 applicable Market Baskets). The analytical results for toluene in the various foods ranged from non-detectable up to 4.4 ppm. Appendix A-3 provides details of the market basket analysis. The sources of the toluene residues are unclear, but are not likely to be a function of the commercial use of the chemical. Toluene is not used in most food processing and is not approved as a

direct or indirect food additive. Toluene is sometimes used in solvent extraction, which is a process used to produce specialty products such as grape seed extracts. A second, and probably more significant, source of exposure could be the concentration of toluene in fatty foods by absorption from air. This may explain the levels reported in fatty materials such as cheese. Finally, toluene was consistently found in a variety of cooked meats. Because of its volatility, solubility and the ability of mammals to metabolize toluene, the compound is not anticipated to bioaccumulate in animals. This suggests that the toluene would not be present in uncontaminated raw meat but may have been formed during the cooking processes.

The toluene food concentrations were entered into the Lifeline program and doses were calculated for the various age ranges. A detailed description of the food consumption modeling process is provided in Appendix A-4.

Exposure concentrations for the determination of toluene exposure from drinking water were obtained from EPA's National Drinking Water Contaminant Occurrence Database (NCOD) for water from public water supplies and the U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) program for a representation of private well users. The typical and high-end concentrations were characterized by mean and 95th percentile values as shown on Table 7.10 and 7.11 below.

Table 7.10: Public Water Supply Summary Statistics (January 1990 through February 2001)[a]

Statistic	Public Water Supply Concentration (N= 42,961) (µg/L)
Maximum Detect	963.6
Mean	0.36
Median	0.25
95th Percentile (by rank)	0.50

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.

Table 7.11: Summary Statistics for Toluene Analyses from Ambient Groundwater and Surface Water (July 1986 through September 2000)[a]

Statistic	Groundwater (N = 3,759) (µg/L)	Surface Water (N = 580) (µg/L)	All (N = 4,282) (µg/L)
Maximum Detect	50	1.4	50
Mean	0.15	0.11	0.14
Median	0.091	0.050	0.064
95th Percentile (by rank)	0.10	0.36	0.11

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.

Details of the determination of exposure concentrations for drinking water and the input into the Lifeline model are contained in Appendix A-5. The results of the food and

drinking water exposure analysis are presented on Tables 7.12 through 7.17 below and are based on model results for specific ages ('actual age') rather then the general age ranges. These actual ages are the median age of each of the age ranges. Both the typical dose and high-end doses are presented. The typical dose is estimated based on the median dose of a simulated population of 1,000 individuals. The high-end is based on the 95th percentile of the 1,000 simulated individuals. For infants in the 0-6 weeks and 7-13 weeks age bins, it was assumed that the children did not consume food, and therefore only exposure from tap water was calculated. Further, because the Lifeline model did not accommodate different age bins for the <1 year old age bin, it was assumed that all infants have the same water consumption rates.

For oral ingestion, the largest high-end total annual average dose that occurs is about 0.00078 mg/kg-day for children ages 1 to 5. The majority of this dose is from oral exposure from diet (0.00072 mg/kg-day). For inhalation and dermal exposures during showering, the largest high-end annual average doses are 0.000072 and 0.000005 mg/kg-day, respectively for children 0-6 weeks old.

The estimated toluene doses from food presented in this exposure assessment are consistent with other estimates made recently. For instance, the UK Ministry of Agriculture, Fisheries and Food (MAFF; now known as the Department for Environment, Food and Rural Affairs) determined in a Total Diet Study that the average UK intake of toluene is less than 7.7 μg/day (MAFF, 1995). The survey consisted of twenty food groups collected at 10 UK locations and included retail food product in amounts representative of UK consumption patterns. The method detection limit of 1 ppb was the same as the FDA's TDS detection limit.

The median dietary intakes (excluding tap water) derived from the Lifeline dose estimates are presented in Table 7.17. The average median intake among the age groups of 6.5 μg/day is consistent with UK estimate of average intake of less than 7.7 μg/day. If the infant age group is excluded, the average Lifeline intake estimate is 7.8 μg/day, or essentially the same as the UK estimate.

Table 7.12: Oral Exposures to Toluene from Tap Water

		Annual Average Daily Dose (mg/kg-day)	
Age Range	**Actual Age**	**Median**	**95th**
0 to 6 wks	[a]	5.84E-05	1.16E-04
7 to 12 wks	[a]	3.89E-05	7.75E-05
13 wks to 1 yr	[a]	2.50E-05	4.98E-05
1 to 5 yr	3	2.61E-05	5.56E-05
6 to 13 yr	9	1.16E-05	2.37E-05
14 to 18 yr Female	16	6.98E-06	1.48E-05
19 to 35 yr	27	8.24E-06	1.62E-05

[a] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.

Table 7.13: Oral Exposures to Toluene from Diet

		Annual Average Daily Dose (mg/kg-day)	
Age Range	**Actual Age**	**Median**	**95th**
0 to 6 wks	[a]	[b]	[b]
7 to 12 wks	[a]	[b]	[b]
13 wks to 1 yr	[a]	1.44E-04	3.19E-04
1 to 5 yr	3	4.26E-04	7.16E-04
6 to 13 yr	9	2.49E-04	4.48E-04
14 to 18 yr	16	1.42E-04	3.20E-04
Female 19 to 35 yr	27	1.18E-04	2.37E-04

[a] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.
[b] Assumed that infants 0 to 12 weeks old do not eat solid food.

Table 7.14: Total Oral Exposures to Toluene from Tap Water and Diet

		Annual Average Daily Dose (mg/kg-day)	
Age Range	**Actual Age**	**Median**	**95th**
0 to 6 wks	[a]	5.84E-05[b]	1.16E-04[b]
7 to 12 wks	[a]	3.89E-05[b]	7.75E-05[b]
13 wks to 1 yr	[a]	1.71E-04	3.69E-04
1 to 5 yr	3	4.51E-04	7.81E-04
6 to 13 yr	9	2.61E-04	4.77E-04
14 to 18 yr	16	1.50E-04	3.46E-04
Female 19 to 35 yr	27	1.26E-04	2.60E-04

[a] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.
[b] Assumed that infants 0 to 12 weeks old do not eat solid food, therefore, this dose is due to tap water ingestion only.

Table 7.15: Inhalation Exposure to Toluene in Tap Water While Showering[a]

		Annual Average Daily Dose (mg/kg-day)	
Age Range	**Actual Age**	**Median**	**95th**
0 to 6 wks	[b]	1.38E-05	7.16E-05
7 to 12 wks	[b]	9.17E-06	4.78E-05
13 wks to 1 yr	[b]	5.90E-06	3.07E-05
1 to 5 yr	3	1.16E-05	3.85E-05
6 to 13 yr	9	1.49E-06	6.49E-06
14 to 18 yr	16	1.04E-06	4.73E-06
Female 19 to 35 yr	27	7.39E-07	4.33E-06

[a]The toluene inhalation absorption factor (ABSi) of 0.5 was applied to the potential dose calculated by the Lifeline™ model.

[b] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.

Table 7.16: Dermal Exposure to Toluene in Tap Water While Showering

		Annual Average Daily Dose (mg/kg-day)	
Age Range	**Actual Age**	**Median**	**95th**
0 to 6 wks	[a]	2.27E-06	5.00E-06
7 to 12 wks	[a]	1.51E-06	3.33E-06
13 wks to 1 yr	[a]	9.71E-07	2.14E-06
1 to 5 yr	3	1.99E-06	3.80E-06
6 to 13 yr	9	1.32E-06	2.75E-06
14 to 18 yr	16	9.81E-07	2.33E-06
Female 19 to 35 yr	27	1.03E-06	2.59E-06

[a] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.

Table 7.17: Oral Intake Based on Lifeline Dietary Doses

Age Range	Actual Age	Body Weight (kg)	Annual Average Intake (μg/day) Median	95th
0 to 6 wks	[a]	3.6	[b]	[b]
7 to 12 wks	[a]	5.4	[b]	[b]
13 wks to 1 yr	[a]	8.4	1.0	2.3
1 to 5 yr	3	15.4	6.6	11.0
6 to 13 yr	9	35	8.7	15.7
14 to 18 yr Female	16	61	8.6	19.5
19 to 35 yr	27	62.4	7.3	14.8
		Average	4.7	9.4

[a] The Lifeline™ model could not accommodate age groups <1 year. Therefore, we adjusted the dose for the 1 year-old by the body weights for the 0-6 week, 7-12 week, and 13 week-1 year age groups to get the dose for that age group.
[b] Assumed that infants 0 to 12 weeks old do not eat solid food.

7.2.1.3 Human Milk

Toluene has been detected in the milk of nursing mothers, and thus was considered as a potential exposure pathway for nursing infants. Only one study was identified in which toluene concentrations were quantified in human milk (Fabietti, et al. 2004). In this study, Fabietti et al. (2004) reported toluene concentrations from 23 samples of human milk which ranged from 0.04 μg/kg to 2.54 μg/kg, with a mean concentration of 0.76 μg/kg. The samples were collected from women in Italy, and the highest concentrations were almost always associated with women that lived in urban, suburban or high traffic areas.

Elimination kinetics data for nonpregnant or nonlactating humans and rats following toluene exposure however, indicate that most absorbed toluene is rapidly eliminated and that which is absorbed into the adipose tissues is slowly eliminated. Hence, nursing mothers who do not work in jobs with occupational exposure are expected to transfer very little toluene in breast milk (ATSDR, 2000). Lactational transfer of toluene to nursing infants whose mothers return to the workplace following birth was assessed by Fisher et al., (1997). Fisher et al. developed a physiologically based pharmacokinetic (PBPK) model for lactating women to estimate the amount of volatile organic chemical that a nursing infant ingests for a given nursing schedule and maternal occupational exposure. Fisher et al., modeled the concentration of toluene in the breast milk assuming that the mother was occupationally exposed at the ACGIH TLV of 50 ppm.

Because of the limited data describing measured levels of toluene in human milk, the PBPK model was used to estimate human milk concentrations for this assessment. Because it is believed that the majority of occupational exposures are well below the TLV (See Section 7.2.3), and non-occupationally exposed mothers have much lower ambient air exposures, the estimation of toluene concentrations in human milk and lactational transfer of toluene were recalculated. In doing so, the maternal exposure levels estimated in this assessment were used in conjunction with the conservative

schedule described by Fisher et al. (1997). Accordingly, during the workday, the mother was assumed to be exposed at the respective workplace TWA concentrations for 8 hours and background concentrations of toluene for the remainder of the day. Eight nursing events were assumed to occur each day, lasting 12 minutes each, with 115 mL of milk ingested per nursing event, yielding a daily milk consumption of 0.92 L. Three individual nursing events were assumed to occur during working hours and the remainder five nursing events were assumed to occur after working hours. The nursing events that occurred during working hours all occurred after the toluene blood concentrations had reached steady-state with the workplace exposures and occurred at 2.1, 4.1 and 7.1 hours into the workday. The remaining five nursing events occurred at 2, 5, 10, 13 and 15 hours post-work-shift. If the working day were assumed to begin at 8:00 a.m., this would amount to nursing events occurring at 2:00 a.m., 5:00 a.m., 7:00 a.m., 10:00 a.m., 12:00 p.m., 3:00 p.m., 6:00 p.m., and 9:00 p.m.

All parameters for the PBPK model of toluene were obtained from Fisher et al. (1997), except the metabolic rate constants for toluene which was obtained from Tardif et al. (1995). The Fisher et al. (1997) model was reproduced successfully before using it to simulate the lactational transfer of toluene according to the defined exposure scenarios. The human milk concentrations for both the non-occupationally exposed mother (i.e., urban, typical & high-end) and the occupationally exposed mother were calculated.

The parameters of the model and the simulations of lactational transfer are included in the Appendix C. The results of the model are summarized in Table 7.18 below.

Table 7.18
Summary of Mass of Toluene Ingested

Scenario	Modeled Human Milk Concentration (mg/L)	Mass Ingested (mg/day)
Urban, typical	0.00002	0.00025
Urban, high-end	0.00008	0.00089
Occupational, typical	0.024	0.108
Occupational, high-end	0.087	0.399

Average daily doses of toluene in terms of mass per body weight for an infant were calculated and are presented on Table 7.19 below.

Table 7.19
Average Daily Doses of Toluene to Nursing Infant of Occupationally Exposed Mothers

Scenario	Average Daily Dose (mg/kg-day)
Urban, typical	3.5E-05
Urban, high-end	1.2E-04
Occupational, typical	1.5E-02
Occupational, high-end	5.5E-02

7.2.1.4 Summary of Ambient Background Toluene Exposures

Of the ambient background sources described in Section 7.2.1, inhalation of indoor air is the predominant pathway of exposure for children and prospective parents (See Figure 7.3). However, for nursing infants of occupationally exposed mothers, the contribution of toluene exposure from breast milk ingestion, results in ingestion being the predominant pathway of exposure to ambient sources, followed by inhalation (See Figure 7.4). Section 7.5 provides further discussion estimated toluene doses from exposure to specific sources.

Figure 7.3. Predominant Pathways of Toluene Exposure for Children (>1 yr) from Ambient Sources

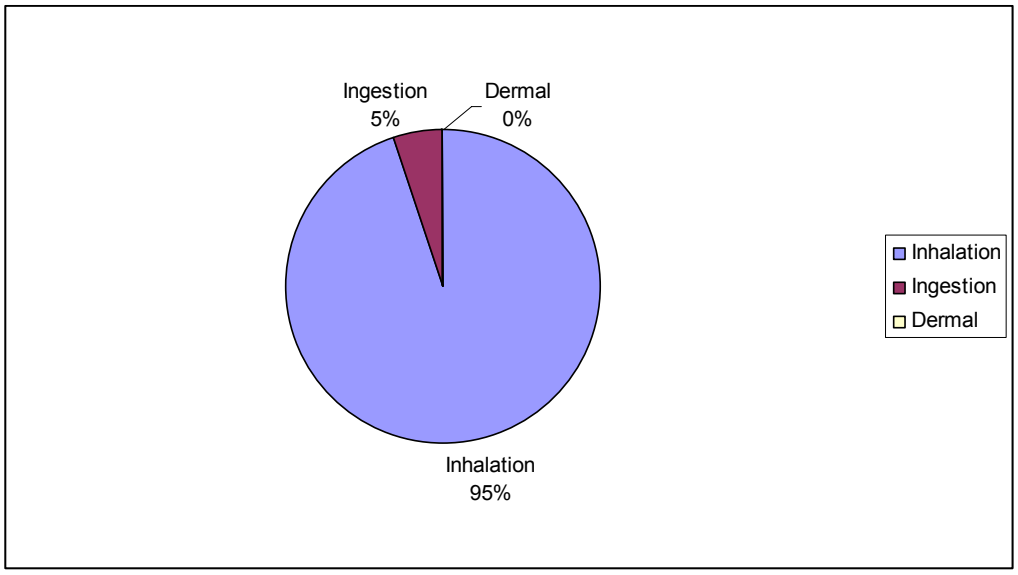
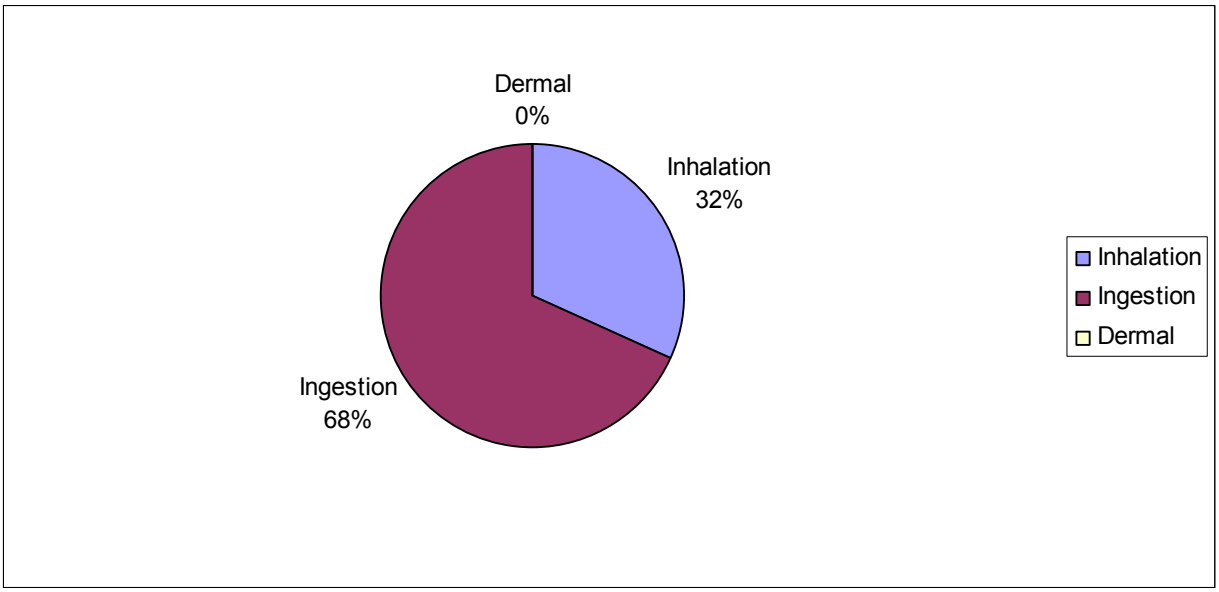


Figure 7.4. Predominant Pathways of Toluene Exposure for Nursing Infants of Occupationally Exposed Mothers from Ambient Sources



7.2.2 Source Specific Exposures

In addition to the ubiquitous sources of toluene which contribute to background exposures in the ambient environment, certain subpopulations of children and prospective mothers may be exposed to toluene in microenvironments depending on specific activities such as transportation via gasoline powered vehicles, use of toluene-containing consumer products, or living in a home where tobacco smoking occurs (either used by parents or teenage children). Exposures to each of these specific sources have been quantified and are discussed below.

7.2.2.1 Gasoline Sources of Exposure

Toluene is present in gasoline mixtures in a range of 5-7% by weight (See Section 3). While toluene from gasoline contributes to the overall concentration of toluene in the ambient air, exposures to gasoline may also occur while riding in a vehicle and during refueling of a vehicle. As such, toluene exposures from these specific activities have been assessed. It is recognized that there are other sources of gasoline exposure beyond those associated with in-vehicle travel and during refueling (i.e., use of small engine equipment such as lawn mowers, chain saws, leaf blowers, edge trimmer, snow blower, ATVs and snowmobiles). However, monitoring data for toluene is not available for characterizing these exposures. While there is some limited data regarding personal exposures to toluene from small engine gasoline sources, it is not sufficient for use in extrapolating potential toluene concentrations from known aromatic content in gasoline. Additionally, while there is a good amount of small engine emissions data, adequate models are not available for predicting personal exposures from these sources. As such, toluene exposures from small engine equipment have not been quantified.

In-Vehicle Toluene Exposure

Vehicle emissions of toluene contribute to toluene concentrations measured inside of vehicles during driving (ATSDR, 2000; Batterman et al., 2002). In-vehicle exposure to toluene is due to the penetration of toluene in roadway air (e.g., tailpipe emissions) and from engine running loss into the vehicle cabin while driving (Fedoruk and Kerger, 2003; Batterman et al., 2002; Weisel et al., 1992). In-vehicle toluene exposure levels can be affected by various conditions including mode of transportation, driving route, time of day (rush vs. non-rush), type of fuel distributions system, season of the year, meteorological conditions and vehicle ventilation conditions (Chan et al., 1991a,b; Dor et al., 1995; Lawryk and Weisel, 1996; Batterman et al., 2002; Fedoruk and Kerger, 2003). In many cases, the findings of the various studies can be conflicting, and in-vehicle VOC concentrations can vary considerably with sampling day and time (Lawryk et al., 1995; Batterman et al., 2002).

Of all modes of transportation involving potential non-occupational exposure to gasoline constituents (e.g., automobile, bus, subway, and walking or biking near traffic), in-vehicle exposures while driving in an automobile are the highest (Chan et al., 1991a). Although many children commute in school buses, studies show that because of variables including vehicle height, location of engine, ventilation conditions and fuel type, exposure in a car is greater than (Chan et al., 1991a; Jo and Choi, 1996; 1999a,b; Jo and Yu, 2000) or similar to (Batterman et al., 2002) that of a bus. The transportation route and traffic density (e.g., urban or rural, following closely or far behind a lead car, rush or non-rush) have been determined to be the most important in-vehicle exposure variables (Batterman, et al., 2002). It is expected that in-vehicle exposures in suburban areas, rural areas and in general, areas with lower automobile densities, will have lower in-vehicle concentrations.

Numerous studies have been conducted in the U.S., which have evaluated in-vehicle toluene exposures (SCAQMD et al., 1989; Chan et al., 1991a,b; Weisel et al., 1992; Lawryk et al., 1995; CARB, 1998; Chang et al., 2000, Fedoruk and Kerger, 2003; Batterman et al., 2002). Due to the emission reduction initiatives, however, only the most recent U.S. data were included in this analysis. The studies used to derive representative exposure concentrations are summarized in Table 7.20 below.

Table 7.20: Summary of Key In-Vehicle Studies

Study	Type of Vehicle Used	Comments
CARB, 1998	Car	Los Angeles and Sacremento, CA Fall 1997. This study was conducted to in both urban and suburban areas using two sedans and one SUV. Samples were collected over 2-hour time periods using SUMMA canisters. The driving protocol required travel behind high polluting vehicles such as buses to provide “high-end” estimates of exposure.

Study	Type of Vehicle Used	Comments
Chang et al., 2000	Minivan, occasionally a bus	Baltimore, MD, Summer 1998 - Winter 1999. This study was designed to simulate activities performed by older adults. Samples were obtained in 1-hour increments. The data used in this study was not published with the paper, but obtained separately. RFG was in regular use in Baltimore at the time of the study.
Batterman et al., 2002	Car	Detroit, MI, Fall 1999. This study was conducted during 2- 3 hour urban rush hour commutes. Information on the car used was not provided. Use of RFG was not required in Detroit.
Fedoruk and Kerger, 2003	Car	Los Angeles, CA, 1997. This study was conducted during urban commutes. 90 minute TWAs were obtained. A 1993 Toyota, in good condition, was used. The time of day that measurements were obtained was not reported. RFG was in regular use in LA at the time of the study.

Although the CARB, 1998 study is relatively recent, it was excluded because the study design required evaluation of highly unusual and unrealistic conditions (i.e., travel behind a high emitting vehicle for 2 hours). It is unlikely that a driver would closely tail a high-polluting vehicle the entirety of his or her driving time. It is more likely that the driver would move from behind such a vehicle, either intentionally or as the result of the general movement of vehicles in traffic, and therefore would be behind a variety of vehicles while driving during any given time period. Each of the automobile studies evaluated specifically excluded smokers and/or the influence of smoking on VOC in-vehicle concentrations.

In-vehicle exposure scenario concentrations were derived from means presented in the studies above and summarized on Table 7.21. It should be noted that the mean in-vehicle toluene concentrations measured in the CARB, 1998 study was 27.2 $\mu g/m^3$, which is more than two times greater than others measured in urban areas. Because this study was conducted using a driving protocol that is believed to be unrealistic, the data were not used in the derivation of an exposure point concentration for the in-vehicle exposure scenario.

Table 7.21: Average of Mean In-Vehicle Toluene Concentrations

Study	Description	Mean In-Vehicle Concentration (µg/m^3)
Chang et al. (2000)	Urban, mean (7.3 µg/m^3) of summer and winter (7.4 µg/m^3)	7.4
Batterman et al. (2002)	Urban	10.2
Fedoruk and Kerger (2003)	LA Freeway	11.8
	Average of study means:	***9.8***

Due to various driving conditions under which a person may be exposed, mean concentrations best portray long-term exposure concentrations. An average concentration was derived using the means of each of the three key studies above. This average is used as the typical representative in-vehicle exposure concentration and is considered to be an average of a high-end scenario, as it is representative of urban exposures where traffic densities are highest.

As noted in Section 4.1, VOC emissions from motor vehicles, including toluene, are on the decline as a result of the 1990 Clean Air Act Amendments, which called for lower tailpipe standards, more stringent emissions testing, expanded inspection and maintenance programs, new vehicle technologies and clean fuels programs. As these programs continue to be implemented, the exposures from use of vehicles will decline. Therefore, the estimates described above are likely to be overestimates of future in-vehicle exposures. The average of the mean study concentrations was presented in Table 7.21 was used to quantify in-vehicle exposures.

Refueling Toluene Exposures

A variety of researchers have reported that self-serve automobile refueling generates the greatest and most common source of gasoline exposure to the general population (Backer et al., 1997; Pope and Rall, 1995; Wixtrom & Brown, 1992). Exposure occurs primarily via inhalation of vapors during refueling. There are many potential sources of exposure to gasoline vapors at service stations, including breathing and working losses from underground storage tanks, displacement air losses from filler pipes during refueling, fill spillage during refueling, and evaporative and exhaust emissions from motor vehicles in the station. The displacement of fuel vapors from the gas tank while refueling, however, generates the majority of exposure to gasoline vapors (Backer et al., 1997; Guldberg, 1992). The toluene exposure of one individual during refueling can vary greatly depending on a number of environmental conditions at the time of sampling and personal filling procedure of the individual.

The Northeast States for Coordinated Air Use Management (NESCAUM) reviewed nine pre-1989 refueling studies and determined mean and high-end exposure concentrations for toluene and other VOCs (NESCAUM, 1989). Data were reviewed and weighted, yielding mean and high-end toluene exposure estimates of 2.3 and 9.0 mg/m^3. Two more recent studies, API, (1993) and Backer et al. (1997), however, were selected as

having the best representative data for this exposure assessment. This is because data collected before 1990 are not reflective of exposures associated with current gasoline formulations, which have reduced VOC concentrations.

The API study was conducted in 3 cities across the U.S and the Backer et al. study was conducted in Fairbanks, AK. These key studies focus on the exposure of a self-service customer while refueling; occupational exposure concentrations were excluded. The gasoline content of toluene in each study is similar (5.1 to 9.6%), and the presence or absence of Vapor Recovery System (VRS) controls at the pump was also documented in the studies. The selected data are representative of potential refueling exposures in different U.S. regions, using different blends, grades and types of gasoline, and using a variety of controls at the pump. A summary of the key studies is provided in Table 7.22.

Table 7.22: Summary of Key Refueling Studies

Study	Date/location data collected	Controls at the Pump	Type of Gasoline
API, 1993	October - November Cincinnati, OH Phoenix, AZ Los Angeles, CA	Only LA had Stage II VRSs and extensively used pump safety latches	Three grades of gasoline were evaluated: regular unleaded, mid-grade
Backer et al., 1997	January - March, 1995 Fairbanks, AK	No Stage II VRS	Regular gasoline and E10 gasoline

An individual will refuel under a variety of conditions, which are collectively represented by the two key studies. For example, they will spend varied amounts of time, under varied meteorological conditions, at different gasoline stations, filling their tanks.

Personal breathing zone exposure measurements have been used as representative exposure point concentrations. Thus, although displacement of vapors from the gas tank is the dominant exposure source, the measurements in the studies will capture the contributions from any other sources of toluene that are present at the gas stations. Exposure data from the key studies are presented in Table 7.23.

Table 7.23: Toluene Air Concentrations During Refueling (mg/m^3)

Study	Mean	Maximum
API, 1993[a,b]	0.91	4.6
	1.94	6.3
	1.19	3.6
Backer, et. al., 1997[c,d]	1.59	4.14
	1.34	4.64
Average	**1.4**	**4.7**

Averaging the mean exposure concentrations in each of the key studies resulted in a mean exposure concentration of 1.4 mg/m^3; this value is used in to describe a typical exposure. Obtaining an average of the maximum concentrations from each study resulted in a high-end exposure concentration of 4.7 mg/m^3.

A comparison of the NESCAUM mean of 2.3 mg/m^3 and high-end estimate of 9.0 mg/m^3 to the exposure concentrations shown on Table 7.23 demonstrates that the refueling exposure concentrations of toluene have decreased by approximately 50% over the years. This decrease can be attributed to the changes in gasoline formulations, pump controls and on-board emission controls of newer vehicles. Thus, toluene exposure concentrations during refueling are likely lower than those represented in the key studies due to RFG phase-in across the country and fleet vehicle changeovers since the mid-1990's. For these reasons, it is expected that exposures during refueling will continue to decline in the future.

It should be noted that, in-vehicle-while-refueling toluene concentrations appear to be lower than ambient concentrations at gasoline service stations and in-vehicle concentrations while commuting. (Vayghani and Weisel, 1999; API, 1993). Thus, a child who remains in the car while it is being refueled was not evaluated, as it was determined that the toluene exposure concentrations were much lower (i.e., about 1 order of magnitude) than measured refueling exposures.

7.2.2.2 Consumer Products

A number of specialty consumer products contain at least a trace amount of toluene. As part of an EPA study, 1,159 consumer products from 65 product categories were analyzed for VOC content by GC/MS with a detection limit of 0.1% by weight (Sack et al., 1992). The Sack et al. (1992) study was reviewed to determine which product categories had products that contained greater than 0.1% by weight toluene. Appendix A-6 contains tables which summarize the toluene containing products. Based on this review, 37 product categories were identified for which at least one product contained toluene.

Because the Sack study is somewhat dated (i.e., 1987), steps were taken to verify the toluene composition information by obtaining current material safety data sheets (MSDS) for the various products. From each of the Sack et al. product categories, five products were randomly selected and the toluene content verified using the product MSDSs. This analysis is presented in Appendix A-7. The sources of consumer product MSDS information included the product manufacturer when possible, as well as:

- Vermont Safety Information Resources, Inc. – 180,000 MSDS archived at http://www.hazard.com
- Cornell University Planning Design and Construction – 250,000 MSDS archived at http://msds.pdc.cornell.edu/msdssrch.asp; and
- Seton Compliance Resource Center – 350,000 MSDS archived at http://www.setonresourcecenter.com/MSDS/index.htm.

The EPA's Source Ranking Database (SRD) (EPA, 2000c), was also reviewed to determine products that contain toluene. The SRD is a compilation of product composition information from a variety of sources. While the SRD has the same limitation that Sack does in that the information is dated, it contains information from a

variety of sources and is not limited to just those products that may have contained chlorinated VOCs. The SRD was developed to rank consumer products for screening a large number of indoor air pollution sources and prioritizing them for future evaluation. Because the Sack et al. study is one of the major sources of data in the SRD, much of the same information from Sack is included in the SRD. When comparing the two consumer product data sources, it was found that the same product categories that contained toluene were identified in Sack and SRD and that the percent toluene composition was similar. Because the SRD was not limited to products only potentially containing chlorinated solvents (as Sack was), an additional product category that includes nail polish was identified.

The National Library of Medicine Household Products Database was also reviewed to determine consumer products that contained toluene. A search of this database revealed products similar to that identified by Sack et al. (1992) and SRD. Results of the search are included in Appendix A-6. Most of the products identified were spray paints, primers and stains; followed by automotive products, adhesives, thinners and removers. The reported toluene content of the product were similar to those measured by Sack et al.

As presented in Appendix A-7, most products contain less than 1% by weight of toluene and therefore are unlikely to be important sources of exposure. Thus, this assessment has focused on those consumer products that have the greatest potential for resulting in significant exposures to children. Those consumer products, which contain toluene greater than 1% by weight, are listed on Table 7.24. Each of these products was then considered in the context of how they would be used and the likelihood of children being exposed during their use.

Table 7.24: Typical and High-End Toluene Content of Consumer Products

Usage Scenario	Product Category[a]	Typical Content (%)[b]	High-End Content (%)[c]
Metal parts degreasing	Paint thinner / neat toluene	21	100
Surface preparation	Paint remover	12	40
Spray painting	Spray primer	14	19
	Spray paint	14	30
Shoe polishing	Spray shoe polish	2.75	20
Mixed Media Art	Adhesive	16	75
	Miscellaneous - glass frosting spray	2.3	40
Wood restoration or cleaning	Wood cleaner	--[d]	90
Automobile maintenance	Battery cleaner / protector	5.6	17
	Belt lubricants / dressing	--[d]	80
	Carburetor and choke cleaner	16	50
Nail polish	Nail polish	--[e]	30[e]

[a]Based on MSDS records for product categories identified by Sack et al. and Source Ranking Database
[b]Average of four lowest weight contents listed on five representative MSDS records. Where the MSDS provided a range, the highest weight content was used.
[c]Maximim weight content listed on five representative MSDS records.
[d]Majority of products in this category sold as toluene-free formulations based on survey of MSDS sheets.
[e]Majority of products in this category sold as toluene-free formulations based on survey of ingredients lists available at http://www.drugstore.com. High-end weight content is the maximum listed toluene concentration in the EPA's Source Ranking database.

It is believed that all of the products listed on Table 7.24 could be used in the home. However, the number of homes where some of these products (i.e. automotive products such as battery cleaner / protector) are used is small and the uses would be restricted to areas of the home (garages) and times when children are less likely to be present.

Evidence of this can be seen in an EPA sponsored consumer product survey (Westat, 1987). This survey found that the fraction of the surveyed individuals ever using battery terminal cleaners, belt lubricants or carburetor cleaners ranged from 7 to 22%. Of those that have used these products, the majority (86 to 88%) reported that the products were used outdoors. Less than 2% of the product users used these products in the home, with the remainder reporting that they were used in a garage.

Other product categories identified in Table 7.24 represent situations where the majority of product brands have toluene-free formulations. Wood cleaners and nail polishes are used in the home, but it is believed that the majority of these products do not contain toluene at levels greater than one percent. Most petroleum-based wood restorers appear to be formulated using mineral spirits with the exception of the one specialty brand identified in Table A-7-1 in Appendix A-7. Similarly, most nail polish brands are formulated with ethyl acetate and butyl acetate rather than toluene, as indicated by a survey of product ingredients listed at http://www.drugstore.com (see Table 7.25) and the California Air Resources Board (CARB) Consumer and Commercial Products Survey (2000), which indicates that toluene represents less than 1% by weight of nail polish emissions.

Table 7.25: Typical nail polish ingredients

Brand	Ethyl Acetate	Butyl Acetate	Isopropyl Alcohol	Toluene
Almay	✓	✓	✓	
Barielle	✓	✓	✓	
OPI	✓	✓	✓	✓
Revlon	✓	✓	✓	
Sally Hansen	✓	✓	✓	

Source: http://www.drugstore.com accessed on August 11, 2003.

For these reasons, the paint-related products, shoe polish, and mixed media art products were selected for a quantitative exposure assessment. The use of the neat solvent was investigated as part of the paint thinner category. Based on market share and the likelihood of use by or in the presence of children, the paint products, shoe polish and arts and crafts products were evaluated for toluene exposure in four scenarios. These scenarios include:

- residential metal parts degreasing scenario (paint thinner);
- residential spray painting scenario (spray primer and spray paint);

- residential mixed media art scenario (liquid adhesive and glass frosting spray); and
- residential spray shoe polish scenario.

Generic Scenario Assumptions

In the consumer scenarios the residence was assumed to be divided into two miroenvironments 1) room of use and 2) other rooms in house. For all of the exposure scenarios (except spray painting) both the product users (older children and a women of child bearing age) and observers (infants and young children) are assumed to be in the room of use. In the case of spray painting non-users (infants and young children) are assumed to be elsewhere in the home while the product is being used.

Current consumer product exposure models are not sufficiently sophisticated to accurately characterize the difference between product users and non-users in the same room (i.e., near field exposures are difficult to accurately predict). Thus, both the user and non-user are assumed to have the same exposures. In addition, in order to best approximate exposure to the product user, a small room size (i.e., 20 m^3) was selected in accordance with default values for the various E-Fast scenarios.

For the spray paint scenario, however, it was determined that it would be unrealistic to assume that there could be a non-user in the room of use because the limited floor area of the room would not physically accommodate the object to be painted, the user, and the non-user without interference in the spray painting activity (i.e., physical closeness to the spray can would likely result in over spray reaching the non-user). As such it was determined that the estimate of exposure for the non-user in the spray paint scenario would be based on the assumption that they were located in another room of the house.

As discussed in Section 7.1, typical and high-end chronic exposure estimates were made based on the amount of product used. One-hour, 8-hr and 24-hr time weighted average exposure concentrations were calculated for the scenarios using the EPA Multi-Chamber Concentration and Exposure Model Version 1.2 (MCCEM) and the conceptual framework (i.e. base exposure scenario including activity pattern, emissions models and interzonal airflow equation) of the EPA Exposure, Fate Assessment Screening Tool Version 1.1 (EFAST) Consumer Exposure Module (CEM). Exposure concentrations were calculated using MCCEM rather than EFAST to take advantage of the more detailed output of MCCEM (e.g. concentration versus time) and the ability to save input files for future review. MCCEM and EFAST use the same computational engine for indoor air quality modeling.

For products formulated with toluene, manufacturers recommend that if using the product indoors, it should be done in a well-ventilated area. Excerpts from a typical toluene-containing consumer product are provided in Table 7.26.

Table 7.26: Excerpts from Typical Consumer Product Label Instructions and Warnings

Label Section	Text	Example Source
Directions	"Use in a well ventilated area."	All Pro Cover Shield Stain Killer Instructions dated March 2002. (http://www.allprocorp.com/ techbuls/SeymourTB/ 7000TB11069CoverShield.cfm accessed 8/12/2003.)
Caution	"**Use only with adequate ventilation**. Do not breathe dust, vapors or spray mist. Open windows and doors or use other means to ensure fresh air entry during application and drying. If you experience eye watering, headaches or dizziness, increase fresh air or wear respiratory equipment protection (NIOSH/MSHA approved) or leave the area. Close container after each use."	

Recently, the EPA conducted a residential ventilation study to determine whole house ACHs under various ventilation conditions of windows and doors open (Johnson et al., 1998; Johnson et al., 1999). This study indicated that median ACHs for a house with at least one window open was 1.34 ACH, and a high-end Air changes per hour (ACH) was 3.0. Higher ACHs are achievable by using a window fan or whole house fan. The Air King™ brand window box fan has a reported airflow ranging from 2100 cfm at low speed to 4300 cfm at high speed. Assuming the fan is 50% efficient (to account for losses due to presence of a screen or an incomplete seal at the window), whole house ACHs of 5 to 10 air changes per hour are achievable in a 369 m^3 home. The importance of using exhaust fans to achieve ACHs in the range of 10 to 15 air changes per hour during large solvent-based projects is discussed as part of a recent exposure modeling study of home paint-stripper users (Riley et al., 2000).

When toluene containing products are used in the home in accordance with consumer product labeling, it is expected that the user will open windows or doors for small to moderate sized projects. For large projects, it was assumed that the user will conduct the activity outside or will introduce additional fresh air into the home by using a window fan or whole house fan. For a typical usage amount, the windows are assumed to be open for a 24-hour period to induce cross-ventilation as specified on product labels found on products containing toluene. For the high-end usage amount, the user is assumed to operate a window fan at the highest speed for the duration of the product use and for one-half hour after use. It is also assumed that the user leaves the windows open for the remainder of the 24-hour period after use began. Therefore, an air exchange rate of 5 ACH was applied during the modeling of the high-end scenario.

It should be noted that the modeled air concentration is relatively linear with the whole house ACHs used in this assessment. If one were to assume that no additional ventilation measures were taken when using the product, the default ACH would be 0.45 ACH. This value is approximately 3 times less than the ACH used for the typical scenario, and approximately 11 times less than the ACH used for the high-end scenarios. Thus, the under a "no additional ventilation" scenario, the predicted air concentrations would be 3 and 11 times higher for the typical and high-end scenarios modeled in this assessment, respectively. It should be noted that the "no additional ventilation" scenario was not considered in this assessment as it is contrary to the manufacturer instructions for product use (See Table 7.26).

Residential Metal Parts Degreasing Scenario

There are no published data on toluene exposures from the use of solvents for metal parts degreasing in the home. Paint thinners or neat solvents are commonly used as metal parts degreasers in hobbies such as firearm restoration or classic automobile restoration. While it is expected that paint thinner mixtures that contain some fraction of toluene are most frequently used in metal parts degreasing, from time to time a hobbyist may choose to use the neat toluene which is commercially available in hardware stores in quart or half-gallon sized containers. In this scenario, the use of a paint thinner mixture represents a typical use, while the use of neat toluene represents a high-end use.

EPA sponsored survey data (Westat, 1987) indicates that among the U.S. population ages 18 years and older, approximately 28% of the population have used a solvent type cleaning fluid or degreaser in their lifetime. Of those that have used a degreaser, 59% used the product in the home. Survey data also indicates that users generally read the directions (68%) and open a door or window during indoor use (57%). With respect to a conservative estimate of children's exposures, the population of interest is those limited number of households where paint thinner is used indoors.

Because degreasers are usually applied to a surface using a cloth, the EFAST “product applied to surface” scenario was selected as the baseline scenario for modeling purposes. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997), the Toxicological Profile for Toluene (ATSDR, 2000), and professional judgment. These values are presented on Tables A-8-1 and A-8-2 in Appendix A-8. Likewise, the activity patterns for users and observers in the room of u se and non-users in the other room, which are based on the default EFAST activity pattern, are presented in Table A-8-3 in Appendix A-8.

The Westat (1987) survey of solvent product usage provides a distribution of the volume of solvent used per degreasing event for the United States population (Table D-18). There are numerous uses for paint thinner as a degreaser by hobbyists (i.e., cleaning during do-it-yourself automobile repair; firearm restoration; metal surface preparation, etc.) However, the degreaser usage data reported by Westat is likely much greater than that which would be used for paint thinner formulated with toluene because it is representative of a wide variety of products including Easy-Off™ oven cleaner, Fuller Brush™ cleaners, Woolite™ and Dawn™, none of which contain toluene. As such, professional judgment was used in combination with a ‘bench scale’ simulation using water to esimtate the amount of degreaser that might be used for a typical indoor project (i.e., small object with a surface area of 1 ft^2) and a high-end usage amount for a larger project (i.e., object with a surface area of 10 ft^2). The estimated usage amounts are provided in Table 7.27.

Table 7.27: Degreaser Usage Amount

Usage	Ounces/use[a]	cups/use	grams paint thinner/use[a]
Typical	0.4	0.05	9.8
High-end	4.0	0.50	98

[a]grams/use= (ounces/use) * (29.57 ml/ounce) * (0.832 g/ml)

For this scenario, a typical use is characterized by typical usage amounts and usage times along with the typical weight content provided in Table 7.24. The high-end use is characterized by high-end usage amount and time, along with the high-end weight content given in Table 7.24.

The model was run to estimate exposure concentrations for users and non-users of paint thinner as a degreaser according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact with paint thinner during use, there is likely to be significant volatilization from the skin surface as it is not expected to be submersed in the product. The predicted toluene air concentrations are shown on Table 7.28.

Table 7.28: Predicted Toluene Concentrations for Residential Metal Parts Degreasing Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24-Hour) Exposure Concentration (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical usage amount with open windows (ACH =1.34)	2.8	0.67	0.40	0.12	0.13	0.041
High-end usage amount with exhaust fan (ACH = 5)	37	11	5.1	1.6	1.7	0.52

TWA = Time weighted average

Residential Spray Painting Scenario

There are no published data on toluene exposures from the use of aerosol painting products in the home. Spray paints are commonly used to coat metal surfaces, such as lawn furniture or automobile parts. A typical project where metal surfaces are being repainted consists of two steps:

- surface priming with an aerosol spray can product; and
- surface painting with an aerosol spray can product.

The Westat, 1987 survey data indicates that among the U.S. population ages 18 years and older, approximately 35.4% of the population have used spray paint in their lifetime. Of those that have used spray paint, only 17.8% painted indoors the last time they used spray paint. Survey data also indicates that spray paint users generally read the directions (73.2%) and open a door or window during indoor spray paint use (62.9%). With respect to a conservative estimate of children's exposures, the population of interest is those limited number of households where spray painting is performed indoors.

The EFAST product sprayed on a surface baseline scenario was used for spray primer and spray paint. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997), the Toxicological Profile for Toluene (ATSDR, 2000), and professional judgment. These values are presented on Tables A-9-1 and A-9-2 of Appendix A-9. Likewise, the activity patterns for users and observers in the room of use and non-users in the other room, which are based on the default EFAST activity patterns, are presented in Table A-9-3 of Appendix A-9. The Westat (1987) survey of solvent product usage provides a distribution of the volume of spray paint used per painting event for the United States population (Table Q-18). The spray paint scenario usage amounts are summarized in Table 7.29.

Table 7.29: Spray Paint Scenario Usage Amount

Product	Usage	Percentile	ounces/ use[a]	ml/ use	cans/ use[b]	grams product/use[c]
Spray Primer	Typical	50th	8	237	0.54	185
	High-end	90th	26	769	1.7	600
Spray Paint	Typical	50th	8	237	0.51	175
	High-end	90th	26	769	1.7	569

[a]The volume of spray paint and spray primer is based on the distribution for spray paint from Westat (1987) Table Q-18. The amount of paint remover used was calculated using the volume of spray paint used by assuming that the wet film thickness of the applied paint remover and spray paint are 2 mils (E-FAST default wet film thickness of water after i mMersion of hands in water) and 4 mils (WPEM default wet film thickness for paint), respectively. The volume of surface preparer equals the volume of paint * film thickness of surface preparer / film thickness of paint.
[b]Cans of spray paint or spray primer calculated using standard can size in Table E-9-1
[c]grams/use= (ounces/use) * (29.57 ml/ounce) * (density g/ml)

The usage amount of both products used in this scenario (spray primer and spray paint) is correlated because each product covers the same amount of surface area. It was assumed that equal amounts of spray primer and spray paint were used based on an

assumption of one coat of primer and paint, and similar wet film thickness for each product.

Despite the likelihood that larger projects involving spray paints would be performed outdoors, the Westat usage survey does not provide separate usage amount distributions for indoor and outdoor uses. Therefore, it was assumed the 90th percentile of the Westat distribution (slightly less than 2 cans of spray paint) represents the high-end usage quantity for spray primer and paint.

The model was run to estimate exposure concentrations for users and non-users of the paint products according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact with these products during use, there is likely to be significant volatilization from the skin surface as it is not expected to be submersed in the product. The predicted toluene air concentrations are shown on Table 7.30.

Table 7.30: Predicted Toluene Concentrations for Residential Spray Painting Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24-Hour) Exposure Concentration (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Spray Primer (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	35	8.4	5.0	1.5	1.7	0.52
High-end usage amount with exhaust fan (ACH = 5)[b]	45	12	6.1	1.8	2.0	0.60
Spray Paint (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	33	7.9	4.7	1.5	1.6	0.49
High-end usage amount with exhaust fan (ACH = 5)[b]	64	19	8.9	2.9	3.0	0.97
Cumulative Scenario (2-hour total usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	37	11	10	3.0	3.2	1.0
High-end usage amount with exhaust fan (ACH = 5)[b]	70	20	15	4.7	5.0	1.6

[a]ACH = air changes per hour.

[b]Exhaust fan is assumed to be turned off one-half hour after end of last product use and the windows are assumed to be left open, resulting in a post-usage ACH of 1.34 hr^{-1}.

Residential Spray Shoe Polish Scenario

There are no published data on toluene exposures from the use of spray shoe polishes in the home. The spray shoe polishes that are formulated with toluene are typically specialty products that are used to enhance or change shoe color or products that are marketed for professional use. It is expected that specialty toluene-formulated spray shoe polish products are occasionally used in the home for tasks such as quickly shining or whitening shoes (i.e., nurse's shoes). In this scenario, a typical use represents the shining of one or two pairs of shoes (i.e. $1/10^{th}$ of a can of spray polish), whereas the high-end use represents the shining of several pairs of shoes (i.e. one-half of a can of spray polish).

The Westat, 1987 survey data indicates that among the U.S. population ages 18 years and older, approximately 12% of the population have used spray shoe polish in their lifetime. Of those that have used a spray polish, 82% used the product in the home. Survey data also indicates that users generally read the directions (71%). Some users reported opening a door or window during indoor use (41%) or using an exhaust fan (11%). With respect to a conservative estimate of children's exposures, the population of interest is those limited number of households where spray shoe polish containing toluene is used in the home.

The EFAST "product sprayed on surface" scenario was selected as the baseline scenario. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997), the Toxicological Profile for Toluene (ATSDR, 2000), and professional judgment. These values are presented on Tables A-10-1 and A-10-2 in Appendix A-10. Likewise, the activity patterns for users and observers in the room of use and non-users in the other room, which are based on the default EFAST activity patterns, are presented in Table A-10-3 in Appendix A-10.

For products formulated with toluene, manufacturers recommend that if using the product indoors, it should be done in a well-ventilated area. The MSDS for the high-end product in this scenario recommends respirator usage when more than one-half can of polish is used continuously. When toluene containing spray shoe polishes are used in the home in accordance with the product labeling, the user would not be expected to open windows or take other actions to increase ventilation for a typical usage (i.e. polishing one pair of shoes). However, it is expected that the user will conduct the activity outdoors or open windows for large polishing projects where the polish is being sprayed continuously (i.e. polishing more than three pairs of shoes). For a typical usage amount, the national median indoor ACH is assumed. For the high-end usage amount, the user is assumed to open the windows in the home, and the open window ACH is used.

The Westat (1987) survey of solvent product usage provides a distribution of the volume of spray polish used per event for the United States population (Table A-18). Spray polish usage amounts are summarized in Table 7.31.

As stated previously, the Westat usage survey does not provide separate usage amount distributions for indoor and outdoor uses. Therefore it was assumed that the 90^{th} percentile of the Westat distribution (about one-half can of spray shoe polish) represents the high-end usage quantity. As mentioned previously, the manufacture's MSDS for the high-end product recommends respirator usage for amounts greater than one-half of a

can. Continuous usage amounts greater than one-half of a can would most likely be limited to occupational settings.

Table 7.31: Spray Shoe Polish Usage Amount

Usage	Percentile	ounces/use[a]	ml/use	cans/use[b]	grams spray polish/use[c]
Typical	50th	1.02	30	0.1	30
High-end	90th	5.74	170	0.5	167

[a]U.S. EPA, Household Solvent Products: A national usage survey. July, 1987. Prepared by Westat. Table A-18: Spray Shoe Polish.
[b]Cans of spray calculated using standard can size in Table E-10-1.
[c]grams/use= (ounces/use) * (29.57 ml/ounce) * (0.987 g/ml)

The model was run to estimate exposure concentrations for users and non-users of spray shoe polish according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact with spray shoe polish during use, there is likely to be significant volatilization from the skin surface as it is not expected to be submersed in the product. The predicted toluene air concentrations are shown on Table 7.32.

Table 7.32: Predicted Toluene Concentrations for Residential Spray Shoe Polish Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24-Hour) Exposure Concentration (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical usage amount with national default ACH (ACH =0.45)[a]	2.5	0.39	0.41	0.13	0.14	0.046
High-end usage amount with open windows (ACH = 1.34)	45	11	6.4	2.0	2.1	0.66

[a]ACH = air changes per hour.

Residential Mixed Media Art Scenario

There are no published data on toluene exposures from the use of adhesive or glass frosting spray during the use of art products in the home. This scenario consists of an art project where the hobbyist uses non-aerosol adhesive to glue plastic pieces and glass frosting spray to coat glass surfaces. Each of these products is available in formulations that contain toluene.

Westat (1987) indicates that among the U.S. population ages 18 years and older, approximately 60.6% and 10.4% of the population have used adhesive and glass frosting spray in their lifetime, respectively. Of those that have used adhesive and glass frosting spray, 81 to 85% used the products inside during the most recent use. Survey

data also indicates that adhesive and glass frosting spray users generally read the directions (70 to 71%). Among adhesive users, 41% report opening a door or window during indoor use and 8.1% report using an exhaust fan. About 24% of users of glass frosting spray users report opening a door or window and about 10% report using an exhaust fan. With respect to a conservative estimate of children's exposures, the population of interest is those households where toluene containing adhesives and glass frosting sprays are used inside the home.

Because plastic adhesives are usually applied from a squeezable tube, the EFAST product applied to surface scenario was selected as the baseline scenario for the adhesives. The EFAST product sprayed on a surface baseline scenario was used for glass frosting spray. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997), the Toxicological Profile for Toluene (ATSDR, 2000), and professional judgment. These values are presented on Tables A-11-1 and A-11-2 in Appendix A-11. Likewise, the activity patterns for users and observers in the room of use and non-users in the other room, which are based on the default EFAST activity patterns, are presented in Table A-11-3 of Appendix A-11.

This scenario consists of the use of an adhesive followed by the use of a glass frosting spray. Since small amounts of adhesive are used, it is assumed that the user opens a window at the beginning of the scenario for both the typical and high-end uses. Relatively large amounts of glass frosting spray are used, therefore, it was assumed that windows were opened or an exhaust fan was used, for the typical and high-end uses, respectively. The ventilation pattern is summarized in Table 7.33.

Table 7.33 Arts and Crafts Scenario Ventilation Pattern

Time	Activity	Typical		High-end	
		Ventilation	ACH (hr^{-1})	Ventilation	ACH (hr^{-1})
9 AM–10 AM	Adhesive	Open window	1.34	Open window	1.34
10 AM–11 AM	Frosting spray	Open window	1.34	Exhaust fan	10
11 AM–11:30 AM		Open window	1.34	Exhaust fan	10
11:30 AM– 9 AM		Open window	1.34	Open window	1.34

The Westat (1987) survey of solvent product usage provides a distribution of the volume of adhesive or glass frosting spray used per event for the United States population (Tables G-18 & U-18). The mixed media art scenario usage amounts are summarized in Table 7.34.

Table 7.34: Mixed Media Art Scenario Usage Amount

Product	Usage	Percentile	ounces/ use[a]	ml/ use	cans/ use[b]	grams product/use[c]
Adhesive	Typical	50th	0.25	7.4	--	6
	High-end	90th	2	59	--	52
Glass frosting	Typical	50th	9	266	0.75	222
	High-end	90th	26	769	2.2	641

[a]U.S. EPA, Household Solvent Products: A national usage survey. July, 1987. Prepared by Westat. Table G-18: Contact cement, super glue and spray adhesives. Table U-18: Glass frostings, window tints, and artificial snow.
[b]Cans of glass frosting spray calculated using standard can size in Table E-11-1.
[c]grams/use= (ounces/use) * (29.57 ml/ounce) * (density g/ml)

There are numerous hobbyist uses for adhesives (e.g. wood glues, scale model building or crafts) and frosting sprays (i.e., application of fake snow, glass frosting for privacy, or arts projects). However, the usage data reported by Westat is likely much greater than that which would be used for adhesive or frosting spray formulated with toluene because it is representative of a wide variety of products including artificial snow (various brands such as Santa's Snow™), Super Glue (various brands such as Krazy Glue™), and Elmer's Glue™, none of which contain toluene. In addition, despite the likelihood that larger projects involving volatile solvents would be performed outdoors, the Westat usage survey also does not provide separate usage amount distributions for indoor and outdoor uses. Therefore, it was assumed the 90th percentile of the Westat distribution represents the high-end usage quantity for adhesive and glass frosting spray.

For this scenario, the average exposure frequency for glass frosting spray from the WESTAT survey was used. Most respondents to the WESTAT survey for adhesives indicated various brands of super glue (which is formulated with ethyl 2-cyanoacrylate and does not contain toluene) when asked to identify the brand for the most recent use. Therefore, the average exposure frequency of 3 events per year for glass frosting spray was deemed more appropriate for estimating the frequency of use of two toluene formulated products in the same scenario.

The model was run to estimate exposure concentrations for users and non-users of the mixed media art products according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact with these products during use, there is likely to be significant volatilization from the skin surface, as it is not expected to be submersed in the product. The predicted toluene air concentrations are shown on Table 7.35.

Table 7.35: Predicted Toluene Concentrations for Residential Mixed Media Arts Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24-Hour) Exposure Concentration (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Adhesive (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	1.3	0.32	0.18	0.057	0.062	0.019
High-end usage amount with open windows (ACH = 1.34)	52	12	6.8	1.6	2.3	0.54
Glass Frosting Spray (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	6.9	1.7	1.0	0.30	0.33	0.10
High-end usage amount with exhaust fan (ACH = 10)[b]	96	28	13.3	4.3	4.5	1.4
Cumulative Scenario (2-hour total usage time)						
Typical usage amount with open windows	7.0	1.8	1.2	0.36	0.39	0.12
High-end usage amount with exhaust fan	98	29	20	5.9	6.7	2.0

[a]ACH = air changes per hour.
[b]Exhaust fan is assumed to be turned off one-half hour after end of last product use and the windows are assumed to be left open, resulting in a post-usage ACH of 1.34 hr^{-1}.

7.2.2.3 Tobacco Smoke

While not a chain-of-commerce source, toluene is present in both the mainstream tobacco smoke inhaled by the smoker directly from the cigarette and sidestream smoke released to the environment from the smoldering end of a cigarette. Because ATSDR indicates that cigarette smoke is a contributor to indoor toluene concentrations and serves as a significant source of exposure for smokers, cigarettes as a source of exposure have been evaluated.

Environmental tobacco smoke (ETS) is comprised of both sidestream smoke and exhaled mainstream smoke (Daisey et al., 1994b, NAP, 1986). Children may be exposed to toluene from tobacco smoke directly as smokers (mainstream smoke) or indirectly as non-smokers (ETS). Numerous studies have been conducted to identify and quantify the individual chemical constituents from tobacco smoke. Researchers have identified over 4,800 individual constituents, including toluene, in both mainstream smoke and ETS. Due to physical and chemical differences in burning conditions, toluene has a higher rate of release per cigarette into sidestream smoke than into

mainstream smoke (Wallace et al., 1987; Daisey et al., 1994b; Fowles and Bates 2000; NAP, 1986; Brunnemann et al., 1989, 1990; Darrall et al., 1998).

Smoking occurs almost anywhere there are people, however, on a daily basis, children spend most of their time inside at home and therefore their greatest potential for toluene exposure from ETS would be if they lived with a smoker. Also, although significant decreases in teenage smoking have been demonstrated in recent years, many teenagers are cigarette smokers. Thus, exposures to toluene via tobacco smoke were quantified for children from mainstream smoke and ETS (teenagers and adults) and ETS alone (children below the age of 13). Since smoking is not permitted on school properties and is now banned in most indoor public places, toluene exposure from ETS has been assumed to occur primarily in the home.

In order to calculate exposure to toluene, from tobacco smoke exposure, the toluene cigarette mainstream and sidestream emission rates were determined. Numerous studies have been conducted to evaluate the chemical emission rates. These are summarized in Table A-12-1 in Appendix A-12-2. In order to evaluate the exposure to toluene from tobacco smoke, the general school year weekday microenvironment activity patterns for children as presented in Table A-1-3 of Appendix A-12 were considered. Exposure to ETS was assumed to occur in the home, as ETS exposure in outdoor environments was assumed to be negligible.

Environmental Tobacco Smoke (ETS) Exposures

The total time spent with smokers was obtained for children and adults from the Exposure Factors Handbook (EFH) (EPA, 1997), and is presented in Table A-12-3 in Appendix A-12. In accordance with the information provided in Table A-12-2, it was assumed that a smoker was actively smoking inside the home for up to 6 hours per day in the presence of a child or female adult. The complete hourly activity patterns for the ETS dose calculations are presented in Table A-12-3 of Appendix A-12.

It was assumed that an adult female smokes one pack of cigarettes per day (i.e, 20 cigarettes) and that half of the pack is smoked indoors at home, which is equivalent to 10 cigarettes smoked at home indoors per day. This assumption is consistent with EPA estimates (EPA, 1997). The total mass of toluene released in cigarette smoke was calculated based on the emission factor presented in Daisey et al. (1994b). The total mass was divided by the 6 hours that the adult is awake and at home to account for smoking “off and on” during this time. Table 7.36 lists the emission factor and resulting emission rate.

Table 7.36: Emission Factor and the Calculated Emission Rate

Chemical	Emission factor (µg/cig)	Usage (cig)	Time (hours)	Emission rate (mg/hr)
Toluene	656	10	6	1.1

Air concentrations were modeled using the Multi-Chamber Concentration and Exposure Model (MCCEM). This model accounts for the emission of toluene over discrete time

periods and exposure of the individual based on their activity patterns (See Section 7). A hypothetical house was created where all the living space was on one floor such that all exposures were modeled to occur in one zone. This scenario was developed because it was assumed that the smoker would move throughout the house and that all areas of the house would have similar toluene air concentrations as it is known that the various rooms of the house come into equilibrium in a short period of time (Johnson et al., 1999). Default values of 0.45 ACH for the air exchange (which assumes no open doors or windows) and 369 m^3 for the volume of the residence were used (EPA, 1997). Age-specific toluene concentrations from ETS exposure in the home were calculated and are presented on Table 7.37.

Table 7.37: Summary of Average Daily Concentrations (ADCs) during ETS Toluene Exposure (μg/m³)

	0-6 week old	7-12 week old	13 weeks – 12 months old	1-5 years old	6-13 Years old	14-18 years old	Female 19-35 years old
Toluene	1.5	1.5	1.5	1.4	1.2	1.1	1.5

As Table 7.37 indicates, the personal exposure concentration increases by 1.1 to 1.5 $\mu g/m^3$ as a result of having one smoker in the home. The personal exposure concentration for a particular age range is a function of the time spent in the home and the number of hours in the home while active smoking is occurring. Additional exposure would be expected if there were more than one smoker residing at the house.

Mainstream Tobacco Smoke Exposures

Exposure to toluene from mainstream smoke was evaluated for female adults (19-35 years) and teenagers (14-18 years) in terms of average daily dose (ADD). Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (EPA, 1992a). Thus, the ADD was calculated according to the following equation and an absorption factor was not used.

$$ADD = \frac{C \times SF \times CF}{BW}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration of toluene in mainstream smoke (μg/cigarette)
SF = smoking frequency (cigarettes/day)
CF = conversion factor (0.001 mg/μg)
BW = body weight (kg)

The dose was calculated using the average toluene emission factor from Brunneman et al. (1990) of 50 µg/cigarette. A teenager smokes an average of about 7 cigarettes per day, whereas, a female smokes an average of 14 cigarettes per day (EPA, 1997), which results in a daily intake of toluene from mainstream smoke of 0.35 mg/day for the teenage smoker and 0.7 mg/day for the adult smoker. The annual average daily doses were calculated and are presented in Table 7.38.

Table 7.38: Summary of ADDs from Exposure to Toluene in Mainstream Smoke (mg/kg-day)

Exposure Parameter	Units	14 – 18 years old	Female 19 – 35 years old
C	µg/cigarette	50	50
SF	cig/day	7	14
CF	mg/µg	0.001	0.001
BW	kg	61	62.4
Dose	***mg/kg-day***	***5.7E-03***	***1.1E-02***

Wallace (1989) assumed a smoking frequency of 32 cigarettes/day. However, of the smoking data reported in EFH, only 14% of smokers indicated that they smoke more than 24 cigarettes in a day and of those who reported smoking at home, only 6% reported smoking more than 24 cigarettes. Thus, the uncertainty surrounding chemical dose from mainstream cigarette smoke is primarily associated with the smoking frequency. The smoking frequency used by Wallace is a high-end estimate.

7.2.3 Occupational Exposures

Occupational exposure to toluene occurs primarily in three types of occupations: (1) production/processing of toluene, (2) use of toluene as feedstock for the manufacturing of other chemicals, and (3) use of chemical products containing toluene in a commercial or skilled trade occupation (e.g. solvents, paints or lacquers). Exposure data relevant to these general occupational settings were obtained from industry trade organizations, the recent peer-reviewed literature, and the "Occupational Exposure Database" – Solvents End-Use" prepared for the American Chemistry Council and European Chemical Industry Council (Caldwell et al., 2000).

Inhalation Exposures

Production/Processing and Manufacturing Exposure Concentrations

In order to assess recent toluene exposure to workers in the chemical manufacturing and distribution industries, industrial hygiene monitoring records from January 1995 through December 2001 were collected from members of the Toluene VCCEP Consortium. As this survey was originally conducted to develop information on actual exposure, only data from employees who were not wearing respirators have been summarized. The analysis of these industrial hygiene data is summarized in Table 7.39.

The exposure concentrations were converted to the units of mg/m^3 for use in subsequent dose calculations by multiplying the units in ppm by 3.77.

Table 7.39: ACC BTX VCCEP Consortium Members' Occupational Toluene Exposure Survey

		Toluene Exposure Concentrations for Normal Full-Shift Operations			
		Mean		95th Percentile	
Operation	Number of Samples	(ppm)	(mg/m^3)	(ppm)	(mg/m^3)
Manufacturing	1546	0.15	0.56	0.35	1.3
Distribution	14522	0.33	1.2	1.2	4.5

Solvent End Use Exposures

To improve the state of knowledge of occupational exposure concentrations of VOCs found in common solvents, a database was prepared for the American Chemistry Council and European Chemical Industry Council (Caldwell et al., 2000). Summary statistics and the database structure were published in the American Industrial Hygiene Association Journal. The database consists of air concentration exposure data from about 100 journal articles from 1961-1988, which were selected from an initial list of 22,000 papers. For the VCCEP parental exposure assessment, this database was accessed and queried for records that met the following criteria:

- The exposure occurred in the United States;
- At least one discrete sample or an average concentration and sample number was available for toluene;
- The sample was collected in the breathing zone and;
- For TWA exposures, the exposure time was greater than 15 minutes.

The toluene query of the database resulted in numerous publications of occupational exposure studies. Based on the above criteria, occupational exposure data for toluene is available to characterize exposures in the following industries:

- Automobile (adhesive, painting);
- Rubber (mixing);
- Furniture (painting);
- Plastics (polyurethane molding);
- Printing (rotogravure);
- Shoes (assembly).

From the database, typical (average of all samples) and high-end (95th percentile of all job task averages) TWA exposure concentrations have been estimated and are presented on Table 7.40 below.

Table 7.40: Toluene End-Use Occupational Exposure Concentrations

Parameter	Exposure Concentration (ppm)	Exposure Concentration (mg/m^3)
TWA – Mean (N=1,208)	6.5	24
TWA –95th Percentile (N=1,208)	23	87

A search of recent occupational literature published since 1997 was also conducted to supplement the Caldwell, et al. database. The primary database searched was the National Library of Medicine's PubMed/Medline citation database, which indexes major occupational hygiene journals and medical journals. In addition to this database, the NIOSH Health Hazard Evaluations and OSHA publications printed since 1997 were reviewed. An emphasis was placed on exposures occurring in the United States. The recently published (i.e. 1997-2001) literature is summarized on Table 7.41.

Table 7.41: Recently Published Data on Occupational Exposure to Toluene

Occupation	Average 8-hour TWA Concentration (ppm)	Reference
Graffiti Removal Personnel	0.008 ppm	Anundi, 2000
Aircraft Maintenance Personnel – Military	0.01 - 3 ppm	Smith, 1997; Lemasters et al., 1999
Painter Applying Stains and Lacquers Used in New Home Construction	42 ppm	Methner et al., 2000
Municipal Firefighter	1.57 ppm	Austin, 2001a,b
Incinerator Employee	0.004 ppm	Thrall, 2001

Upon review of Tables 7.39 – 7.41, it is apparent that the recently published data and data from the manufacturing and production industries is consistent with the results obtained using the extensive database of Caldwell et al. (2000). The only exception is the painter applying lacquer or stain during new home construction, where the TWA exposure concentrations exceed the estimates based upon the database. These sample results may not be representative of typical conditions as a very limited number of samples were collected (three samples). It appears that the painter may not have been adequately ventilating the workspace when these samples were collected. Further, because use of consumer products such as paint and lacquers are evaluated more comprehensively in Section 7.2.2.2, the values presented in Table 7.40 were used in the occupational toluene exposure assessment.

Dermal Exposures

Occupational chemical exposure studies typically do not report dermal dose due to the difficulty of properly estimating the contribution of the dermal route, and very few *in vivo* human studies of dermal exposure to solvents have been published (Kezic et al., 2001). It is important to note that because inhalation and dermal exposure could co-occur in an occupational environment, interpretation of occupational *in vivo* studies can be difficult. Controlled *in vivo* studies are relatively rare (Kezic et al., 2000). Therefore, screening level dermal doses were estimated using the European Union approach to estimating applied dermal doses and absorption fractions (i.e. the fraction of applied dose that is absorbed through the skin) published by the U.S. EPA.

Permeability coefficient data (i.e. the rate at which a chemical penetrates the outer layer of epidermis normalized by concentration) are presented on Table 7.42.

Table 7.42: Toluene Permeability Coefficients

Chemical	Vehicle	Study Type	Skin	Permeability Constant (cm/h)	Primary Author	Year
Toluene	Neat Liquid	*In vitro*	Human breast skin (viable)	9.30E-05	Ursin	1995
Toluene	Neat Liquid	*in vitro*	Human cadaver skin	1.60E-04	Boman	2000
Toluene	Jet Fuel	*in vitro*	Human cadaver skin	1.97E-04	Kanikkannan	2001
Toluene	Neat Liquid	*in vivo*	Human forearm skin	1.43E-03	Kezic	2001
Toluene	Water	Predictive Equation	--	4.50E-02	EPA	1992a
Toluene	Toluene Vapor	*in vivo*	Human forearm skin	1.40E-01	Kezic	2000

Two published occupational studies that investigated exposure to toluene in the autobody painting (Daniell et al., 1992) and rotogravure printing (Monster et al., 1993) industries did not find an observable correlation between a biological exposure index (i.e. hippuric acid in urine) and dermal exposure to toluene. In a separate controlled experiment, Monster et al. (1993) observed toluene in the breath of volunteers following 5 minutes of immersion of the hands in a toluene bath. In an *in vitro* study, Boman and Maibach (2000) found that 1.9% of an applied dose of toluene was absorbed by the skin under fully occluded conditions. These studies indicate that a very low proportion of the applied volatile chemical is actually absorbed by the skin.

In an occupational setting such as the petroleum processing or chemical manufacturing industries, toluene or toluene containing products are handled in nearly 100% closed

systems. Thus, dermal exposure to the product is not common except under "upset" conditions, where personal protective clothing including gloves and suits would be worn. However, it is likely that from time to time dermal occupational exposure to toluene will occur during use of a chemical product containing toluene such as by a skilled tradesperson.

There are few screening level exposure models available for occupational dermal exposure to chemicals. As of this time, the best screening level model is EASE (United Kingdom Health and Safety Executive, 1997), which is a knowledge-based system that can be used when exposure data are limited or not available. This model provides estimates of product adherence to the skin during the work shift based on use pattern and contact level. Estimates are provided in units of mg of product per area of skin per day.

In evaluating dose of toluene from occupational dermal exposures assumptions have been made regarding the quantity of toluene containing chemical product that is in contact with the skin and the percent weight content of the toluene in the product. As such, it has been assumed that the adult female of average body weight and skin surface area exposes her hands to toluene during application of a stain or varnish. During the work shift, the coating covers about half of each hand during application (European Union, 2003). Exposures are assumed to occur under non-occluded skin conditions. For typical exposures, the coating was assumed to contain 10% toluene. For high-end exposures, it was assumed that the coating contains 20% toluene. Typical exposures are characterized by the intermittent, non-dispersive use of the toluene-containing product in contact with the skin and high-end dermal exposures are characterized by extensive wide dispersive use of the toluene-containing product (United Kingdom Health and Safety Executive, 1997).

Typical and high-end doses of toluene from occupational dermal exposures have been quantified using the following equation:

$$AD_{dermal} = \frac{Q_{dermal} \times F_{toluene} \times ABS_{toluene} \times A_{skin} \times EF}{BW \times 365 \frac{\text{day}}{\text{year}}}$$

where,

AD_{dermal}	Absorbed dose (mg/kg/day)
Q_{dermal}	Quantity of commercial product (paint, solvent, etc.) adhering to skin (mg/cm^2-day) from EASE model
$F_{toluene}$	Fraction of applied product that contains toluene by weight (unitless)
$ABS_{toluene}$	Absorption factor for toluene, equal to 0.03
A_{skin}	Area of skin exposed to commercial product (cm^2)
EF	Exposure frequency (days/year)
BW	Body weight (kg)

The dermal dose results are presented in Table 7.43

Table 7.43: Dose of toluene from typical and high-end occupational dermal exposures

Exposure Parameter	Units	Typical Female 19-35 year old	High-end Female 19-35 year old
Q_{dermal}	mg/cm^2-day	0.55	10
A_{skin}	cm^2	373	373
EF	day/year	12	12
$F_{toluene}$	% weight	0.1	0.2
$ABS_{toluene}$	--	0.03	0.03
BW	kg	62.4	62.4
AD_{dermal}	***mg/kg-d***	***3.2E-04***	***1.2E-02***

7.3 Discussion of Biomonitoring Data

In addition to the NHANES III blood concentration data for toluene (See Section 2.1), a focused study on children's blood levels of toluene is reported by Sexton et al. (2005). In this study, blood concentrations of 11 VOCs were measured up to four times over two years in a probability sample of more than 150 children from Minneapolis, MN. The blood concentrations for toluene reported by Sexton et al. are presented on Table 7.44.

Table 7.44: Blood Concentrations of Toluene in Children from Sexton et al. (2005)

Chemical Name	Date	Number of Samples	Detection Frequency (%)	Percentile (µg/L)			
				10th	50th	75th	95th
Toluene	Feb. 2000	106	73.9	0.06	0.10	0.13	0.25
	May 2000	102	55.6	0.07	0.08	0.11	0.20
	Feb. 2001	60	45.3	0.09	0.11	0.14	0.19
	May 2001	79	75.3	0.10	0.17	0.25	0.37

The median levels of toluene are 2 to 3 times lower than the NHANES III concentrations.

Sexton et al. (2005) also collected matched personal air samples for each child and analyzed them for toluene. The mean toluene concentration was 7.7 µg/m^3 (Adgate et al., 2004b). Although the authors found that the personal air samples were primarily influenced by time spent in the home, they also found only moderate statistical correlation (i.e., R^2=0.26) between matched personal air concentrations of toluene and blood concentrations of toluene.

Human physiologically-based pharmacokinetic (PBPK) models can be used to estimate internal doses of a chemical from external exposures. A human PBPK model for toluene

was used to estimate blood concentrations that would be predicted in children of various ages given the inhalation exposure concentrations for background exposures used in this assessment (see Appendix C for additional information). The results are provided on Table 7.45.

Table 7.45: Predicted Average Blood Concentrations in School-Aged Children Based on VCCEP Exposure Estimates

Age Group	Exposure Pathways		Toluene blood concentration, µg/L	
	Inhalation	Food/water	Peak	Avg.
6-13 yrs	Urban, typical, non-school day	Typical	0.11	0.09
	Urban, upper end, non-school day	Upper end	0.36	0.31
14-18 yrs	Urban, typical, non-school day	Typical		
	Urban, upper end, non-school day	Upper end	0.30	0.27

The blood levels were predicted using the inhalation exposure information based on the typical 24- hr time weighted average air concentrations and toluene doses received via oral ingestion and dermal contact. As shown on Table 7.45, the predicted toluene blood concentrations range from 0.09 µg/L, for average levels for typical exposures to 6-13 year olds to 0.36 µg/L for peak levels for high-end exposures of 6-13 year olds. The average predicted blood values (range, 0.09-0.31 µg/L) are similar to the median concentrations reported by Sexton et al. (2005) (range, 0.08-0.17 µg/L). Similarly, the predicted peak blood concentrations (range, 0.11 – 0.36 µg/L) are similar to the Sexton et al. (2005) 95th percentile toluene blood concentrations (range, 0.19 – 0.37 µg/L).

7.4 Uncertainties in the Exposure Assessment

Uncertainties are associated with any exposure assessment and for this Tier I assessment they are primarily associated with the use of published monitoring data to represent exposures for the U.S. population, and in the absence of monitoring data, the use of mathematical models to estimate human exposures. Each of these is described further below.

7.4.1 Monitoring Data

Published monitoring data was used to characterize children's and prospective mothers' exposures to toluene from ambient air, in-vehicle exposures, vehicle refueling activities, occupational environments and drinking water. Each of these is discussed further below.

Outdoor Ambient Air

The outdoor ambient air monitoring data for toluene was obtained from EPA databases, which included data from 18 rural counties and 32 urban counties nationwide. This monitoring data may not be representative of the entire U.S. outdoor ambient air because the monitoring stations are sparsely distributed geographically. However, ambient air concentrations vary by geographical area and the monitoring data that is available includes that for both rural and urban settings. Furthermore, the urban settings include those city locations, which have the greatest population densities (e.g. Los Angeles, Chicago, New York and Philadelphia) and thus the highest potential for toluene loading to the ambient air from mobile and non-mobile sources. Therefore, while there may be significant variation around the typical exposures estimated from use of the monitoring data, it is believed that the high-end exposure concentrations are reasonable high-end estimates.

Indoor Ambient Air

There is little monitoring data that is representative of current indoor toluene concentrations throughout the U.S. Although earlier data is available, use of monitoring data from the 1980s would have introduced a good deal of uncertainty into the exposure assessment because of the dramatic decrease in outdoor air concentrations, and improved emissions controls on automobiles and gasoline reformulations which can impact in-home toluene concentrations from attached garages and infiltration from ambient air. Additionally, in most of the studies reviewed, insufficient information is provided to understand the potential indoor sources of toluene, which results in a wide range of reported concentrations. Therefore, efforts were made to determine more realistic exposures that might capture some of the differences between current indoor air toluene levels and those from the 1980s. To do so, a delta value representing the incremental increase in toluene concentrations due to indoor sources was applied to the outdoor ambient air values. The typical delta used was 20 $\mu g/m^3$ and the high-end delta was 74 $\mu g/m^3$, both of which were derived from series of studies done in Minnesota. These deltas, therefore may be higher or lower than in individual homes across the country. Insufficient data is currently available to determine the range of indoor to outdoor deltas, which would account for all variations in housing characteristics, whole house ACHs and personal characteristics of the residents of individual houses. However, it is unlikely that the indoor to outdoor deltas would vary by more than an order of magnitude on a long term basis and therefore the uncertainty associated with the use of the delta is unlikely to be inconsequential in terms of estimating chronic background exposure from the indoor air. It is recognized that over short durations, the I/O delta may be more than an order of magnitude higher that that used in this exposure assessment, however that condition would likely result from introduction of a toluene source into the home. This has been demonstrated by Bozzelli et al. (1995) in their study of kerosene heater use, and by Ilgen et al. (2001b) during redecoration activities using of certain paint products. However, since these types of source specific exposure concentrations have been estimated in the consumer products section, aggregate exposures from background indoor air and temporary excursions of toluene concentrations due to consumer product use can be determined.

In-Vehicle Exposures

In-vehicle toluene exposure levels can be affected by various conditions including mode of transportation, driving route, time of day (rush vs. non-rush), type of fuel distributions system, season of the year, meteorological conditions and vehicle ventilation conditions. The data used in this exposure assessment to characterize in-vehicle toluene exposures come from three studies, all of which were conducted in urban areas. Because in-vehicle exposures are influenced by the ambient air immediately outside of the vehicle, toluene data collected in vehicles during an urban commute are likely to be higher than those which would occur in-vehicle during a typical rural commute. Thus, the data used in this exposure assessment likely overestimate in-vehicle exposures in rural areas.

In addition to ambient environmental conditions surrounding the vehicle, on-board emission controls also affect the in-vehicle toluene levels. Only one of the three in-vehicle studies provided information on the model year of the vehicle in which the toluene measurements were made (i.e., Fedourek and Kerger, 2003). Because the study dates for the other investigations were 1998 and 1999, it is likely that the vehicles were of the early 1990s fleet. Given that present day vehicles have better on-board emission controls that will continue to improve with future models, it is likely that use of data from older model years overestimates current and future in-vehicle toluene exposures.

It is recognized than a high-end in-vehicle exposure estimate has not been quantified. This is because the studies used in this assessment only provided mean toluene concentrations and the data does not support use of professional judgment to estimate a high-end exposure concentration. A high-end exposure, however, could be defined by increasing the exposure time (i.e., time spent in the vehicle each day). Because the indoor air concentrations are higher than the mean in-vehicle concentrations, increasing the in-vehicle exposure time would result in a decreased exposure time at the higher indoor air concentration estimate. The net result therefore would be an overall reduction in aggregate toluene exposure as, increased time in-vehicle would translate to decreased time in home at a higher toluene exposure concentration.

Vehicle Refueling

The data used to represent toluene exposures during refueling were collected in 3 cities across the continental U.S. and in Fairbanks, AK. Additionally, a variety of refueling scenarios were evaluated and use of various grades of gasoline was considered. Thus, it is believed that while the data are generally representative of typical and high-end refueling exposures, some uncertainty exists and is related to on-board emission controls, use of vapor recover systems at the pump, and continued reduction in aromatic content in gasoline blends. The three studies used to quantify refueling exposures were conducted in 1993 through 1997. As such, the vehicle fleet represented would have included vehicles without significant on-board vapor controls. Additionally, only one of the cities where toluene measurements were made had Stage II VRS at the pump. Thus, based on the technology available for later fleet years and the requirement for use of Stage II VRS in some ozone non-attainment areas, the data used in this assessment is likely to overestimate current and future toluene exposures during refueling.

Occupational Exposure Estimates and Human Milk Estimates from Occupationally Exposed Mothers

The monitoring data used to derive typical and high-end exposure estimates come from an extensive database of occupational solvent exposures including 100 studies where toluene was specifically evaluated (Caldwell et al. 2000). Additionally, while the data from Caldwell et al., is compiled from studies conducted from 1968-1997, current data derived from the peer-reviewed literature is consistent with that in the database. Thus, there is high confidence that the occupational exposures have been well characterized by the typical and high-end exposure estimates used in this assessment. However, based on the data from the toluene producers/manufacturers, occupational toluene exposures in the manufacturing sector are likely to be much lower than those from general solvent use. Thus, the typical and high-end exposure estimates used in this assessment likely overestimate prospective mothers' exposures in the manufacturing sector by as much as an order of magnitude.

The toluene human milk exposure estimates for children of occupationally exposed mothers assumes a mother returning to work 6 weeks after the birth of her child, being exposed up to high-end (95^{th} percentile) occupational exposures, and following a regular schedule of expressing milk during her work shift. In addition to the conservatism in the underlying occupational exposure data, the scenario used to derive these human milk exposure estimates is also anticipated to be rather conservative based on the early post-partum return to work and the likelihood of employers' administrative and management controls that remove nursing mothers from high exposure jobs.

Tap Water

The monitoring data used to characterize exposures to toluene from tap water were obtained from 42,961 recent measurements of public water systems from 32 states throughout the U.S. and 4,283 measurements from non-public water systems including groundwater and surface water sources. As such, a robust dataset was available for evaluation. Because toluene in drinking water is regulated, public water supplies are unlikely to serve a source of elevated toluene levels on a chronic basis and therefore it is believed that the children's and prospective mother's exposure estimates made in this assessment adequately characterize the typical and high-end exposures from tap water. Contamination of groundwater in source specific areas is, however, uncertain. While contamination of groundwater from various sources has occurred, potential childhood exposures for these conditions have not been quantified in this VCCEP exposure assessment, as regulatory programs are in place whereby site-specific risk assessments are performed for clean-up purposes.

7.4.2 Exposure Modeling

The uncertainties associated with any modeling exercise are typically those associated with the various model parameters. However, it is believed that in this exposure assessment most of the uncertainty errs on the conservative side. To address the uncertainties with the consumer product exposure modeling, a sensitivity analysis was conducted to determine which of the parameters had the greatest affect on predicted air concentrations. The parameters most sensitive were 1) amount of product used, 2) whole house ACH and 3) total home volume. A complete discussion of the sensitivity analysis is presented in Appendix A-13.

In addition to modeling parameter uncertainties, there are also scenario specific uncertainties. Each is briefly described below.

Residential Metal Parts Degreasing Scenario: The primary uncertainty with this scenario is the assumption that paint thinner formulated with toluene and neat toluene sold in bulk and used as a general degreaser would have usage amount distributions similar to that of other degreasers. The Westat survey data regarding product usage amounts is likely to be much greater than for a toluene paint thinner or for neat toluene because it is representative of a wide variety of products including Easy Off™ oven cleaner, Fuller Brush™ cleaners, Woolite™ and Dawn™, none of which contain toluene. As such, the usage amount assumed under typical conditions likely overestimates actual toluene containing paint thinner usage quantities. To minimize this uncertainty under high-end conditions, professional judgment was used to set the high-end usage amount for the neat toluene at approximately 2 cups of solvent or the 90th percentile for the product usage distribution. This quantity is believed to be a reasonable high-end for indoor use of neat toluene as a degreaser.

An additional uncertainty is that regarding human behavior when using toluene containing paint thinner or the neat solvent; specifically whether the product is used under adequate ventilation conditions. Because the Westat survey indicated that most people read the product directions (most of which recommend additional ventilation) and some opened windows or doors, the toluene exposures were modeled assuming adequate ventilation. Although, it is recognized that some people will not follow the directions or heed the warnings, reasonable exposure bounds have been evaluated in this assessment given the conservative nature of the other assumptions including: 1) small room of use (i.e., 20 m^3), and 2) usage quantities that likely exceed actual quantities as the data comes from products that do not contain toluene. If it were assumed that adequate ventilation is not provided, the whole house ACH would be assumed to be 0.45 ACH, which is approximately one-third of the ventilation rate under open windows/door conditions. Thus, because the ACH and the predicted air concentrations are linearly related over this range, the predicted toluene concentrations would be 3-fold higher. Likewise, if adequate ventilation were not used in the high-end usage scenario, the ventilation rate would be 11-fold higher.

Residential Spray Painting Scenario – The uncertainties associated with this scenario are the amount of products used, the correlation of amount of product used to location of use (inside versus outside), the steps taken to ventilate space (opening windows or exhaust fans) and the compounding effect in the high-end scenario regarding the use of three paint products, all with high-end toluene weight content. The Westat survey provides some useful information on these points. Some of the relevant details of the survey results include:

Over 80% of the survey respondents indicated that the last time they used spray paint, it was used outside or in a garage. In the residential spray paint scenario presented in Section 14.2, the assumption was made that the activity would take place within a room integral to the house. However, according to the Westat survey, this is not a common practice for most spray paint users. Thus, the assumption of indoor use may overestimate the toluene exposure during spray painting, particularly for high-end usage amounts (i.e., 2 cans of spray paint), which are unlikely to be used indoors.

For those survey respondents that used products inside, 63% opened a window, 10% used an exhaust fan, and 61% left the inside door of the room open. In the sensitivity analysis, the whole house ACH was determined to be a sensitive parameter, thus using a default value for the ACH would not be representative of typical use conditions. Of the survey respondents, 73% indicated that they read the directions on the label. Most spray paint labels contain a warning to use the product outdoors or in a well-ventilated space. Thus, it is reasonable to assume that a majority of the product users will heed the warnings and that the additional ventilation will minimize typical exposures during spray painting. As indicated in the degreaser uncertainty discussion, failure to use adequate ventilation would result in estimates of exposure approximately 3-fold higher.

The use of two paint products each containing high-end weight content of toluene on the same day within a 3 hour window is uncertain, but not likely. Although, consumer product data regarding the correlation between the uses of related paint products was not identified, this scenario was evaluated in an effort to capture a reasonable high-end estimate for a single day use.

Although it is often preferable to use actual air monitoring data to characterize exposures, no studies of residential use of spray paint were identified. It is believed however, because of the wide variation in consumers' use of various products, the modeled exposure assessment likely provides a broader picture of potential exposures. For instance, in using the consumer product models, various scenario conditions can be evaluated (i.e., usage amounts, various ventilation conditions, rates of application, etc.). These types of variables are not likely to be documented or accounted for in a monitoring study, thus limiting the usefulness of the monitoring data. To assess reasonableness of the toluene exposure estimates for the spray paint scenario, comparisons can be made to the limited occupational spray paint studies that have been conducted. For instance, in the Methner (2000) occupational study of residential construction activities, the toluene concentration from application of spray lacquer over a 1.7-hour period was 76 ppm. The commercial use of spray lacquer in a residential construction project is representative of a high-end indoor use of a product containing toluene. The 1- hr time weighted average in the modeled residential spray paint scenario was consistent with a concentration of 70 ppm predicted. Therefore, while limited, the data does demonstrate that reasonable exposure estimates have been derived in our assessment.

Residential Spray Shoe Polish – The primary uncertainty associated with this scenario is the amount of product used in the home. Very little data exists to understand individual practices when using large quantities of spray shoe polish. It is reasonable to expect that for projects that involve the use of more than one-half of a can of polish, the activities would take place out doors. Additionally, the product manufacturers recommend use of a respirator when using more than half of a can of product. Because of this, the high-end scenario was defined as the 90^{th} percentile of usage distribution data from the Westat survey.

Residential Mixed Media Art Scenario – The uncertainties associated with this scenario are similar to those for the residential metal degreasing and spray painting scenarios including the amount of products used, the correlation of amount of product used to location of use (inside versus outside), and the steps taken to ventilate space (opening windows or exhaust fans). While over 80% of the survey respondents indicated that the last time they used adhesive or glass frosting spray paint, it was used inside, the usage

amounts and actions by the user (i.e., ventilation) are not correlated with products that specifically contain toluene. In fact, the usage data reported by Westat is likely much greater than that which would be used for adhesive or frosting spray formulated with toluene, because it is representative of a wide range of products including those which do not contain toluene. Additionally, the Westat survey does not provide separate usage amount distributions for indoor an outdoor uses. Thus, while most respondents did not use additional ventilation when using the adhesive or glass frosting spray, it was assumed that due to label guidance and odor annoyance issues, when using toluene-containing products for large projects, the activities would take place either outdoors or in a well ventilated room. As indicated in the degreaser uncertainty discussion, failure to use adequate ventilation would result in estimates of exposure approximately 3- to 11-fold higher.

7.5 Summary of Exposures

Childhood exposure to toluene has been quantified in terms of background exposures (i.e., ambient air, food, and water) and specific source exposures, some of which are associated with toluene chain of commerce (i.e., consumer products) and some that are non-chain of commerce sources (i.e., gasoline, and tobacco smoke). In order to understand the contribution of various routes and sources of exposure to overall aggregate exposure, all exposure estimates were converted to average daily doses (ADDs) with the common unit of mg/kg-day. Thus, for inhalation exposures, various exposure parameters were combined with air concentrations for each age bin. The dose calculations are presented in Appendix A-14. Table 7.46 is a summary of annual average daily doses calculated for each exposure due to background sources. Table 7.46 shows that the inhalation pathway is the primary exposure route with doses at least one order of magnitude higher than those received from ingestion or dermal contact for all age groups except the infant. For the infant, the dose received from ingestion of human milk from occupationally exposed mothers increases the total dose from the food and water pathway to that approximately equal to that from inhalation. Of the inhalation sources of exposures, indoor air contributes the most to overall inhalation doses. These findings are illustrated on Figures 7.5 and 7.6, which show doses from background exposures to toluene from typical and high-end urban exposures.

Age-specific doses for chronic exposures to toluene from specific sources are presented on Table 7.47. From this table, it can be seen that for children up to 13 yrs old exposure to ETS is the only chronic source specific exposure that was identified, and exposures are approximately 10-fold lower than that from typical urban background. For the teenagers and adults, ETS adds insignificantly to background doses, as does exposure to toluene from refueling. However, on a chronic basis exposure to toluene from mainstream smoke adds a dose similar to that of high-end background exposures. These findings are graphically presented on Figure 7.7, which show the comparison of the total typical urban background dose for children to that received from other chronic-type exposures to tobacco smoke, and fuel-related sources.

As described in Section 8, for the purposes of the risk assessment, the inhalation exposures have also been characterized as 24-hr time weighted averages for both rural and urban settings; these are presented in Table 7.48.

Table 7.46: Summary of Age-Specific Toluene Doses (mg/kg-day)

Scenario	Age Group						
	0-6 weeks old	7-12 weeks old	13 weeks - 12 months old	1-5 year old	6-13 year old	14-18 year old	female 19-35 year old
BACKGROUND DOSES - OUTDOOR AIR							
Ambient Outdoor Air - School Day							
Rural - Typical	--	--	--	1.5E-05	1.0E-05	6.5E-06	--
Rural - Upper Bound	--	--	--	3.0E-05	2.1E-05	1.3E-05	--
Urban - Typical	--	--	--	3.8E-05	2.6E-05	1.7E-05	--
Urban - Upper Bound	--	--	--	9.6E-05	6.6E-05	4.2E-05	--
Ambient Outdoor Air - Non-School Day							
Rural - Typical	5.2E-05	3.4E-05	2.2E-05	2.2E-05	1.1E-05	8.0E-06	7.9E-06
Rural - Upper Bound	1.1E-04	7.1E-05	4.6E-05	4.6E-05	2.4E-05	1.7E-05	1.6E-05
Urban - Typical	1.3E-04	8.9E-05	5.7E-05	5.7E-05	2.9E-05	2.1E-05	2.0E-05
Urban - Upper Bound	3.4E-04	2.3E-04	1.5E-04	1.5E-04	7.5E-05	5.3E-05	5.2E-05
Ambient Outdoor Air - Total							
Rural - Typical	5.2E-05	3.4E-05	2.2E-05	3.7E-05	2.1E-05	1.4E-05	7.9E-06
Rural - Upper Bound	1.1E-04	7.1E-05	4.6E-05	7.6E-05	4.4E-05	3.0E-05	1.6E-05
Urban - Typical	1.3E-04	8.9E-05	5.7E-05	9.4E-05	5.5E-05	3.7E-05	2.0E-05
Urban - Upper Bound	3.4E-04	2.3E-04	1.5E-04	2.4E-04	1.4E-04	9.5E-05	5.2E-05
BACKGROUND DOSES - INDOOR AIR							
In Home - School Day							
Rural - Typical	--	--	--	1.9E-03	1.1E-03	7.2E-04	--
Rural - Upper Bound	--	--	--	6.8E-03	4.1E-03	2.7E-03	--
Urban - Typical	--	--	--	2.1E-03	1.3E-03	8.3E-04	--
Urban - Upper Bound	--	--	--	7.6E-03	4.6E-03	3.0E-03	--
In Home - Non-School Day							
Rural - Typical	1.2E-02	7.9E-03	5.1E-03	2.1E-03	1.6E-03	1.1E-03	1.7E-03
Rural - Upper Bound	4.3E-02	2.9E-02	1.9E-02	7.7E-03	5.9E-03	3.9E-03	6.1E-03
Urban - Typical	1.4E-02	9.0E-03	5.8E-03	2.4E-03	1.8E-03	1.2E-03	1.9E-03
Urban - Upper Bound	4.9E-02	3.2E-02	2.1E-02	8.6E-03	6.6E-03	4.4E-03	6.9E-03
In Home - Total							
Rural - Typical	1.2E-02	7.9E-03	5.1E-03	4.0E-03	2.7E-03	1.8E-03	1.7E-03
Rural - Upper Bound	4.3E-02	2.9E-02	1.9E-02	1.5E-02	1.0E-02	6.5E-03	6.1E-03
Urban - Typical	1.4E-02	9.0E-03	5.8E-03	4.5E-03	3.1E-03	2.0E-03	1.9E-03
Urban - Upper Bound	4.9E-02	3.2E-02	2.1E-02	1.6E-02	1.1E-02	7.3E-03	6.9E-03
In School							
Typical	--	--	--	5.6E-05	8.4E-05	6.1E-05	--
Upper Bound	--	--	--	9.4E-04	1.4E-03	1.0E-03	--
In-Vehicle							
Typical	3.1E-04	2.1E-04	1.3E-04	1.2E-04	7.1E-05	6.7E-05	6.3E-05

Table 7.46 - Continued

Scenario	0-6 weeks old	7-12 weeks old	13 weeks - 12 months old	1-5 year old	6-13 year old	14-18 year old	female 19-35 year old
BACKGROUND DOSES - FOOD & WATER							
Food & Tap Water Ingestion							
Typical	5.8E-05	3.9E-05	1.7E-04	4.5E-04	2.6E-04	1.5E-04	1.3E-04
Upper Bound	1.2E-04	7.7E-05	3.7E-04	7.8E-04	4.8E-04	3.5E-04	2.6E-04
Human Milk							
Non-Occupational - Typical	7.0E-05	4.7E-05	3.0E-05	--	--	--	--
Non-Occupational - Upper Bound	2.5E-04	1.6E-04	1.1E-04	--	--	--	--
Occupational - Typical	7.0E-05	2.0E-02	1.3E-02	--	--	--	--
Occupational - Upper Bound	2.5E-04	7.4E-02	4.8E-02	--	--	--	--
Showering - Dermal							
Typical	2.3E-06	1.5E-06	9.7E-07	2.0E-06	1.3E-06	9.8E-07	1.0E-06
Upper Bound	5.0E-06	3.3E-06	2.1E-06	3.8E-06	2.7E-06	2.3E-06	2.6E-06
Showering - Inhalation							
Typical	1.4E-05	9.2E-06	5.9E-06	1.2E-05	1.5E-06	1.0E-06	7.4E-07
Upper Bound	7.2E-05	4.8E-05	3.1E-05	3.9E-05	6.5E-06	4.7E-06	4.3E-06
BACKGROUND DOSES - SUM OF AMBIENT AIR, INDOOR AIR, FOOD & WATER							
Inhalation Pathway							
Rural - Typical	1.2E-02	8.2E-03	5.2E-03	4.2E-03	2.9E-03	1.9E-03	1.7E-03
Rural - Upper Bound	4.4E-02	2.9E-02	1.9E-02	1.6E-02	1.2E-02	7.7E-03	6.2E-03
Urban - Typical	1.4E-02	9.3E-03	6.0E-03	4.8E-03	3.3E-03	2.2E-03	2.0E-03
Urban - Upper Bound	4.9E-02	3.3E-02	2.1E-02	1.8E-02	1.3E-02	8.5E-03	7.0E-03
Ingestion Pathway							
Typical	7.0E-05	4.7E-05	2.0E-04	4.5E-04	2.6E-04	1.5E-04	1.3E-04
Upper Bound	2.5E-04	1.6E-04	4.7E-04	7.8E-04	4.8E-04	3.5E-04	2.6E-04
Occupational - Typical	7.0E-05	2.0E-02	1.3E-02	--	--	--	--
Occupational - Upper Bound	2.5E-04	7.4E-02	4.8E-02	--	--	--	--
Dermal Pathway							
Typical	2.3E-06	1.5E-06	9.7E-07	1.1E-06	1.3E-06	9.8E-07	1.0E-06
Upper Bound	5.0E-06	3.3E-06	2.1E-06	2.5E-06	2.7E-06	2.3E-06	2.6E-06

Table 7.47. Summary of Chronic Source Specific Doses (mg/kg-d)

	Age Group						
Scenario	0-6 weeks old	7-12 weeks old	13 weeks - 12 months old	1-5 year old	6-13 year old	14-18 year old	female 19-35 year old
SOURCE SPECIFIC DOSES							
Tobacco Smoke							
ETS (nonsmoker's dose)	9.5E-04	6.3E-04	4.1E-04	3.4E-04	2.1E-04	1.3E-04	1.4E-04
Mainstream (smoker's dose)	--	--	--	--	--	5.7E-03	1.1E-02
Refueling							
Typical	--	--	--	--	--	3.5E-05	2.9E-05
Upper Bound	--	--	--	--	--	4.1E-04	3.3E-04

Figure 7.5: Contribution of Various Ambient Sources to Typical Total Background Dose

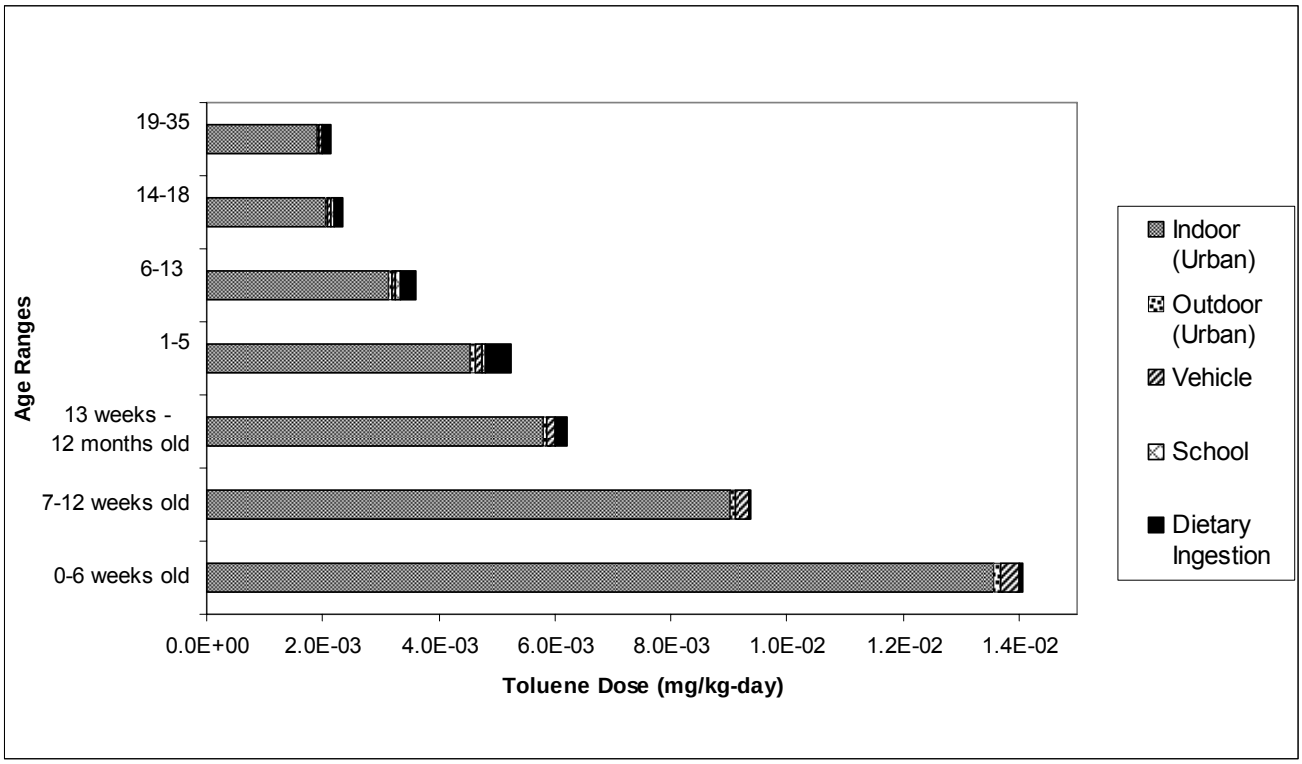
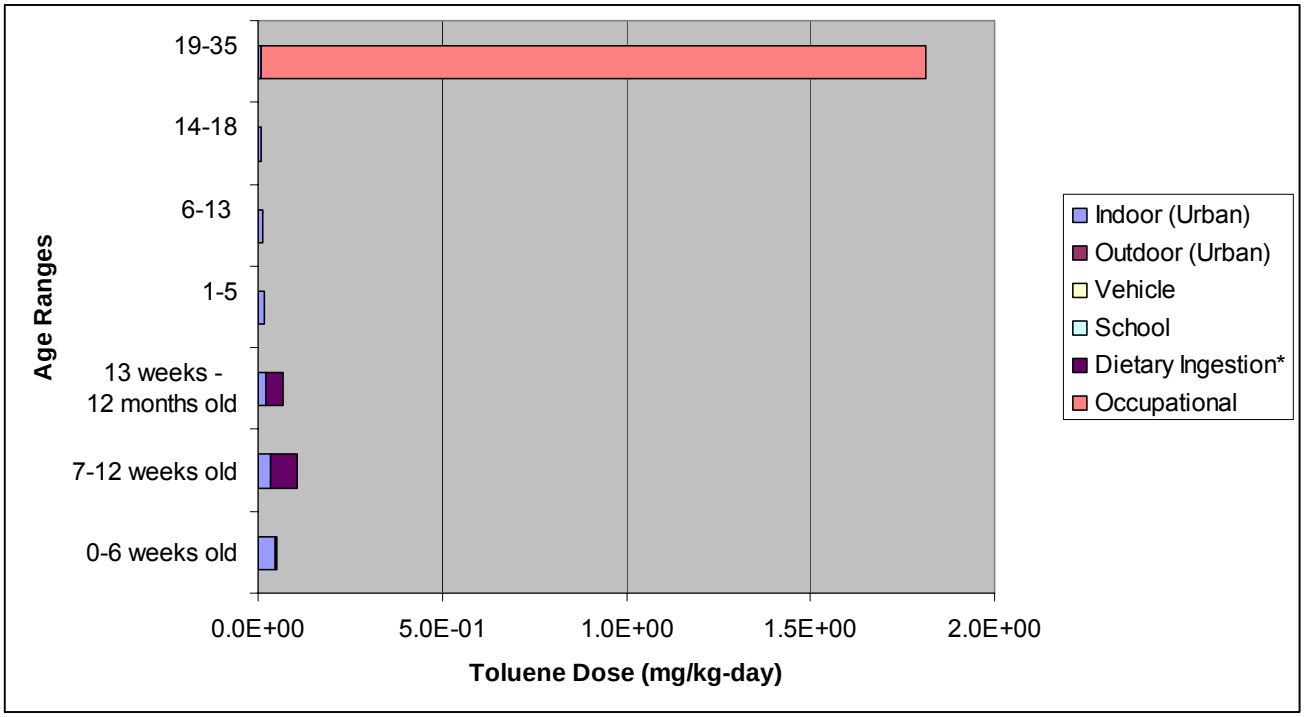


Figure 7.6: Contribution of Various Ambient Sources to High-End Total Background Dose



*The doses for the 7-12 week old and 13 week -12 month old includes exposure from human milk of a high-end occupationally exposed mother.

Figure 7.7: Comparison of Doses from Typical Urban Background (Ambient) Sources to Typical Specific Sources

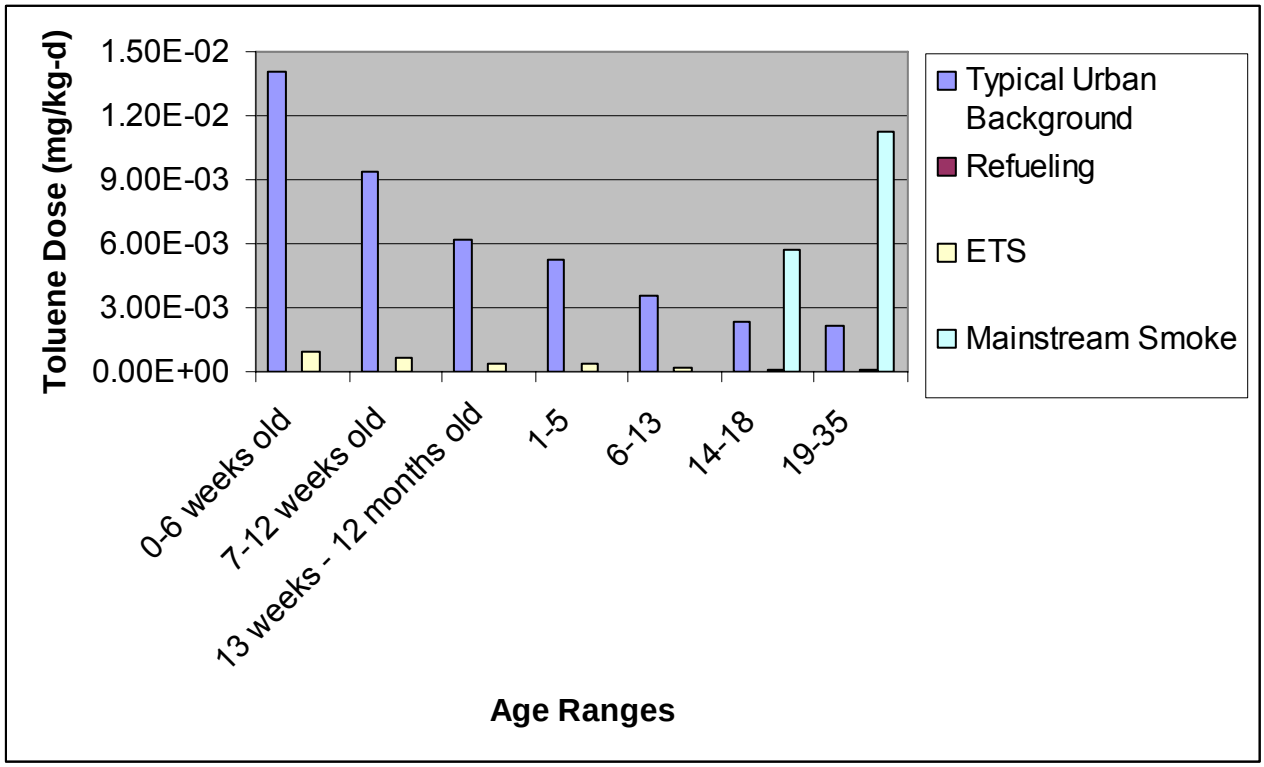


Table 7.48 Typical and High-End Time Weighted Average Toluene Exposures

	Rural Setting		Urban Setting	
Age Group	Typical 24-hr TWA (µg/m3)	High-End 24-hr TWA (µg/m3)	Typical 24-hr TWA (µg/m3)	High-End 24-hr TWA (µg/m3)
0-6 weeks	19	69	22	78
7-12 weeks	19	69	22	78
13 weeks – 12 months	19	69	22	78
1 to 5 years old	17	65	20	73
6 to 13 years old	17	66	19	74
14 to 18 years old	16	65	19	72
Female 19 to 35 years old *	19	69	22	78

* Non-occupationally exposed

8. Risk Assessment

Risk assessment is the integration of the findings of the hazard assessment and the exposure assessment to provide numerical characterizations of risk. As discussed in the hazard assessment (Section 6), toluene may pose both acute and chronic health effects. This risk assessment presents an evaluation of the potential for the occurrence of these effects in the exposed populations. The chronic effects of toluene occur at lower doses than the acute effects; however, they require that the exposures persist over much longer periods of time than acute exposures.

The potential health risks associated with background exposures to toluene from environmental sources were evaluated in two ways:

- The first method used a conventional risk assessment based on external exposure estimates using the exposure concentrations and annual average daily doses presented in Section 7. These were compared to EPA's chronic health benchmarks (Reference Concentration and Reference Dose) to estimate hazard indices and hazard quotients according to the methodology detailed below.

- The second method used PBPK models to predict blood levels associated with chronic exposure at EPA's chronic health benchmarks. Age-specific PBPK models were then used to predict blood levels associated with the exposure scenarios estimated in Section 7. The scenario-specific modeled blood levels (accounting for inhalation and ingestion exposures) were then compared to the blood levels associated with exposure at the EPA chronic health benchmarks (Reference Concentration and Reference Dose). This procedure is discussed in more detail below.

Acute exposures to toluene through specific product usage scenarios were assessed separately. The general EPA guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure (EPA, 1998b). Therefore, the short-term episodic exposures such as those associated with the consumer products, were evaluated in terms of the potential risks from the acute effects of toluene using the peak 4-hour exposure concentrations. This approach is appropriate for acute exposures for volatile solvents because concentration plays a stronger role in determining the strength of the effects than does time (Bushnell, 1987; Boyes 2005). Acute health effects appear to be more closely related to momentary and maximum exposures rather than cumulative exposure. Therefore, short term exposures were compared against acute health benchmarks such as the Acute Exposure Guideline Levels (AEGLs) established by EPA.

This risk assessment is organized so that the following sections provide: (1) a brief overview of the toluene hazard assessment information and explanation of relevant health benchmarks; (2) a description of the methodology used to conduct the quantitative risk assessment; and (3) the evaluation of the potential health risks of toluene using both the conventional approach and the PBPK-based approach, from both chronic ambient exposures and short term acute exposures resulting from the use of selected consumer products. Uncertainties are also discussed, and finally, overall conclusions are presented concerning the potential for toluene exposure to pose health risks to children.

8.1 Benchmarks Used to Characterize Chronic and Acute Adverse Health Effects of Toluene

This section presents a brief overview of the EPA IRIS chronic exposure benchmarks and PBPK modeling of toluene blood concentration profiles in the studies underlying the derivation of the RfD and RfC. Table 8.1 describes the studies, critical toxic endpoints, and uncertainty factors used in the derivation of the current toxicity criteria.

Table 8.1
Summary of IRIS RfD and RfC derivation

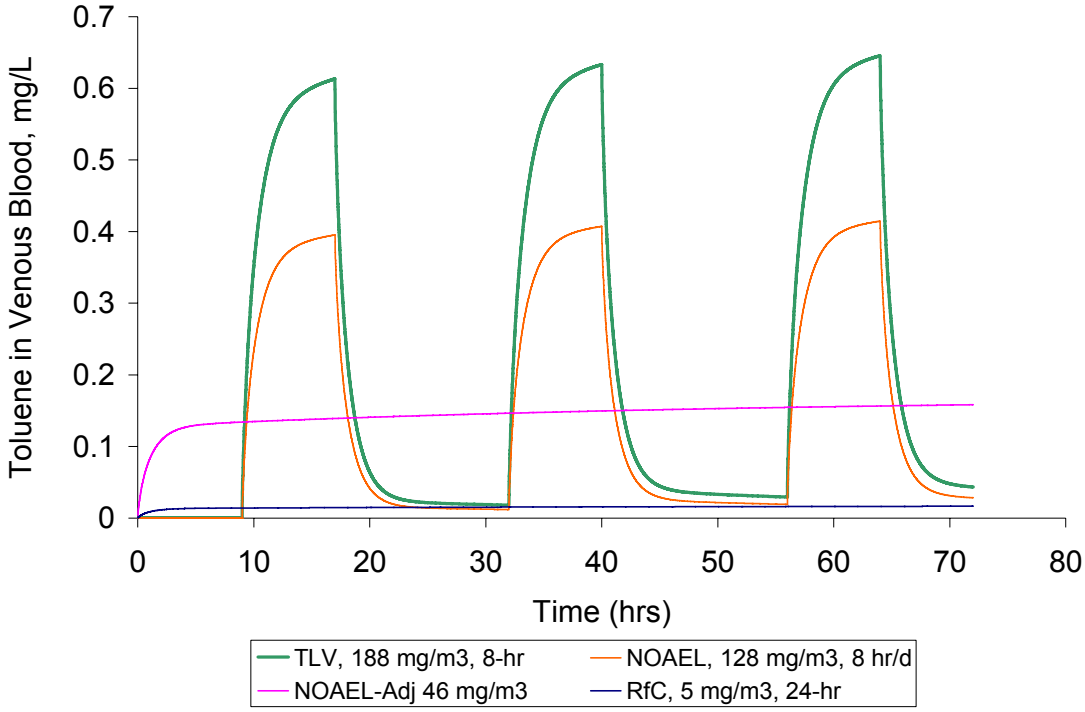
Criteria	Study Description	Critical Endpoint and Dose	Uncertainty Factors	Value
RfC	Multiple studies of humans occupationally exposed populations	Neurological effects NOAEL (average): 34 ppm (128 mg/m^3) NOAEL (adjusted for 24-hr, 7 d/wk exposure): 46 mg/m^3	10 – total 10 – interindividual	5 mg/m^3
RfD	Rat gavage, 13 wk (NTP, 1990) NOAEL: 223 mg/kg-d LOAEL: 446 mg/kg-d	Kidney weight changes as a precursor to kidney toxicity at higher doses BMDL: 228 mg/kg-d	3000 – total 10 – interspecies 10 – interindividual 10 – subchronic to chronic 3 – database uncertainties	0.08 mg/kg-d

8.1.1 IRIS RfC

The RfC for toluene derived by IRIS is based on evaluation of potential neurotoxicity, which appears to be the most sensitive endpoint identified in numerous studies of long-term occupationally exposed populations (see EPA 2005 for a complete description of these studies and populations). These studies are characterized by long-term exposure with monitored air concentrations. The mechanisms underlying the observed neurotoxicity are not fully understood, but appear to be related to concentrations of the parent compound (rather than metabolites) reaching the brain (van Asperen et al., 2003; Bushnell et al., 2006). Several studies provide clear NOAEL values for all types of neurological changes including both transient and persistent effects, as well as for a wide range of other biochemical and health effect endpoints. Based on an evaluation of these studies as a group, the EPA selected an average NOAEL of 34 ppm (128 mg/m^3) as an occupational air level not associated with any adverse effects over long term exposure. Adjusting to an equivalent continuous exposure concentration from the occupational exposure schedule (multiplying by 5/7 days and 10/20 m^3/day) resulted in a NOAEL-adjusted of 46 mg/m^3. Note that this adjustment implicitly assumes that the average concentration (or area-under-the-curve) is the critical dose metric. However, it is likely that peak concentrations or time above a threshold level is as or more important

than average concentration in producing neurotoxic effects. EPA applied a 10-fold interindividual uncertainty factor to the NOAEL-adjusted concentration to derive the RfC of 5 mg/m^3. The predicted adult human blood levels associated with the NOAEL, the NOAEL-adjusted, and the RfC are presented in Figure 8.1, along with predicted blood levels from exposure at the current ACGIH TLV of 50 ppm (188 mg/m^3) on an occupational schedule for comparison.

Figure 8.1



Predicted toluene blood concentrations associated with the derivation of the RfC. The blood profiles associated with occupational exposure at the current TLV of 50 ppm (188 mg/m^3) and the IRIS-identified occupational NOAEL of 128 mg/m^3 show the characteristic work-day exposure pattern. The blood level predicted to result from steady-state exposure at the NOAEL-adjusted of 46 mg/m^3, 24 hours per day, is equivalent to an average blood level from the occupational (NOAEL) exposure pattern. The RfC-associated blood level is 10-fold lower than the blood level associated with the NOAEL-adjusted air concentration.

8.1.2 IRIS RfD

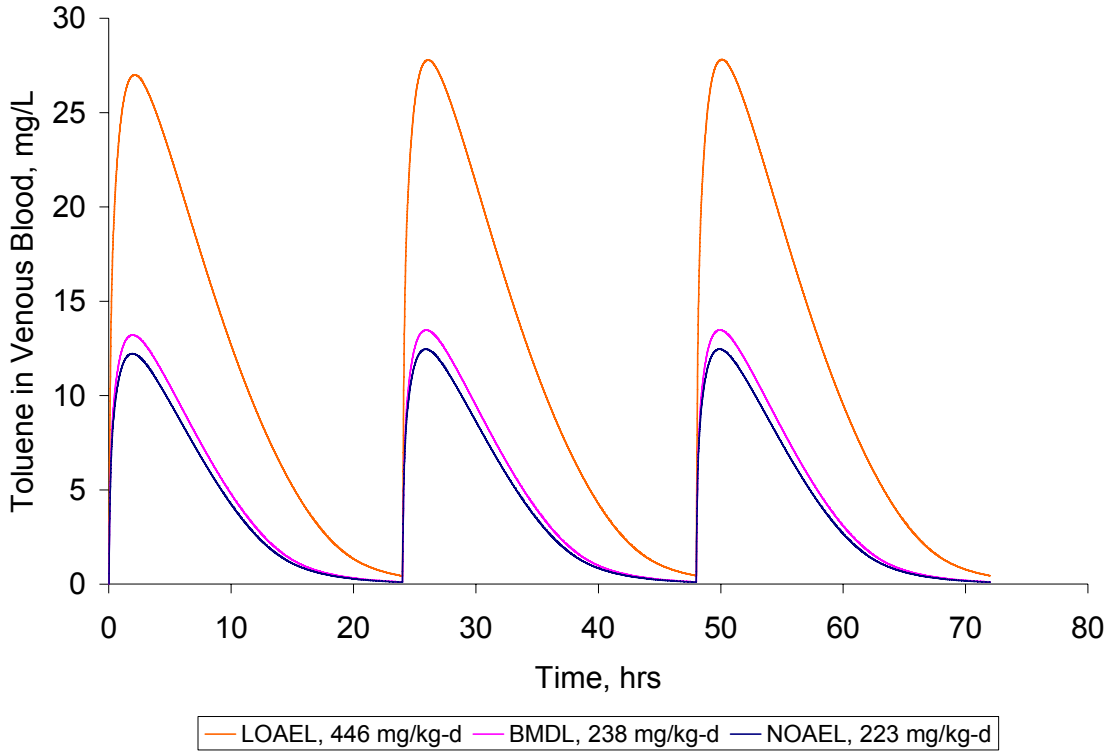
The oral RfD described by IRIS is based on a study of subchronic (13-week) administration of toluene by gavage to rats at doses of 223, 446, 893, 1786, or 3571 mg/kg-d (NTP, 1990). At the three highest doses, clear signs of kidney toxicity occurred, while at 446 mg/kg-d and above an increase in kidney weight occurred. Therefore, the NOAEL in this study was determined to be the lowest tested dose, 223 mg/kg-d. Benchmark dose modeling for kidney weight changes (considered by EPA to serve as a precursor to kidney toxicity) resulted in a BMDL of 238 mg/kg-d for a one standard deviation change in kidney weight. This dose level (similar to the NOAEL of 223 mg/kg-d) was selected as the starting point for the derivation of the RfD.

The mechanism of the renal toxicity observed in this study is unknown, but recent in vitro studies by Al-Ghamdi et al. (2003a, b) in proximal tubule cell cultures suggest that the toxicity may be attributable to benzyl alcohol, a toluene metabolite produced via CYP2E1. Al-Ghamdi et al. showed that inhibiting CYP2E1 activity prevented toxicity in cell culture following toluene exposure. Renal toxicity has also been observed in humans exposed to toluene following intentional or accidental ingestion of large amounts and following chronic inhalation abuse (Stengel et al., 1998). But, such toxicity has not been reported in occupational populations exposed to more moderate air concentrations: Stengel et al., 1998 reported a clear NOAEL of 50 ppm (188 mg/m^3) for renal function changes in a chronically exposed occupational cohort. Renal toxicity is not expected to be an oral-exposure specific effect, but rather is most likely a phenomenon associated with high peak toluene blood levels resulting in high rates of metabolism and subsequent accumulation of metabolites in the kidney.

Figure 8.2 presents the modeled toluene blood concentration profiles in rats at the NOAEL, LOAEL, and BMDL from the NTP (1990) study. These dose levels are all within the dose range of the dataset used to confirm the accuracy of the rat oral PBPK model (see Appendix D). The oral RfD was derived by application of a 3,000-fold composite uncertainty factor to the BMDL derived from this study. The composite uncertainty factor contains 10-fold inter- and intra-species uncertainty factors, a 10-fold factor for subchronic to chronic extrapolation, and a 3-fold uncertainty factor for database deficiencies including the lack of a comprehensive study of oral neurotoxicity, a 2-generation reproduction study, and a sufficiently robust immunotoxicity data set. Application of the 3,000-fold composite uncertainty factor to the BMDL of 238 mg/kg-d results in the RfD of 0.08 mg/kg-d.

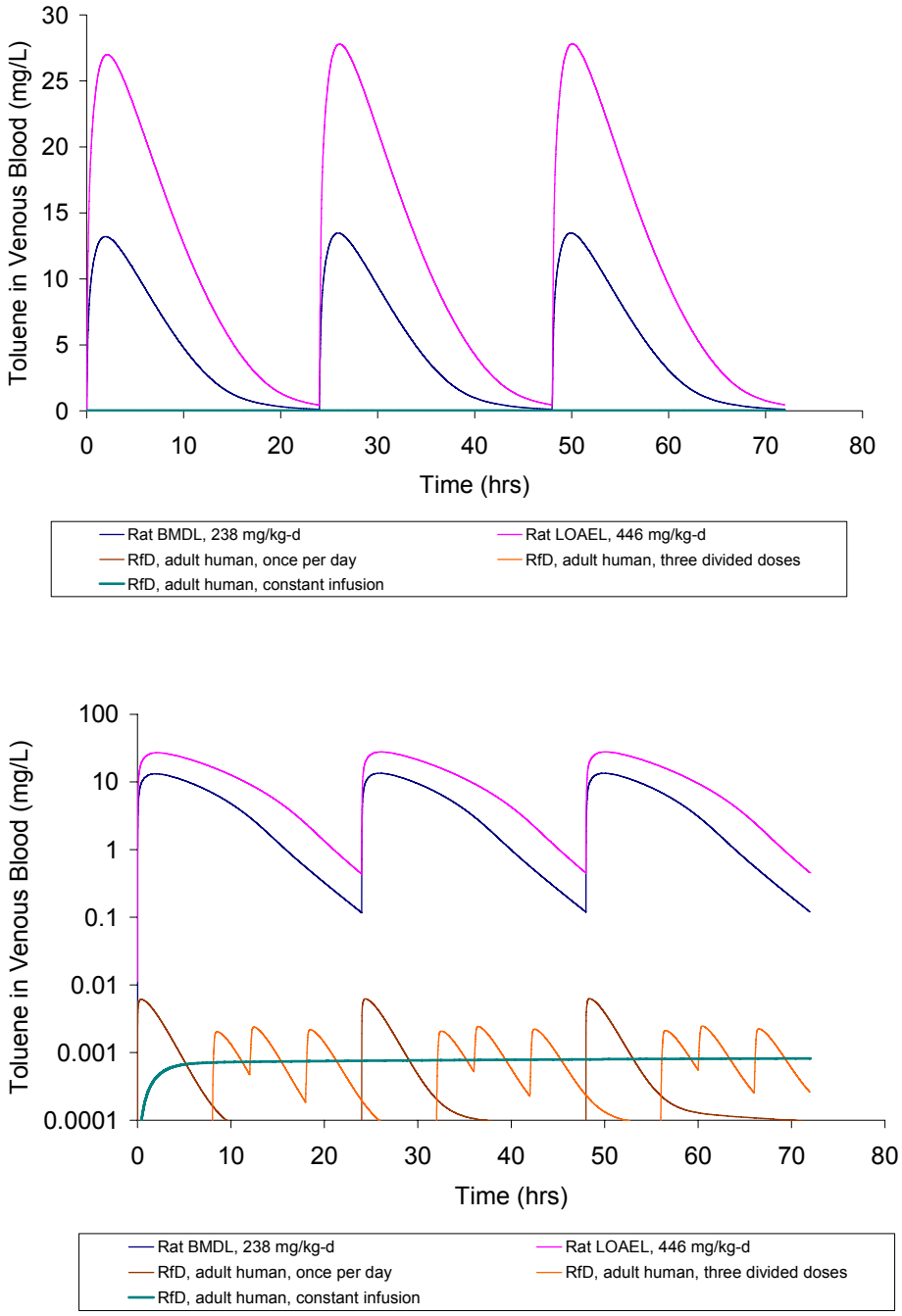
Figure 8.3 presents the modeled rat study data again, this time in conjunction with modeled human blood levels following oral exposure to toluene at the RfD under three different exposure scenarios: a single bolus oral exposure once per day (directly analogous to the rodent bioassay dosing regimen), three oral exposures per day (consistent with intake in water or food during meal times), or via a theoretical continuous infusion (resulting in a constant average blood level associated with exposure at the RfD). The highest transient blood concentration predicted in humans exposed at the RfD in a bolus dose is approximately 2200-fold lower than the corresponding peak blood toluene concentrations predicted for the rat gavage study with oral exposures at the BMDL.

Figure 8.2



Modeled toluene blood concentrations in rats from the NTP (1990) 13-wk gavage study, which serves as the basis for the IRIS oral RfD, at the NOAEL, BMDL, and LOAEL from the study.

Figure 8.3



Linear (top) and log scale (bottom) presentations of predicted toluene blood concentration profiles for the rat gavage study LOAEL and BMDL dosing and for three variations on adult human exposure at the RfD: a single bolus exposure, three divided doses, or constant infusion. On the linear scale, predicted blood levels associated with human exposure scenarios cannot be seen. Plot b presents the same data on a log scale. Peak concentrations in human blood following bolus dosing at the RfD are more

than 2200-fold lower than predicted peaks in rat blood concentration at the BMDL, which was approximately the same dose as the NOAEL in the rat study.

8.1.3 Comparison of RfD- and RfC-Associated Blood Levels

According to the US EPA, the RfD and RfC designate exposure levels that are protective of human health. For toluene, both the RfC and RfD were established to protect against systemic toxicity (rather than local, route of entry effects). However, as previously discussed, the two toxicity criteria for toluene are based on substantially different types of data with significantly different uncertainty factors applied. As such, it is informative to compare the predicted blood levels associated with these two criteria and the underlying data sets.

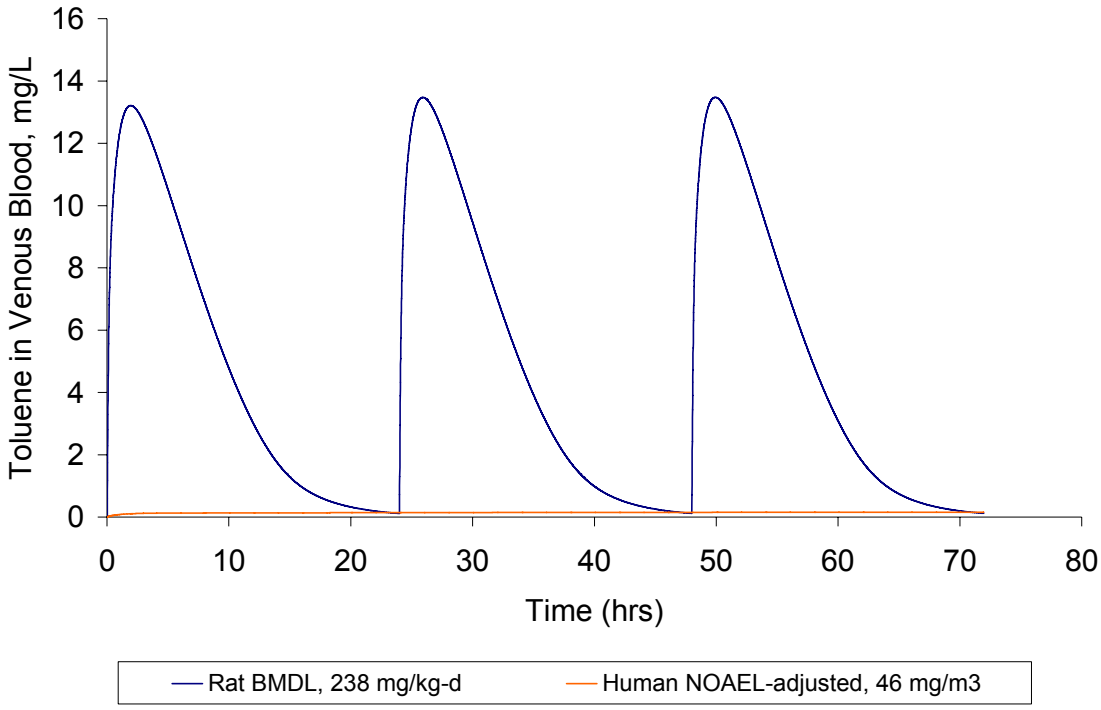
Both criteria are derived starting from no-observed-adverse-effect-levels (NOAELs) or the equivalent, a lower bound on a benchmark dose (BMDL). The RfC is based on a NOAEL-adjusted (46 mg/m^3) for neurotoxicity from human data, while the RfD is based on the BMDL (238 mg/kg-d) for kidney weight changes in rats exposed by gavage. Figure 8.4 presents the predicted blood level profiles associated with these exposure levels. The steady-state blood concentration associated with exposure at the inhalation NOAEL-adjusted level is in general far lower than the modeled blood levels predicted for the rodent study, approximately 2 orders of magnitude lower than the peak blood concentrations predicted from the gavage exposure. Because these are both exposure levels associated with no adverse effects, the human inhalation data-based value appears to be a far more conservative value.

In contrast, the modeled blood levels in humans after exposure at the RfC and at the RfD show the opposite pattern. Oral exposure to the RfD under both a bolus dose scenario and under a more realistic scenario of three divided doses results in predicted blood levels that are lower than those resulting from exposure at the RfC (Figure 8.5). Exposures at the RfD under a variety of exposure scenarios all result in peak blood levels below, but within an order of magnitude of, the blood level associated with the RfC in adults. The peak concentrations associated with the bolus and divided doses are approximately 50% and 15% of the RfC-associated blood level, respectively. In this comparison, the RfD appears to be the more conservative of the two toxicity criteria.

Comparison of Figures 8.4 and 8.5 illustrate the key conclusion regarding the relative exposures described by the RfC and the RfD: the lower blood level associated with the RfD does not reflect greater toxicity for the oral route and renal toxicity endpoint, but rather reflects the greater uncertainty in the derivation of this toxicity value compared to the RfC. The RfD is based on subchronic animal data from a gavage study with application of a large composite uncertainty factor, while the RfC is based on a consensus NOAEL exposure level identified from a substantial group of human studies with a smaller uncertainty factor applied.

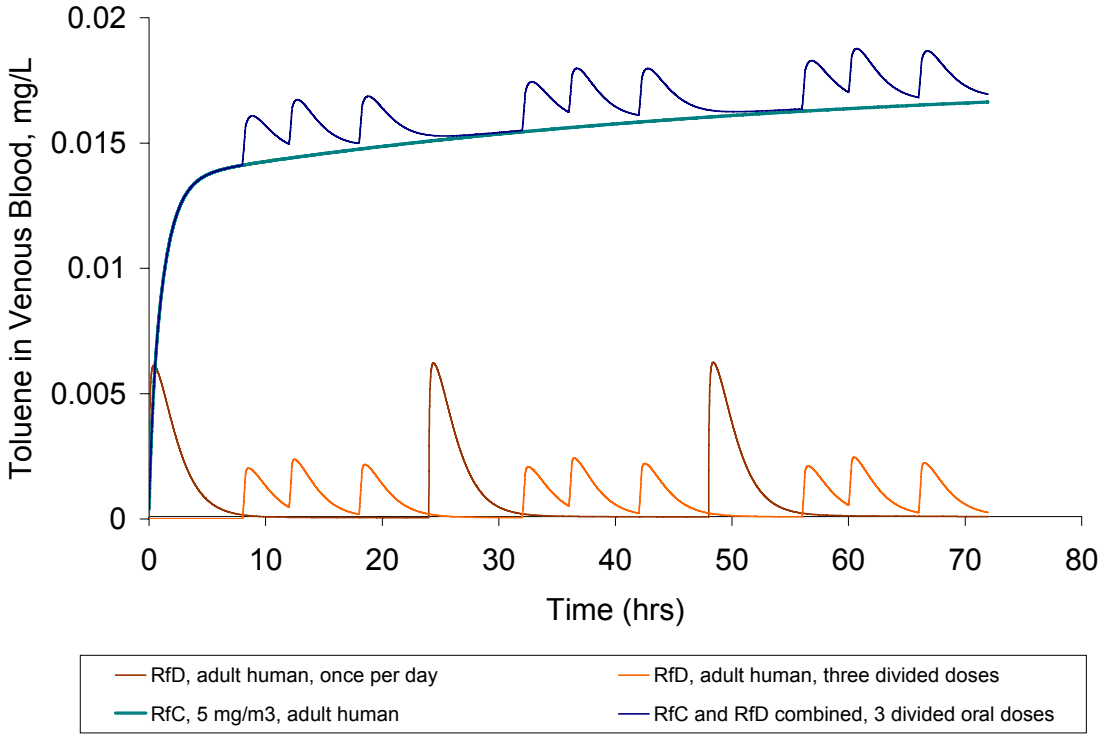
Figure 8.6 presents the predicted blood level profile associated with combined exposure to the RfC and the RfD (under a realistic, but conservative, exposure profile of 3 divided doses per day at meal times) at the same time. Note that the contribution of oral exposure only marginally increases the blood levels associated with the RfC.

Figure 8.4



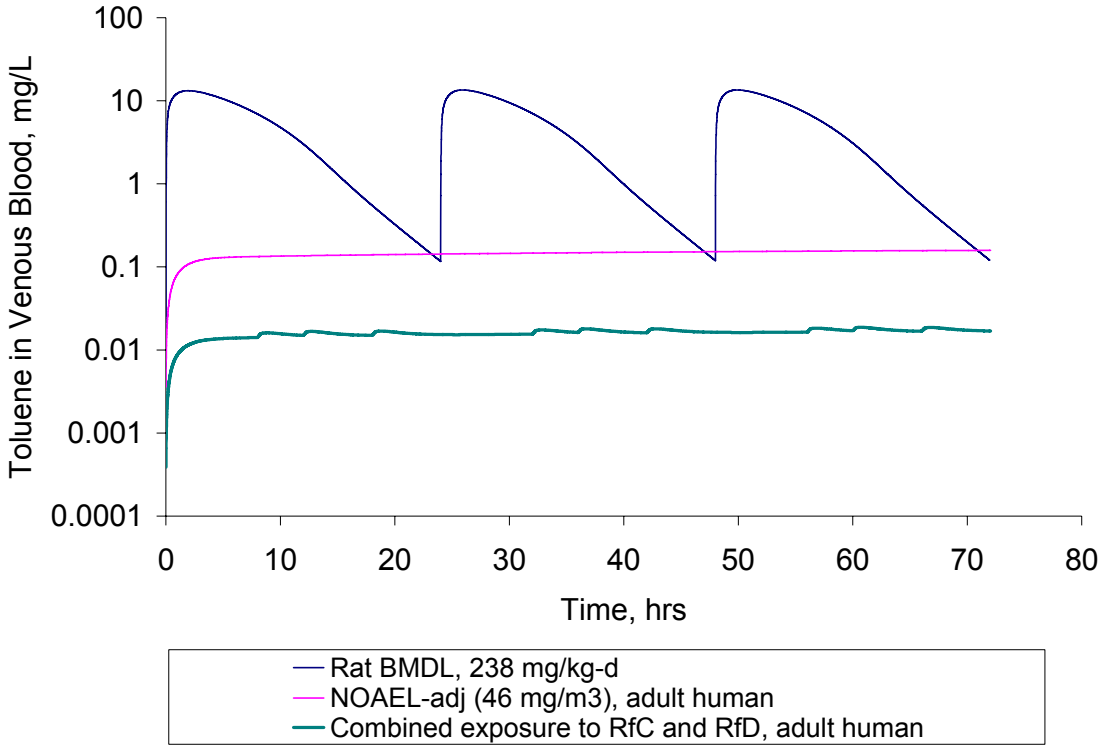
Comparison of predicted toluene blood levels in studies underlying the RfD and RfC (linear scale). The rat BMDL was nearly equivalent to the NOAEL dose in the NTP (1990) bioassay. The blood levels predicted for the NOAEL-adjusted exposure concentration of 46 mg/m^3 represents the average blood levels associated with exposures identified as clear NOAELs in several occupational studies of workers with long-term, well-characterized exposures to toluene vapor.

Figure 8.5



Predicted blood levels associated with exposure at the RfC, RfD (under two dosing scenarios), and combined inhalation and oral exposure at the RfC and RfD (three divided doses).

Figure 8.6



Log scale presentation of predicted blood levels associated with combined exposure to the RfC and RfD (three divided doses per day) compared to the blood levels predicted for exposures underlying the two criteria: the occupational NOAEL-adjusted and the BMDL from the rat gavage study.

As noted above, the toxic endpoints underlying the derivation of the RfD and RfC differ. The concentration of parent compound in blood is likely to be a reasonable surrogate for the relevant dose to the brain responsible for the observed neurological effects. However, the renal toxicity observed in the rat gavage study and in humans following poisoning ingestion incidents and inhalation abuse scenarios may be related to production of a metabolite catalyzed by CYP2E1 (EPA, 2005), which is the major metabolizing enzyme for toluene. The PBPK models can also be used to evaluate the rate of metabolism of toluene to provide an assessment of this potentially relevant internal dose metric for renal toxicity across exposure scenarios as well.

The PBPK model estimates a rate of metabolism for toluene using a Michaelis-Menten equation in terms of V_{max}, the maximal rate of metabolism, and K_m, the affinity constant for CYP2E1 for toluene which can be used to describe the hepatic concentration of half-maximal metabolic rate. The rate of metabolism in mg/hr achieved for any given exposure scenario in humans and rats can be estimated from the models and normalized to bodyweight$^{3/4}$ or to liver tissue weight for comparison across species. Table 8.2 reports the estimated maximal metabolic rates for the various scenarios underlying the RfD and RfC derivations as described above.

Table 8.2
Maximal metabolic rates (mg/hr-kg $BW^{3/4}$ or mg/hr-kg liver) associated with dosing regimens in studies underlying the RfD and RfC and for human exposure at these criteria levels

Dose Description	Maximal achieved metabolic rate	
	mg/hr-$kg^{3/4}$	mg/hr-kg liver
Rat gavage LOAEL, 446 mg/kg-d	4.73	136.54
Rat gavage BMDL, 238 mg/kg-d	4.66	134.55
Human occupational NOAEL, 128 mg/m^3, 8 h/d	1.29	17.76
Human occupational NOAEL-adj., 46 mg/m^3, 24 h/d	0.58	7.25
Human RfC, 5 mg/m^3, 24 hr/d	0.06	0.8
Human RfD, bolus dose, 0.08 mg/kg-d	0.11	1.47
Human RfD, three divided doses	0.04	0.54
Combined human exposure at the RfC and RfD, three divided doses	0.10	1.29

The maximal metabolic rates associated with human exposure at the RfD, RfC, or combined oral and inhalation exposure are approximately 50 to 100 times lower than those at the BMDL (essentially the NOAEL for renal effects) in the rat gavage study. Exposure at the RfC, although it produces somewhat higher blood levels than exposures at the RfD, actually results in a lower maximal metabolic rate than the RfD under the bolus dosing scenario due to the more gradual increment in dosing to the liver.

We suggest that the most appropriate benchmark for assessment of modeled and measured blood concentrations is the RfC-associated blood level. The scientific bases for this choice follow:

- The RfD is based on a subchronic rat gavage study. As a result, the BMDL from this study was reduced by the maximum composite uncertainty factor typically used in RfD derivations, 3,000-fold. This magnitude of uncertainty factors results in an RfD that may be unnecessarily low, and the relatively low resulting RfD is primarily reflective of uncertainty regarding the relevance of the underlying data:

    - The endpoint, kidney weight changes is relatively subtle. Further histopathological signs of nephrotoxicity did not occur until doses approximately four times higher than the BMDL were reached.

    - The endpoint is not the most relevant endpoint in humans exposed chronically to low background levels of toluene. Although renal toxicity has been observed in lethal- and near-lethal poisoning incidents and in persons with a history of long term inhalation abuse, studies of occupationally exposed populations, which is a more relevant data set, do not report renal toxicity at exposure levels at which more subtle neurological effects are reported (Stengel et al., 1998 found a NOAEL of 50 ppm (188 mg/m^3) for renal effects among occupationally exposed humans).

        - The gavage dosing regimen used in the underlying study may be of limited relevance for predicting effects from environmental exposures that are three orders of magnitude lower.

- The RfC is based on a NOAEL from human data from a robust set of studies on populations with long-term exposure to toluene at measured air concentrations. This value is robust for several reasons:

    - The NOAEL air level was identified with the most sensitive known human responses, both transient and chronic neurological effects, taken into account.

    - Other effects, including biochemical changes potentially related to renal effects, have not been reported at similar chronic occupational exposures (Stengel et al., 1998). Although renal toxicity has been seen in more highly exposed (abuse related) populations, as noted above, it is not as sensitive as neurotoxicity.

    - A 2-generation rat inhalation study reported a clear NOAEL for both parental animals and offspring of 500 ppm (1880 mg/m^3) (Roberts et al. 2003), suggesting that any reproductive or developmental effects would not be more sensitive than the neurological effects considered in the identification of the human occupational NOAEL.

    - The NOAEL-adjusted incorporates an additional protective assumption; the neurological effects that occur at higher exposure levels are associated with average (or AUC) air levels (and resulting average blood levels) rather than peak levels experienced repeatedly during occupational exposures.

- The robust nature of the data underlying the RfC is reflected in the smaller composite uncertainty factor of 10 applied to the NOAEL-adjusted. As discussed above, differences between the blood levels associated with exposures at the RfD and RfC are primarily differences attributable to levels of uncertainty associated with the underlying data.

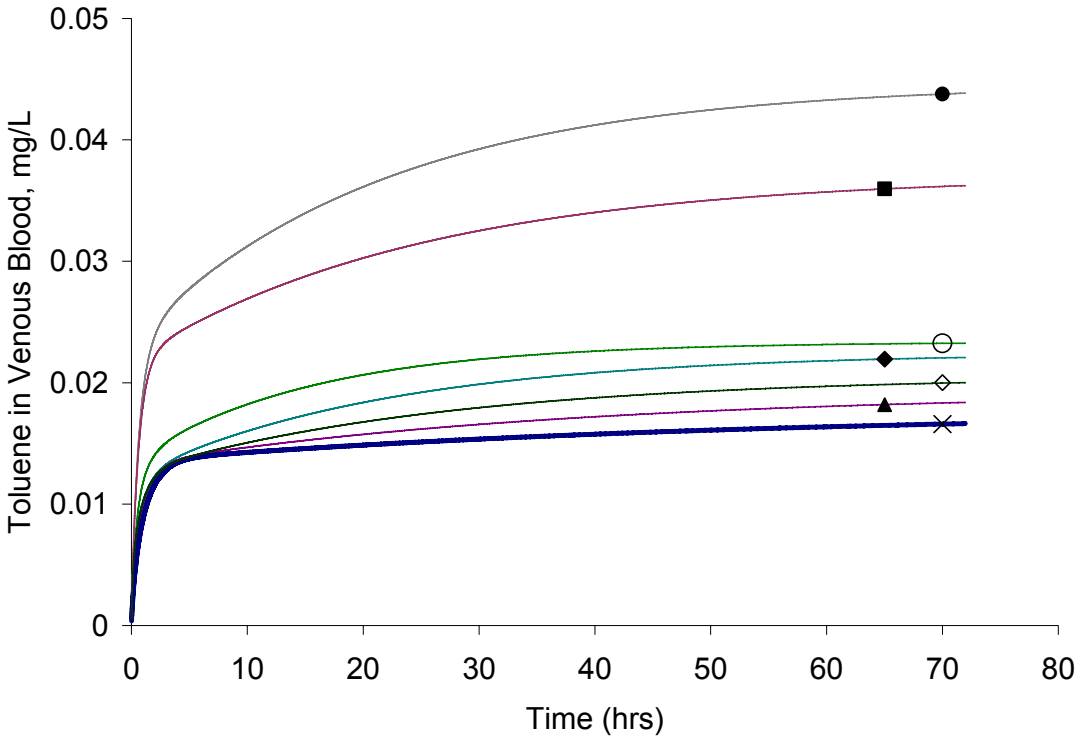
For these reasons, the blood level in adults resulting from long-term exposure at the RfC (designated here as the RfC_{blood}), approximately 17.5 µg/L (see Figure 8.5), appears to be a protective toluene blood level for the most subtle effects reported in chronically exposed humans. There is no evidence in the robust database on human exposure to toluene suggesting that lower blood levels associated with the RfD are necessary to protect even the most sensitive humans. Thus, the RfC_{blood} represents a reasonable benchmark as a safe limit for toluene in blood. If one were to rely on the studies underlying the RfD for an internal-dose based risk assessment, the most relevant dose metric would be predicted to be maximal rate of metabolism. Use of this internal dose metric in conjunction with the RfC_{blood} should provide a protective set of benchmarks for evaluating exposures using internal dose metrics.

8.1.3.1 Impact of Physiological and Metabolic Differences on Predicted Blood Levels in Children Compared to Adults

In general, physiological differences between children and adults can result in different blood level profiles following the same external exposure. This is true even if the metabolic capability is identical, due to differences in cardiac output and ventilation on a bodyweight basis, however, such differences may be small for volatile organic compounds (VOCs) (Pelekis et al., 2001). In addition, for toluene, age-related differences in metabolic capability exist. For toluene, metabolism is a major route of elimination compared to exhalation of unchanged compound and CYP2E1 is a major catalyzing enzyme responsible for metabolism (EPA, 2005). Hepatic CYP2E1 protein concentration is very low in neonates and young infants, but increases through infancy and childhood (Johnsrud et al., 2003). The available quantitative information on age-related differences in physiology and ontogeny of CYP2E1 protein was analyzed and incorporated into a toluene PBPK model by Nong et al. (2006) for a variety of age groups. The PBPK model developed by Nong et al. (2006) was implemented here for neonates, young infants, older infants, young children, older children, and adolescents (see Appendix D). These models provide an indication of the differences in blood levels of toluene or rate of toluene metabolism in children of varying ages compared to adults that may be expected for the same external exposure profiles.

Figure 8.7 shows the predicted blood levels associated with continuous inhalation exposure at the RfC in infants, children, and adults. Predicted steady-state blood concentrations in neonates are approximately 3 times higher than those in adults, a magnitude of divergence consistent with the interindividual pharmacokinetic uncertainty factor incorporated in the RfC derivation (Dorne and Renwick, 2005). Predicted blood concentrations in other age groups are within a factor of 2 of predicted levels in adults.

Figure 8.7



Predicted toluene blood concentrations (mg/L) in neonates (●), young infants (■), older infants (○), children 1-5 yr (◆), children 6-11 yrs (◇), adolescents 12-17 yrs (▲), and adults (×) resulting from continuous exposure at the RfC. Models as reported by Nong et al. (2006) account for age-related differences in hepatic CYP2E1 protein concentration as well as age-specific physiological parameters.

The low concentrations of hepatic CYP2E1 protein in neonates, infants, and children results in reduced rates of toluene metabolism and contribute to the elevated blood concentrations of toluene compared to adults exposed to the same air concentrations (Table 8.3). To the extent that rate of production of metabolite is related to renal toxicity, the immature CYP2E1 capacity of infants and children may result in a decreased risk of renal toxicity compared to adults.

Table 8.3
Maximal achieved metabolic rate, mg/hr-kg$^{3/4}$ during continuous exposure at the RfC for different age groups.

Age Group	Maximal achieved metabolic rate, mg/hr-kg$^{3/4}$
Adult	0.06
Adolescent, 14-18 yrs	0.06
Child, 6-13 yrs	0.05
Child, 1-5 yrs	0.05
Older infant, 13 wks – 12 m	0.04
Young infant, 7-12 wks	0.04
Neonate, <6wks	0.03

Based on these assessments, the known physiological and metabolic differences of infants and children compared to adults results in increased blood levels of toluene from the same external exposures, which could be relevant to understanding the potential risk of neurological effects. The magnitude of this difference is consistent with the magnitude typically allotted for pharmacokinetic (PK) differences in the application of the interindividual uncertainty factor (√10 attributed to PK differences). In contrast, to the extent that mechanisms of renal toxicity have been postulated for toluene, the relative lack of CYP2E1 in infants and children compared to adults may provide a modest protective effect for this endpoint, although no adverse effects would be expected in either adults or children since actual metabolic rates associated with both the RfD and RfC are far below those predicted for the rat gavage dosing regimen at the NOAEL.

8.1.4 Benchmark Used to Evaluate the Acute Effects of Toluene

Acute exposure guidelines have been developed for toluene to protect against the potential development of acute, transient health effects associated with short-term high-level exposures to toluene. In the case of toluene the short-term acute exposures are overwhelmingly dominated by inhalation exposures. For this reason, an inhalation-based criterion was used to evaluate acute effects. The criterion used is the Acute Exposure Guideline Level (AEGL-1) of 200 ppm or 754 mg/m^3 (EPA, 2003a). This air concentration was identified as appropriate for use with 1-hr, 4-hr, and 8-hr exposures. AEGLs represent threshold exposure limits that the EPA believes are applicable to the general population (including children and susceptible subpopulations) for emergency periods ranging from 10 minutes to 8-hours. Three AEGL levels have been developed for the various time periods and are differentiated by varying degrees of severity of toxic effects. The AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population could experience notable discomfort, irritation or

certain asymptomatic, non-sensory effects. Importantly, the effects are not disabling and are transient and reversible upon cessation of exposure.

The AEGL-1 for toluene was derived from a human exposure study in which volunteers were exposed to toluene at concentrations ranging from 100 to 700 ppm for 20 minute periods and one 5-minute break for a total exposure time of 85 minutes (Gamberale and Hultengren, 1972). The sensitive endpoint for this study was subtle CNS effects. An interspecies uncertainty factor was not applied because the key study used human data. However, an intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals.

For the conventional risk assessment, modeled air concentrations associated with short-term acute exposures were compared to the AEGL-1 value of 200 ppm. For the PBPK-based assessment, modeled peak blood levels associated with the acute exposure scenarios were compared to the peak blood levels associated with exposure at the AEGL-1 for 4 hours.

8.2 Risk Assessment Methodology

As discussed above, two approaches were used for the risk characterization for toluene, one based on a conventional Hazard Quotient (HQ) approach and the other based on evaluation of PBPK-modeled blood levels, both of which are described in more detail here.

The first approach employed a Hazard Quotient (HQ) method where calculated chronic inhalation exposures and ingestion doses were compared to the EPA IRIS RfC and RfD, respectively, and short-term toluene exposure concentrations resulting from infrequent consumer product use or other intermittent exposures were evaluated using an HQ based on the peak 1- hr concentration and the EPA Acute Exposure Guideline Level -1 (AEGL-1) (EPA, 2003a). Hazard quotients represent the potential occurrence of adverse effects from single exposure scenarios, or single route exposures. HQs were determined for both chronic and acute exposures to toluene based on the following equation:

$$HQ = \frac{Exposure}{Health\ Benchmark}$$

where:

HQ	= Hazard quotient (unitless)
Exposure	= Annual average daily dose (mg/kg-d) or exposure concentration (mg/m^3) or short-term acute exposures (mg/m^3)
Health Benchmark	= Reference Dose (RfD), Reference Concentration (RfC), or Acute Exposure Guideline Level -1 (AEGL-1).

When a person receives concurrent doses (i.e., has exposures from more than one scenario or exposure pathway), the HQs associated with each dose are summed to give a hazard index (HI).

$$HI = HQ_1 + HQ_2 + \ldots HQ_i$$

where:

HI	= Cumulative Hazard Index (unitless)
HQ_i	= Hazard Quotient (unitless) for the i^{th} exposure route and source

A complete description of this approach is given in Risk Assessment Guidance for Superfund Sites (EPA, 1989). EPA uses a similar approach for the evaluation of air toxics[1]. Under this approach, HQs are determined for each exposure scenario (both ambient and source specific) in the assessment. Findings of values less than 1 indicate that adverse effects are unlikely to occur in even sensitive members of the exposed population. Where exposures to multiple sources occur to the same individual at the same time, the values of the relevant HQs are added to produce the HI values. If the total HI one or less than one (≤1), risks from all routes of exposure are considered negligible. It is important to note that an HI >1 is not a bright line dividing actual health hazard from non-hazard. Given that the toluene RfC is based on an average of human NOAELs (adjusted for continuous exposure) and incorporates a total uncertainty factor of 10, an HI of 2 for example, still leaves a factor of 5 between the estimated exposure and the NOAEL. This line of reasoning is the basis for the recommended risk-based prioritization scheme within the 1990 Amendments to the Clean Air Act for determining and managing residual risk after MACT implementation (Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). In this guidance, it has been recommended that if after a screening level risk assessment of an air toxic, the HI is less than 10, further action is not deemed necessary in terms of a more detailed assessment or risk control options.

The second approach used the PBPK-based approach. As discussed above, the availability of age-specific PBPK models provides the opportunity to conduct an alternative, internal dose-based risk assessment. The same exposure estimates can be modeled using the age-specific integrated oral and inhalation PBPK models to evaluate the predicted patterns of blood levels (and metabolic rates) resulting from these exposures. The modeled blood levels can then be assessed in several ways:

- Modeled blood levels can be divided by the estimated steady-state blood levels in adults exposed at the RfC to provide an estimate of the HQ.

- Maximal metabolic rates in children under the estimated exposure scenarios can also be compared to those reported above for key studies and during exposure regimens consistent with exposure at the RfD and RfC to provide another perspective on a HQ.

- Modeled blood levels can be compared to previously-reported biomonitoring data to provide a reality check on both the estimated doses and the modeling results.

[1] http://www.epa.gov/ttn/atw/nata/riskbg.html#Z7

The blood level associated with chronic exposure at the RfC (RfC_{blood}) was used as the health benchmark for evaluating chronic exposures (see above, Section 8.2).

For chronic ambient exposures, estimated exposures from both inhalation and ingestion exposure were modeled jointly for each age group for the high-end urban scenarios (those associated with the highest hazard quotients and indices for each age group) to provide an integrated evaluation of the blood levels associated with the estimated exposure levels and patterns on an age-specific basis. Both peak and average modeled blood levels resulting from the integrated exposure scenarios were compared to the RfC_{blood} to estimate hazard indices from ambient chronic exposure scenarios:

$$HI_{peak} = \frac{Modeled_{peak}}{RfC_{blood}}$$

and

$$HI_{average} = \frac{Modeled_{average}}{RfC_{blood}}$$

where:

HI_{peak} = Hazard index (unitless) for peak modeled blood exposures integrated over all oral and inhalation exposure pathways and sources

$HI_{average}$ = Hazard index (unitless) for average modeled blood exposures integrated over all oral and inhalation exposure pathways and sources

$Modeled_{peak}$ = Modeled peak blood concentration resulting from multipathway oral and inhalation exposures

$Modeled_{average}$ = Modeled average blood concentration resulting from multipathway oral and inhalation exposures

RfC_{blood} = Modeled blood level associated with chronic exposure at the Reference Concentration (RfC)

These calculated values are hazard indices rather than hazard quotients because the multiple pathways and sources of exposure are already integrated in the exposure term (modeled blood concentrations).

For acute or intermittent exposures to toluene from infrequent use of consumer products or other short term scenarios, a hazard quotient based on the AEGL-1 was calculated:

$$HQ_{acute} = \frac{Modeled_{peak}}{AEGL-1_{blood,\,peak}}$$

where:

HI_{acute} = Hazard index (unitless) for peak modeled blood exposures integrated over all oral and inhalation exposure pathways and sources

$Modeled_{peak}$ = Modeled peak blood concentration resulting from multipathway oral and inhalation exposures

$AEGL\text{-}1_{blood,\ peak}$ = Modeled peak blood level associated with exposure to the 4-hour AEGL-1 (3.5 mg/L)

The hazard index associated with the acute exposure scenarios was added to the chronic hazard indices from upper end background exposure scenarios to evaluate the additional impact of these exposures.

8.3 Risk Evaluation: Health Risks from Chronic Exposures

8.3.1 Background Sources of Exposure

8.3.1.1 Applied Dose-Based Risk Assessment

The HQs associated with the oral, dermal and inhalation doses from exposure to background sources (ambient air, food and tap water, and in-vehicle exposures) were summed to generate a total background HI. For the background evaluation, ambient air incorporates outdoor and indoor air, as well as in-vehicle exposures. In-vehicle exposures have been considered as part of a person's background exposure because, while they may be thought of as source-specific, in the general population they occur on a daily basis. The age-specific HIs for typical and high-end exposures are presented in Table 8.4. The results indicate that the largest HI is for the urban infant where the dose from human milk resulting from maternal occupational exposures results in typical and high-end HIs of 0.3 and 0.9, respectively. For all other age groups, background exposures result in HI values ranging from 0.003 to 0.02. Thus, the health risks from background exposures to toluene are negligible.

8.3.1.2 PBPK-Based Risk Assessment

For each age group, the upper end urban exposure scenarios described above encompass the highest chronic exposure levels and hazard indices. The blood level profiles associated with these scenarios (including both oral and inhalation exposures) were modeled and hazard indices calculated as described above using the PBPK-based approach. Dermal exposures and specific showering inhalation exposures were not included in these scenarios due to the low contribution of these routes to overall exposures (see Table 7.46).

Daily time patterns of exposure were also implemented in order to explore both peak and average blood levels that might be anticipated from each exposure scenario. For example, the daily breastfeeding schedule described in Chapter 7, with eight episodes each lasting 12 minutes, was implemented for all breastfeeding exposures in the modeling. Similarly, dietary and tap water intakes were divided into three 15-minute mealtime exposures. Although actual ingestion exposures would likely be divided into additional episodes during the day, the three-meals-per-day assumption will result in a more conservative (more likely to overestimate) estimate of the potential peak blood

levels associated with ingestion. Finally, inhalation exposures to home indoor, outdoor ambient, and in-vehicle air were divided into time increments consistent with typical behavior patterns and consistent with the exposure durations reported in Appendix A-14. Figure 8.8 illustrates the exposure vs. time profiles for two age groups.

Table 8.4
Chronic Risk Evaluation for Children's Background Exposures to Toluene

	Typical Exposure Hazard Quotients (HQs) and Total Hazard Indices (HIs)							Upper Bound Exposure Hazard Quotients (HQs) and Total Hazard Indices (HIs)						
Background Sources	0-6 weeks old	7-12 weeks old*	13 weeks - 12 months old*	1-5 year old	6-13 year old	14-18 year old	19-35 year old	0-6 weeks old	7-12 weeks old*	13 weeks - 12 months old*	1-5 year old	6-13 year old	14-18 year old	19-35 year old
Air														
Rural	0.004	0.004	0.004	0.003	0.003	0.003	0.004	0.01	0.01	0.01	0.013	0.013	0.013	0.014
Urban	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.02	0.02	0.02	0.015	0.015	0.014	0.015
Food & Tapwater Ingestion	0.0009	0.0006	0.003	0.006	0.003	0.002	0.002	0.003	0.002	0.006	0.010	0.006	0.004	0.003
Breast Milk - Occupational	0.0009	0.3	0.2	--	--	--	--	0.003	0.9	0.6	--	--	--	--
Showering - dermal	0.00003	0.00002	0.00001	0.00003	0.00002	0.00001	0.00001	0.0001	0.00004	0.00003	0.000048	0.000035	0.000029	0.000033
Showering - inhalation	0.000004	0.000004	0.000004	0.00001	0.000002	0.000002	0.000002	0.00002	0.00002	0.00002	0.000032	0.000007	0.000008	0.00001
Ambient HIs														
Rural	0.006	0.3	0.2	0.009	0.007	0.005	0.006	0.02	0.9	0.6	0.02	0.02	0.02	0.02
Urban	0.006	0.3	0.2	0.010	0.007	0.006	0.006	0.02	0.9	0.6	0.02	0.02	0.02	0.02

*The total HI for the 7-12 week and 13 week-12 month olds includes ingestion of breast milk from an occupationally exposed mother. The HI for the nursing infant of a non-occupationally exposed mother would be less.

Table 8.5 summarizes the modeled exposure scenarios and reports the peak and average blood toluene concentrations estimated for each scenario. These peaks and averages are compared to the blood level benchmark identified above in section 8.1, the predicted steady-state blood level associated with exposure of adults to the RfC (17.5 µg/L), to estimate a Hazard Quotient (HQ) for each exposure scenario. Figure 8.9 illustrates the modeled blood levels for infants aged 7-12 wks (the age group with the highest predicted blood levels).

Table 8.5

Selected exposure scenarios for each age group with results of PBPK modeling (peak and average blood concentrations) and estimate of hazard index based on RfC_{blood} (17.5 µg/L)

	Exposure Pathways			Toluene blood concentration, µg/L		Hazard index	
Age Group	Inhalation	Food/water	Human milk (mother's exposure scenario)	Peak	Avg.	Peak	Avg.
<6 wks	Urban, upper end	--	Upper end (non-occupational)	0.71	0.66	0.04	0.04
7-12 wks	Urban, upper end	--	Upper end (non-occupational)	0.59	0.55	0.03	0.03
			Typical (occupational)	1.16	0.93	0.07	0.05
			Upper end (occupational)	2.54	1.83	0.1	0.1
13 wks-12 m	Urban, upper end		Upper end (occupational)	0.89	0.70	0.05	0.04
1-5 yrs	Urban, upper end, non-school day	Upper end	--	0.42	0.34	0.02	0.02
6-13 yrs	Urban, upper end, non-school day	Upper end	--	0.36	0.31	0.02	0.02
14-18 yrs	Urban, upper end, non-school day	Upper end	--	0.30	0.27	0.02	0.02

Figure 8.8

Schematic showing the modeled daily exposure vs. time profiles for two age groups: A) Child, age 1-5 yr, and B) Infant, age 3-12 m.

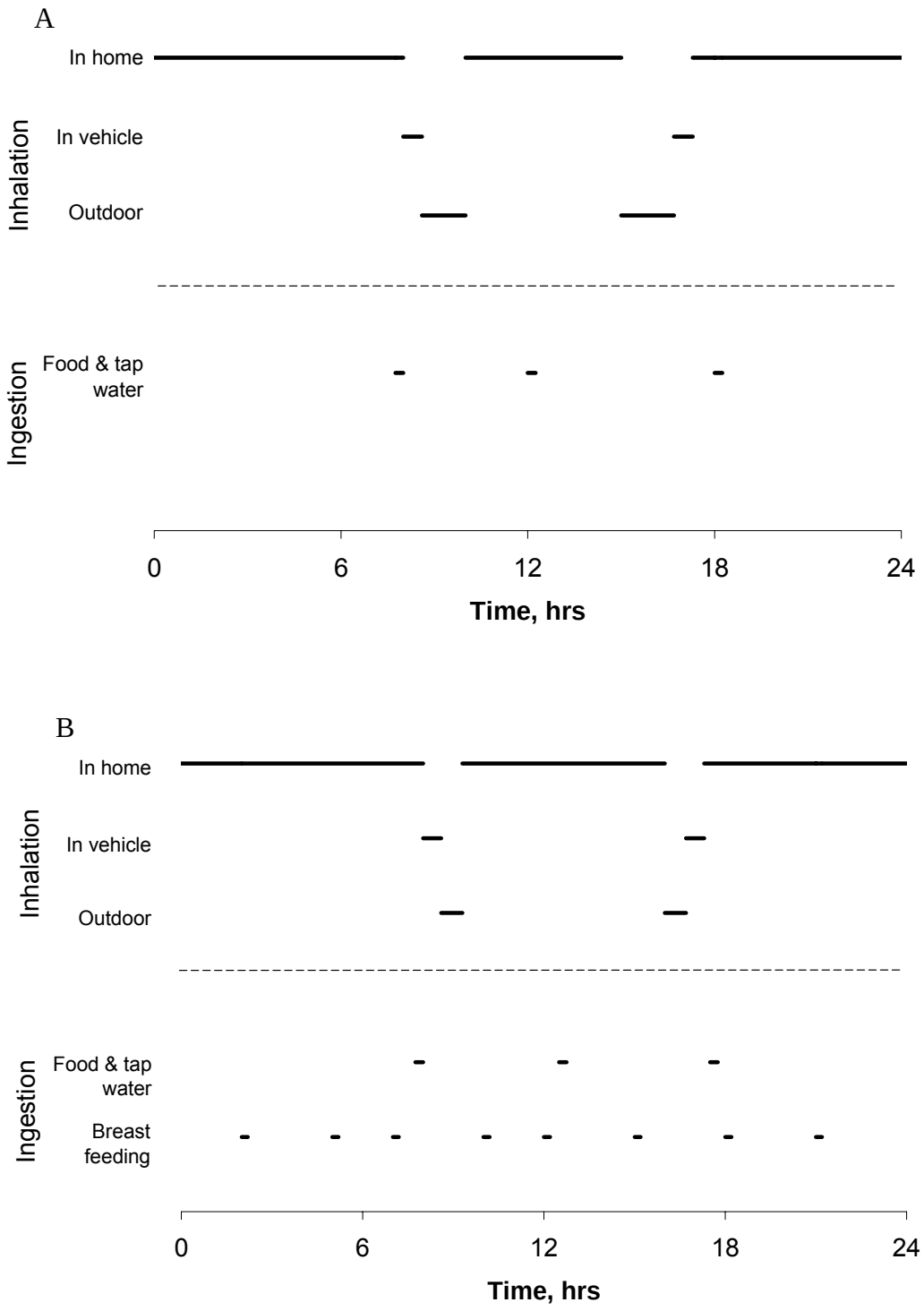
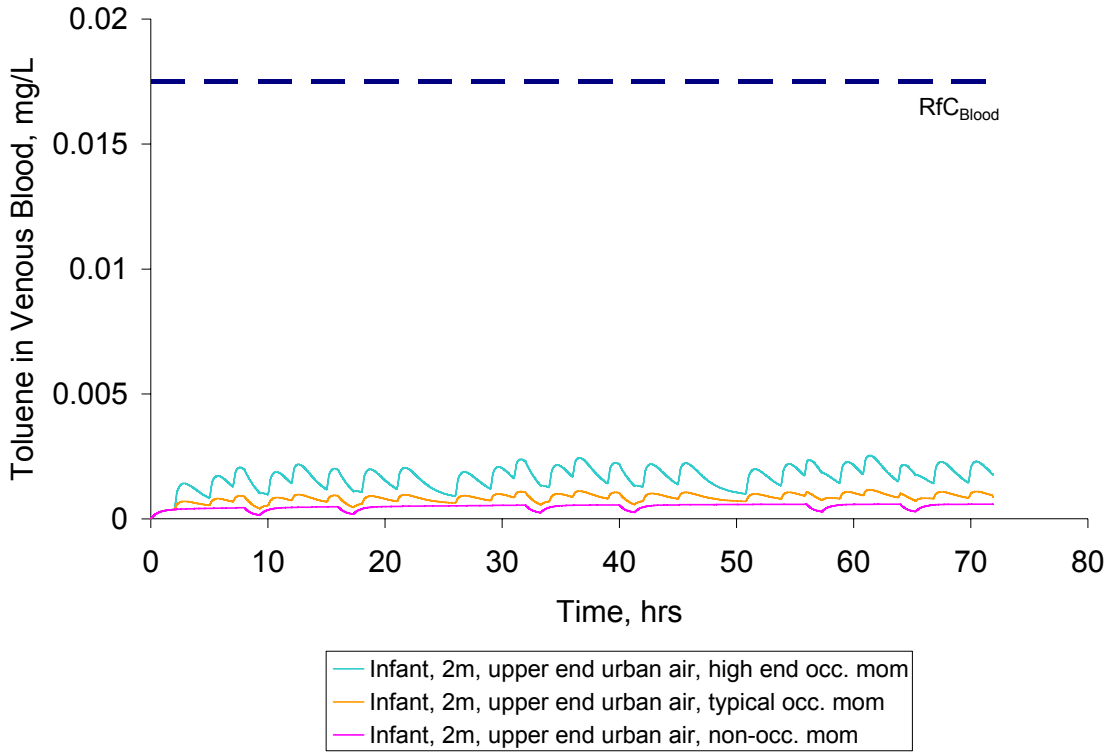


Figure 8.9



Predicted blood levels for infants, age 7-12 wks, under urban upper end air exposure conditions and assuming breastfeeding from a non-occupationally exposed mother or occupationally exposed mother (typical or high-end occupational exposure). The upper blood level is the predicted blood level for adults exposed at the RfC. As shown in Table 8.5 and illustrated above, there are significant margins between the blood level at the RfC and the highest peak and average infant blood levels.

8.3.1.3 Interpretation of Biomonitoring Data

The modeled blood levels from children can also be compared to recently reported blood level data from Sexton et al. (2005) from the Minneapolis School Health Initiative: Environment, Learning, Disease (SHIELD) study. Toluene blood levels were recorded at four time periods among elementary school age participants *in* the study: February 2000, May 2000, February 2001, and May 2001. The upper 95th percentiles of toluene blood concentrations recorded among participants (the number varied from 60 to 106 depending on the sampling time point) for those four times were 0.25, 0.20, 0.19, and 0.37 µg/L, respectively. In comparison, the predicted blood levels associated with the upper end exposure estimates for school age children in this modeling exercise were 0.31 µg/L (daily average) and 0.36 µg/L (daily peak). The median blood levels measured by Sexton et al. (2005) over the same time periods were 0.10, 0.08, 0.11, and 0.17 µg/L. The modeled blood levels associated with typical urban exposures in this evaluation were 0.08 and 0.11 (daily average and daily peak, respectively). These results suggest excellent agreement between a real-world sampling effort and the estimated upper end and typical exposures modeled here. The close agreement between these two approaches lends confidence to both the exposure estimates and modeling results reported here.

The RfC_{blood} of 17.5 µg/L can be used to put these biomonitoring results for children into a risk assessment context by calculating Hazard Quotients. Measured blood toluene levels were divided by the RfC_{blood}. Using the median blood values reported by Sexton et al. (2005), the HQ would range from approximately 0.005 to 0.01. Using the upper 95th percentiles reported by Sexton, the HQ would range from approximately 0.01 to 0.02.

8.3.2 Evaluation of the Risk of Chronic Effects from Source-Specific Exposures

Source specific exposures may occur on a frequent or infrequent basis. The source-specific exposures that are frequent or continuous in nature, such as from refueling and smoking have been evaluated for chronic health risks. Tables 8.7 and 8.8 present the HIs for refueling and smoking and the aggregate result when high-end background is considered as well.

The HIs resulting from refueling exposures range from 0.00007 to 0.0001, and the total HIs, including background toluene exposures, range from 0.006 to 0.02. Thus, as shown on Table 8.7, the addition of toluene exposures from refueling, do not appreciably change the potential health risk beyond that of typical and high-end background exposures.

Table 8.7
Chronic Hazard Evaluation of Children's Exposure to Toluene from Refueling

Source	Typical Exposure HQs[a]		High-End Exposure HQs[a]	
	14-18 year old	19-35 year old	14-18 year old	19-35 year old
Refueling	0.00007	0.00007	0.0001	0.0001
Background HI (urban)[b]	0.006	0.006	0.02	0.02
	Typical Refueling HI		**High-End Refueling HI**	
Total HI	0.006	0.006	0.02	0.02

The HIs from tobacco smoke exposures range from 0.0002 for ETS to 0.025 for mainstream smoke. The total HIs incorporating background exposures and tobacco smoke therefore range from 0.006 to 0.3. As shown on Table 8.8, the contribution of toluene from ETS to background health risks is not significant. However, for mainstream smoking, the total HI increases by a factor of 5, although the total HI is still far less than 1 when aggregated with background exposures.

Table 8.8
Chronic Hazard Evaluation of Children's Exposure to Toluene from Tobacco Smoke

Source	Tobacco Smoke Exposure HQs						
	0-6 wks	7-12 wks	3-12 months	1-5 year old	6-13 year old	14-18 year old	19-35 year old
ETS	0.0003	0.0003	0.0003	0.0003	0.0002	0.0002	0.0003
Mainstream Smoke	--	--	--	--	--	0.010	0.025
Background HI (urban)*	0.006	0.3	0.3	0.01	0.007	0.006	0.006
	Typical Tobacco Smoke HI						
Total HI	0.006	0.006	0.3	0.01	0.007	0.02	0.03

*Assumes nursing infant of an occupationally exposed mother for the age ranges 7-12 weeks and 3-12 months.

8.3.3 Evaluation of the Risk of Acute Effects from Short-Term Infrequent Sources of Exposure

The risks from the acute effects of toluene were evaluated using the short-term exposure concentrations that result during consumer product use. The estimates of concentration used in this analysis were the time weighted air concentrations for 1-hour and 8-hour exposure durations previously presented in Section 7.2.2.2 of the Exposure Assessment. The HI values for the consumer product scenarios using the applied dose methodology are presented in Tables 8.6 – 8.9.

Table 8.6 Hazard Quotients for Home Metal Parts Degreasing

Exposure Scenario		Typical Exposure HQ	High-End Exposure HQs
1-hr TWA	User	0.01	0.2
	Non-User	0.003	0.06
8-hr TWA	User	0.002	0.03
	Non-User	0.0006	0.008

Table 8.7 Hazard Quotients for Home Spray Painting Scenario

Exposure Scenario		Typical Exposure HQs	High-End Exposure HQs
1-hr TWA	User	0.2	0.4
	Non-User	0.06	0.1
8-hr TWA	User	0.05	0.08
	Non-User	0.02	0.02

Table 8.8 Hazard Quotient for Home Spray Shoe Polish Scenario

Exposure Scenario		Typical Exposure HQs	High-End Exposure HQs
1-hr TWA	User	0.01	0.2
	Non-User	0.002	0.06
8-hr TWA	User	0.002	0.03
	Non-User	0.0007	0.01

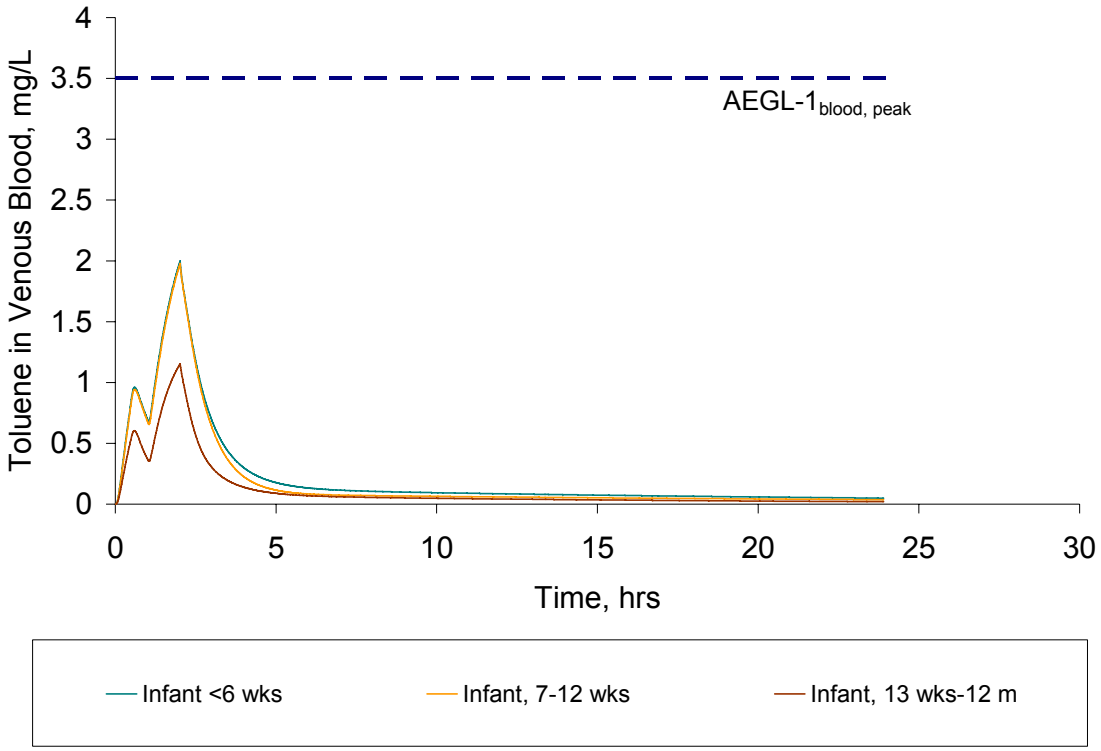
Table 8.9 Hazard Quotient for Home Mixed Media Art Scenario

Exposure Scenario		Typical Exposure HQs	High-End Exposure HQs
1-hr TWA	User	0.04	0.5
	Non-User	0.009	0.2
8-hr TWA	User	0.006	0.1
	Non-User	0.002	0.03

The HIs for both the consumer product users and non-users range from 0.0007 to 0.5. Thus, the short-term exposure concentrations associated with the indoor use of toluene as a degreaser or as a component of adhesives, shoe polish, or spray paint in accordance with manufacturer instructions are unlikely to produce noticeable discomfort or irritation to the general public and susceptible individuals.

The highest acute HQ estimated from the consumer product scenarios was the upper end exposure for a user in the Mixed Media Arts Scenario. The blood concentrations that would result for an infant exposed under the conditions of product use, in the room of use, were modeled (infants would develop higher blood levels than older children exposed to the same air concentrations- see Section 8.1.3.1 above). Figure 8.10 shows the predicted blood concentrations in infants resulting from the Mixed Media Arts Scenario in comparison to the AEGL-$1_{blood,\ peak}$. The peak blood levels predicted for infants are approximately 60% of the AEGL-$1_{blood,\ peak}$, resulting in a HQ based on blood levels of 0.6, similar to the value obtained using the conventional applied dose approach (0.5).

Figure 8.10
Modeled blood levels associated with exposure to the Mixed Media Arts Scenario for infants exposed at the same air concentrations as the upper end user



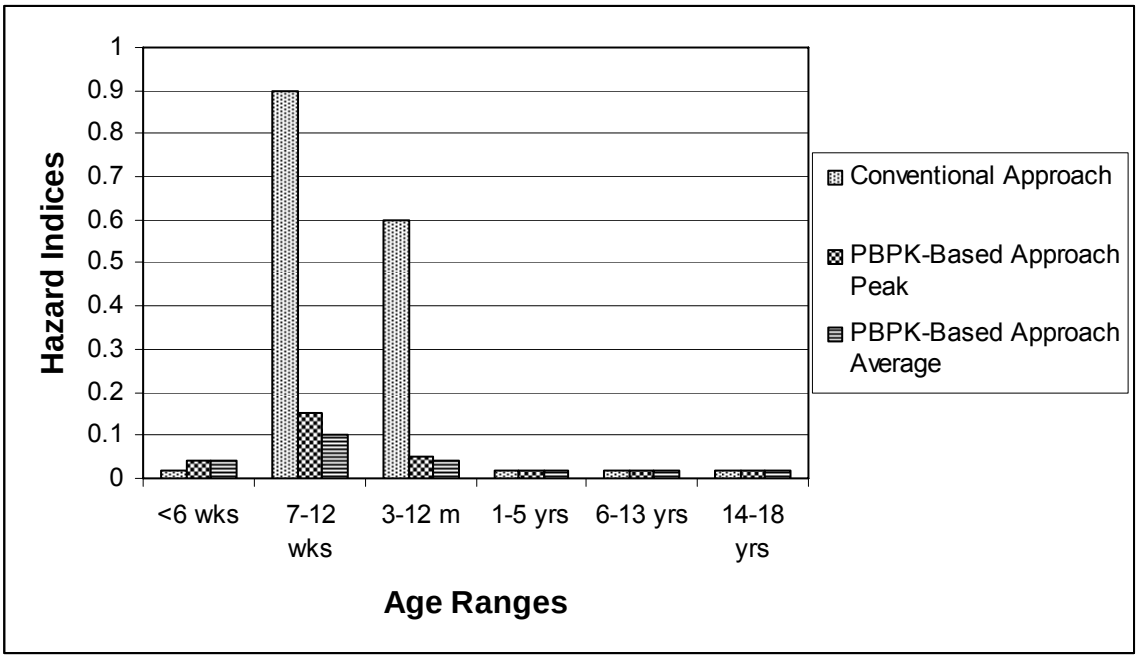
8.4 Discussion of Uncertainties

Uncertainties in the exposure estimates are described in the Exposure Assessment (Section 7). The strengths and weakness of the underlying hazard data used in the development of the health benchmarks are discussed in Section 8.1 of the Risk Assessment Section. Neither hazard assessment nor exposure assessment is an exact science, but conservative (i.e., health protective) assumptions have been employed in each area, such that hazard indices are more likely to be overprotective than underprotective.

Figure 8.11 presents the hazard indices derived for the highest estimated chronic exposure scenarios for each age group from both the conventional and PBPK-based approaches. The major differences in hazard indices estimated for using the two approaches occur in the exposure scenarios dominated by the high-end human milk exposures from an occupationally exposed mother. The differences are due to two factors. First, the PBPK-based approach captures the impact on blood levels of the division of oral exposures over the period of a full day. While the total ingested dose is close to the RfD, the oral exposures are spread out over a day to mimic realistic exposure patterns. As such, the peak levels do not approach the peaks that would be predicted from the once-a-day gavage scenario underlying the RfD derivation. Second, the PBPK-based approach compares estimated blood levels to the levels associated with steady-state exposure at the RfC (RfC_{blood}, see section 8.2 above) rather than directly to the RfD. Finally, it is also important to note in any discussion of uncertainty that these highest estimated HIs are due to human milk exposures that

assume a mother returning to work 6 weeks after the birth of her child, being exposed up to high-end (95th percentile) occupational exposures, and following a regular schedule of expressing milk during her work shift. As stated above, such a conservative exposure scenario is much more likely to overpredicted exposures than underpredict them.

Figure 8.11: Comparison of Hazard Indices from IRIS RfC and RfD and And PBPK Approaches



8.5 Conclusions

The information in this risk assessment and the underlying hazard assessment and exposure assessment demonstrate the following:

- Very low toluene exposures are received from everyday background sources of exposure such as ambient air, water, food, and in-vehicle exposures. Aggregated background doses result in HIs that are less than 0.02 at the high-end for all age groups, except the nursing infant of an occupationally exposed mother.

- Total toluene doses to the nursing infant of an occupationally exposed mother range from a typical dose of 0.01 mg/kg-day to a high-end dose of 0.07 mg/kg-day, which results in HQs ranging from 0.2 to 0.9, using the traditional risk assessment approach and 0.02 – 0.1 using the PBPK approach.

- Chronic, source-specific, inhalation exposures to toluene from tobacco smoking and vehicle refueling scenarios do not result in exceedances of the health benchmark, even when aggregated with background ambient doses. Tobacco smoke HIs range from 0.0002 for a child exposed only to ETS to 0.025 for an adult exposed to ETS and mainstream smoke. Refueling HIs do not exceed 0.00006 for a high-end exposure.

- Short term air concentrations of toluene to which children may be exposed during use of various consumer products are not expected to exceed the AEGL-1 value of 200 ppm under typical or high-end exposure conditions. HIs for the room of use 1-hr TWAs were the highest and ranged from 0.01 to 0.5. The PBPK based approach yields similar results for the short-term exposure scenarios.

- Published biomonitoring data for children correspond well with the predicted blood levels of toluene derived from the use of the PBPK model with the estimates of exposure determined in this assessment, giving confidence to both the exposure assessment and risk assessment.

- Use of an age-specific PBPK model allowed for assessment of quantitative differences in ADME between children and adults.

- The PBPK based approach is predicated on the selection of an appropriate internal dose metric. For neurological effects, toluene concentrations in the blood are the most useful dose metric. For effects on the kidney, the peak rate of toluene metabolism is the most appropriate dose metric. The most relevant endpoint, and dose metric, for children exposed to toluene in the environment is neurological effects and thus peak or average toluene blood concentrations are the critical endpoints.

- A comparison of the blood profiles predicted to occur in a human exposed at the RfC and RfD provides insights into the reasonableness, or lack thereof, for the RfD. The conservative nature of the RfD, resulting from the use of a large composite uncertainty factor, have been predicted to yield blood toluene levels that are much lower than those associated with exposures at the RfC.

- The PBPK based risk assessment approach yields results that are significantly different from the administered dose based approach, especially for nursing infants. The reason for the large disparity is due to:

- The administered dose approach only evaluates a total daily dose and does not capture the fractional dose consumed over several exposure (e.g., nursing) events throughout the day.

- Whereas the PBPK approach evaluates the peak or average blood profiles associated with all exposure sources and routes and captures the fractional daily doses associated with nursing events spread throughout the day. The result is a blood profile (and thus internal dose metric) that has smaller peaks spread throughout the day. When compared to the internal dose metrics associated with exposures at the RfC, the Hazard Quotient is much smaller than using the administered daily dose approach.

- The RfD for toluene provides little additional insights into potential risks because of the large degree of uncertainty associated with its development (total composite UF of 3000). The levels of toluene in a human exposed at the RfD are small in comparison to the levels of toluene associated with exposures at the RfC. The disparity between the two blood profiles highlights the conservatism associated with the use of the administered daily dose based RfD for toluene.

- The quantitative risk characterization indicates that reasonably anticipated children's exposures to toluene from the ambient background environment and specific sources such as gasoline during refueling and consumer product use are unlikely to pose significant health risks.

9. VCCEP Tier 2 Data Needs Assessment

9.1 Hazard

Toxicity data on toluene are available for all the Tier 1 VCCEP endpoints and all of the higher tiered endpoints, including subchronic and chronic repeated-dose, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, carcinogenicity and metabolism. Importantly, epidemiology and other human health data on toluene are extensive and have been used as the basis for human risk assessment for this VCCEP assessment and other assessments, such as the U.S. EPA IRIS assessment. These human and animal toxicology data are reviewed in Section 6 (Hazard Assessment).

For Tier 2, the VCCEP Federal Register Notice (Dec. 26, 2000) outlines six animal toxicity study types that could be considered:

- 90-day Subchronic toxicity in rodents
- Reproductive and fertility effects
- Prenatal developmental toxicity (two species)
- *In Vivo* mammalian bone marrow chromosomal aberrations OR *in vivo* mammalian erythrocyte micronucleus
- Immunotoxicity
- Metabolism and pharmacokinetics.

As mentioned above, there are extensive hazard data for toluene that cover all of these possible Tier 2 tests: there are numerous 90-day studies, there is a 2-generation reproductive effects study, there are developmental toxicology studies, in vivo genotoxicity studies, immunotoxicity studies, and a number of studies on metabolism and pharmacokinetics (including PBPK models). As such, the Consortium is not proposing to conduct any further testing on toluene for purposes of the VCCEP program.

9.2 Exposure

For compounds, like toluene, which are used in consumer products and occur in many environments, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is adequate to identify and characterize the exposure sources to toluene. Long-term ambient and background exposures to toluene are well below established health benchmarks and doses from typical and reasonably worst case exposures from the use of consumer products, consistent with product label information, are also not anticipated to present a health risks to children. Toluene exposures have been declining for many years due to extensive environmental regulations (see Section 4), such as emission control improvements for cars and trucks, VOC limitations on products, air toxics regulations, and other factors. This downward exposure trend for toluene will continue with the introduction of additional regulations and controls and future exposure data will likely be lower then the data presented in this assessment. Accordingly, the VCCEP sponsors are not proposing additional exposure assessment work on toluene.

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