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Ambient Water Quality Criteria for Toluene

AMBIENT WATER QUALITY CRITERIA FOR

TOLUENE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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TABLE OF CONTENTS

CRITERIA DOCUMENT

TOLUENE

CRITERIA

Aquatic Life

The available data for toluene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 17,500 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of toluene to sensitive freshwater aquatic life.

The available data for toluene indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 6,300 and 5,000 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Human Health

For the protection of human health from the toxic properties of toluene ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 14.3 mg/l.

For the protection of human health from the toxic properties of toluene ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 424 mg/l.

INTRODUCTION

Toluene is a clear, colorless, noncorrosive liquid with a sweet, pungent, benzene-like odor. The production of toluene in the United States has increased steadily since 1940 when approximately 31 million gallons were produced; in 1970, production was 694 million gallons. Approximately 70 percent of the toluene produced is converted to benzene, another 15 percent is used to produce chemicals, and the remainder is used as a solvent for paints and as a gasoline additive [National Institute for Occupational Safety and Health (NIOSH), 1973].

Toluene is produced primarily from petroleum or petrochemical processes (96 percent), and on a small scale from metallurgical coke manufacturing (Kirk and Othmer, 1963). Approximately 70 percent of the toluene produced is converted to benzene, another 15 percent is used as a feedstock, 15 percent is used for the production of other chemicals and the balance is used directly as a component of gasoline or as a solvent for paints and coatings. The total annual discharge of toluene to the environment by industry is estimated at 691,800 metric tons; 99.3 percent (686,960 kkg) is in the form of atmospheric emissions and 0.7 percent (4,840 kkg) as a constituent in wastewater.

Toluene, also referred to as toluol, methylbenzene, methacide, and phenylmethane, is an aromatic hydrocarbon which is both volatile and flammable (40 FR 194). The molecular structure is distinguished from that of benzene by the substitution of a methyl group for one hydrogen atom.

Toluene has the molecular formula C_7H_8, a molecular weight of 92.13 g, a boiling point of 110.625°C, a freezing point of -94.9°C (Stecher, 1968), a density of 0.86694 at 20°C, a vapor pressure of 30 mm Hg at

26.03°C, a refractive index of 1.4893 at 24°C (Kirk and Othmer, 1963), and a log octanol/water partition coefficient of 2.69 (Tute, 1971). Toluene is only slightly soluble in water, 534.8 ± 4.9 mg/l in freshwater and 379.3 ± 2.8 mg/l in seawater (Sutton and Calder, 1975). It is miscible with alcohol, chloroform, ether, acetone, glacial acetic acid, carbon disulfide and other organic solvents (Shell and Ettre, 1971).

The nucleus of toluene, like that of benzene, undergoes substitution reactions. Substitution occurs almost exclusively in the ortho (2) and para (4) positions and occurs faster with toluene than with benzene (Bradsher, 1971). The presence of a methyl group offers additional possibilities for reaction; the most important is dealkylation to produce benzene. Hydrogenation of toluene takes place readily to form methyl-cyclohexane (Kirk and Othmer, 1963). Toluene may be oxidized with air in the presence of manganese or cobalt naphthenates to form benzoic acid; controlled chlorination of toluene yields benzol dichloride which may be hydrolyzed to benzaldehyde (Gait, 1967). Most reactions, however, require specialized conditions and are carried out commercially.

Although toluene is a volatile compound and has been shown to be readily transferred from water surfaces to the atmosphere under ideal conditions (Mackay and Wolkoff, 1973), its transport and persistence under environmental conditions is not well known. In the atmosphere, toluene is subject to photochemical degradation to benzaldehyde and traces of peroxybenzoyl nitrate. It is known also that toluene can re-enter the hydrosphere in rain (Walker, 1976).

Toluene has been detected in municipal finished water supplies at levels ranging from 0.1 µg/l to 11 µg/l. The toluene metabolites benzaldehyde and benzoic acid were also found in finished water at concentrations up to 19 µg/l.

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Aquatic Life Toxicology*

INTRODUCTION

Acute toxicity tests have been conducted with toluene and a variety of freshwater fishes and Daphnia magna; the latter appears to be more resistant than the fishes. All but one of the tests were conducted using static procedures with unmeasured concentrations.

Three saltwater fish species have been acutely exposed to toluene as have several invertebrate species. Results of these tests indicate a range of 50 percent effect concentrations from 3,700 µg/l for the bay shrimp to 1,050,000 µg/l for the Pacific oyster. All of these tests were conducted using static procedures although concentrations were measured in several tests.

EFFECTS

Acute Toxicity

Daphnia magna is the only tested freshwater invertebrate species; and the 48-hour EC_{50} values for this species were 60,000 and 313,000 µg/l (Table 1).

The range of 96-hour LC_{50} values for the goldfish, fathead minnow, guppy, and bluegill is 12,700 to 59,300 µg/l (Table 1).

Potera (1975) conducted a variety of 24-hour exposures with the grass shrimp, Palaemonetes pugio, using static procedures with measured concentrations (Table 5). Temperature (10 and 20°C), salinity (15 and 25 g/kg, and life stage (larvae and adults) were the variables considered. The total

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

range of LC_{50} values for the six tests was 17,200 to 38,100 µg/l which relatively small difference indicates that the variables did not have a very great effect. The LC_{50} values for the bay shrimp, grass shrimp, mysid shrimp, and Pacific oyster range from 3,700 to 1,050,000 µg/l (Table 1).

The 96-hour LC_{50} values for the striped bass (Benville and Korn, 1977) and coho salmon (Morrow, et al. 1975) were 6,300 and between 10,000 and 50,000 µg/l, respectively (Tables 1 and 5). The sheepshead minnow (U.S. EPA, 1978) appears to be much more resistant to toluene with an LC_{50} between 277,000 and 485,000 µg/l (Table 5).

Chronic Toxicity

A chronic value of 5,000 µg/l (Table 2) has been obtained from an embryo-larval test with the sheepshead minnow in which the observed adverse effect was on hatching and survival (U.S. EPA, 1978). The 96-hour LC_{50} for the sheepshead minnow in the same study (U.S. EPA, 1978) is between 277,000 and 485,000 µg/l and this results in an acute-chronic ratio between 55 and 97. No chronic data are available for any saltwater invertebrate species and toluene, nor for any freshwater species.

The species mean acute and chronic values are summarized in Table 3.

Plant Effects

Two freshwater algal species have been exposed to toluene and the results (Table 4) demonstrate that these species are relatively insensitive compared to the fishes. There was a 50 percent reduction in cell numbers of the alga, Chlorella vulgaris, at 245,000 µg/l (Kauss and Hutchinson, 1975).

Several studies have been conducted with saltwater algal species and one has been conducted with kelp, Macrocystis pyrifera (Table 4). Effects on growth, respiration and photosynthesis occurred at toluene concentrations

from 8,000 to greater than 433,000 µg/l. The results are quite variable since these extreme values are for the same species, Skeletonema costatum.

Miscellaneous

Wallen et al. (1957) exposed mosquitofish to toluene in the presence of high concentrations of suspended solids and calculated a 96-hour LC_{50} value of 1,180,000 µg/l (Table 5).

Most of the data for saltwater species has been discussed. In addition, Potera (1975) observed narcosis of grass shrimp within 15 minutes during an exposure to 19,800 µg/l, and obtained 24-hour LC_{50} values of 24,200 and 74,200 for a saltwater copepod species (Table 5).

Summary

Five freshwater species have been acutely tested with toluene, and the cladoceran, Daphnia magna, was more resistant than four fish species. The EC_{50} and LC_{50} values for all species were in the range of 12,700 to 313,000 µg/l. The EC_{50} values for two algal species were 245,000 µg/l and higher. No chronic tests have been conducted with toluene and freshwater species.

There was a wide range of EC_{50} and LC_{50} values for saltwater species of 3,700 µg/l for the bay shrimp to 1,050,000 µg/l for the Pacific oyster. An embryo-larval test has been conducted for the sheepshead minnow and effects were observed at 7,700 µg/l but not at 3,200 µg/l. The acute-chronic ratio for this species is between 55 and 97. Several saltwater algal species and kelp have been tested and effects were observed between 8,000 and greater than 433,000 µg/l. Studies with the grass shrimp resulted in no observed effect of salinity, temperature, or life stage on acute lethality.

CRITERIA

The available data for toluene indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 17,500 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of toluene to sensitive freshwater aquatic life.

The available data for toluene indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 6,300 and 5,000 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Table 1. Acute values for toluene

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, Daphnia magna	S, U	60,000	-	Bringman & Kuhn, 1959
Cladoceran, Daphnia magna	S, U	313,000	137,000	U.S. EPA, 1978
Goldfish, Carassius auratus	FT, M	22,800	-	Brenniman, et al. 1976
Goldfish, Carassius auratus	S, U	57,680	22,800	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S, U	34,270	-	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S, U	42,330	38,100	Pickering & Henderson, 1966
Guppy, Poecilia reticulata	S, U	59,300	59,300	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S, U	24,000	-	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S, U	12,700	17,500	U.S. EPA, 1978
		SALTWATER SPECIES		
Pacific oyster, Crassostrea gigas	S, U	1,050,000	1,050,000	LeGore, 1974
Mysid shrimp, Mysidopsis bahia	S, U	56,300	56,300	U.S. EPA, 1978
Bay shrimp, Crago franciscorum	S, M	3,700	3,700	Benville and Korn, 1977
Grass shrimp, Palaemonetes pugio	S, U	9,500	9,500	Tatem, 1975

Table 1. (Continued)

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
Striped bass, Morone saxatilis	S, M	6,300	6,300	Benville and Korn, 1977

* S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for toluene (U.S. EPA, 1978)

Species	Method*	Limits (µg/l)	Chronic Value (µg/l)
SALTWATER SPECIES			
Sheepshead minnow, Cyprinodon variegatus	E-L	3,200-7,700	5,000

* E-L = embryo-larval

Acute-Chronic Ratio

Species	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Sheepshead minnow, Cyprinodon variegatus	5,000	277,000-485,000	55-97

Table 3. Species mean acute and chronic values for toluene

Number	Species	Species Mean Acute Value* (µg/l)	Species Mean Chronic Value (µg/l)	Acute-Chronic Ratio**
		FRESHWATER SPECIES		
5	Cladoceran, *Daphnia magna*	137,000	-	-
4	Guppy, *Poecilia reticulata*	59,300	-	-
3	Fathead minnow, *Pimephales promelas*	38,100	-	-
2	Goldfish, *Carassius auratus*	22,800	-	-
1	Bluegill, *Lepomis macrochirus*	17,500	-	-
		SALTWATER SPECIES		
6	Pacific oyster, *Crassostrea gigas*	1,050,000	-	-
5	Sheepshead minnow, *Cyprinodon variegatus*	277,000-485,000	5,000	55-97
4	Mysid shrimp, *Mysidopsis bahia*	56,300	-	-
3	Grass shrimp, *Palaemonetes pugio*	9,500	-	-
2	Striped bass, *Morone saxatilis*	6,300	-	-
1	Bay shrimp, *Crago franciscorum*	3,700	-	-

* Rank from high concentration to low concentration by species mean acute value.

**See the Guidelines for derivation of this ratio.

Table 4. Plant values for toluene

Species	Effect	Result (µg/l)	Reference
	FRESHWATER SPECIES		
Alga, *Chlorella vulgaris*	Cell numbers 24-hr EC50	245,000	Kauss & Hutchinson, 1975
Alga, *Selenastrum capricornutum*	96-hr EC50 for chlorophyll *a* production	>433,000	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	Cell numbers 96-hr EC50	>433,000	U.S. EPA, 1978
	SALTWATER SPECIES		
Kelp, *Macrocystis pyrifera*	Photosynthesis	10,000	Anonymous, 1964
Alga, *Amphidinium carteri*	Growth	100,000	Dunstan, et al. 1975
Alga, *Chlorella* sp	Photosynthesis respiration	34,000	Potera, 1975
Alga, *Chlorella* sp	Photosynthesis respiration	85,000	Potera, 1975
Alga, *Cricosphaera carterae*	Growth	100,000	Dunstan, et al. 1975
Alga, *Dunaliella tertiolecta*	Growth	100,000	Dunstan, et al. 1975
Alga, *Skeletonema costatum*	Growth	8,000	Dunstan, et al. 1975
Alga, *Skeletonema costatum*	96-hr EC50 for chlorophyll *a* production	>433,000	U.S. EPA, 1978
Alga, *Skeletonema costatum*	96-hr EC50 for reduction in cell numbers	>433,000	U.S. EPA, 1978

Table 5. Other data for toluene

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Mosquitofish, *Gambusia affinis*	96 hrs	LC50 in turbid water	1,180,000	Wallen, et al. 1957
		SALTWATER SPECIES		
Copepod, *Nitocra spinipes*	24 hrs	LC50	24,200	Potera, 1975
Copepod, *Nitocra spinipes*	24 hrs	LC50	74,200	Potera, 1975
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	20,200	Potera, 1975
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	17,200	Potera, 1975
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	37,600	Potera, 1975
Grass shrimp (adult), *Palaemonetes pugio*	24 hrs	LC50	38,100	Potera, 1975
Grass shrimp (larva), *Palaemonetes pugio*	24 hrs	LC50	30,600	Potera, 1975
Grass shrimp (larva), *Palaemonetes pugio*	24 hrs	LC50	25,800	Potera, 1975
Grass shrimp, *Palaemonetes pugio*	15 mins	Narcosis	19,800	Potera, 1975
Coho salmon, *Oncorhynchus kisutch*	96 hrs	LC50	10,000-50,000	Morrow, et al. 1975
Sheepshead minnow, *Cyprinodon variegatus*	96 hrs	LC50	>277,000 <485,000	U.S. EPA, 1978

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Toluene has recently been identified in both raw water and finished water supplies of several communities in the United States. Levels of up to 11 µg/l were found in November 1974, in finished water from the New Orleans area (U.S. EPA, 1975a). After the results of the study were publicized, a nationwide survey, the National Organics Reconnaissance Survey (NORS), was undertaken to determine the concentration of organic chemicals in drinking water. Ten cities across the country were selected to represent the major types of raw water sources. A total of 72 compounds were identified in the first five water supplies surveyed (Coleman, et al. 1976). Toluene was 1 of 18 compounds occurring in more than one-half of the finished waters of the 10 cities (U.S. EPA, 1975b). Six of the ten water supplies contained toluene. Levels of 0.1 and 0.7 µg/l were measured in the two water supplies where quantitative results were available. Benzaldehyde, a toluene metabolite, was identified in three water supplies. Fifteen µg/l of benzoic acid, a second metabolite, was found in another city's water.

A second nationwide survey of levels of organic chemicals in the Nation's water supplies, the National Organic Monitoring Survey (NOMS), was conducted in three phases in 1976 (U.S. EPA, 1977). In the first phase of this survey, toluene was apparently not included in the analytical screen. Toluene was, however, detected in 1 of 111 community finished water supplies during the second phase of

the program. In the third and most recent phase, toluene was found in one raw water and three finished water supplies of 11 communities surveyed. A level of 19 µg/l was measured by gas chromatography/mass spectrometry (GC/MS) in one of these finished waters, while 0.5 µg/l was found in another. Concentrations of 0.1 and 0.5 µg/l of benzaldehyde were present in the drinking water of two cities.

Although little information is apparently available concerning potential sources of organics in drinking water, investigations of the phenomenon are underway (U.S. EPA, 1975b). Suspected sources include industrial effluents, spills, discharges of oil and gasoline from boats, municipal waste treatment facilities, agricultural runoff, and landfills. Volatile hydrocarbons such as benzene and toluene would be expected to evaporate rapidly into the atmosphere from bodies of water. Mackay and Wolkoff (1973) calculated the evaporative half-life for toluene in water to be 30.6 minutes at 25°C. The half-life for benzene was slightly longer, 37.3 minutes, although the vapor pressure of benzene is about three times that of toluene. This discrepancy can be explained by the higher water solubility of benzene, 1,780 mg/l, versus 515 mg/l for toluene. Mackay and Wolkoff (1973) point out that actual rates of evaporation in the environment may be substantially reduced from these estimates, due to insufficient diffusion of organics in water to the air-water interface to replace those organics being lost by evaporation. Insufficient diffusion can be the result of inadequate mixing of the water and absorption/solubilization of the organic on or in particulates and sediments. The half-life would

therefore be expected to be considerably shorter for toluene in a fast-flowing, shallow river than for that in a deep lake or the ocean.

Ingestion from Food

Very little data on levels of toluene in foods are available. Apparently this is largely due to the lack of concern for toxicity of the chemical. Ogata and Miyake (1973) detected toluene in seawater and fish after an offensive odor appeared in fish caught from harbor waters in the proximity of petroleum and petrochemical plants near Mizushima, Japan. Identification of toluene was confirmed by gas chromatography, infrared absorption spectrometry, ultraviolet absorption spectrometry, and mass spectrometry. The flesh of one representative fish was found to contain toluene at 5 µg/g of flesh. Ogata and Miyake (1973) confirmed that toluene was readily taken up into the muscle and liver of eels kept in tanks containing water to which either petroleum industrial wastes or toluene and other aromatic hydrocarbons were added. In a subsequent publication (Ohmori, et al. 1975), the same group of investigators reported that eel liver homogenate was inferior to that of rats in the metabolism of p-nitrotoluene and p-nitrobenzyl alcohol, analogues of toluene and benzyl alcohol. The authors speculated that this metabolic deficit might contribute to accumulation of toluene in fish.

Two of the major metabolites of toluene, benzaldehyde and benzoic acid, are found in substantial levels in foods. Benzaldehyde occurs as a natural constituent of bitter almond, peach, and apricot kernel oils and is added intentionally as a flavoring agent.

Benzoic acid is used as an antimicrobial agent or food preservative (National Academy of Sciences (NAS), 1972). Benzoic acid appears to have a very large margin of safety in animals and man (World Health Organization (WHO), 1974). It is rapidly and effectively metabolized and seems to have little potential to produce tissue injury. Estimated acceptable daily intake in man is placed at 0 to 5 mg/kg, based largely upon an observed no-effect level in rats of approximately 500 mg/kg.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state bioconcentration factor (BCF) is available for toluene, but the equation "Log BCF = (0.85 Log P) - 0.70"

can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol/water partition coefficient (P). Based on an average measured log P value of 2.51 (Hansch and Leo, 1979; Dec, et al. Manuscript), the steady-state bioconcentration factor for toluene is estimated to be 27.1. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for toluene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 27.1 x 0.395 = 10.7.

Inhalation

Although toluene has been detected in the atmosphere, current levels are only a fraction of the vapor concentrations considered potentially harmful in occupational settings. One of the first reports of atmospheric toluene was by Williams in 1965, who detected it in air samples in Vancouver, Canada. Grob and Grob (1971) identified 108 hydrocarbons including 39 ppb toluene by gas chromatography in the air of Zurich, Switzerland. They noted that the composition of their atmosphere bore a striking resemblance to that of gasoline. Pilar and Graydon (1973), upon analysis of air samples taken at different times of the day from areas of Toronto with high and low traffic density, concluded that the toluene and benzene contamination in their city was closely linked with automotive transportation. Altshuller, et al. (1971) also found that

atmospheric levels of toluene in Los Angeles were largely associated with motor vehicle emissions. Pilar and Graydon (1973) measured a maximum level of 188 ppb toluene in Toronto and an average level of 30 ppb. These values are comparable to those seen several years before in Los Angeles by Lonneman, et al. (1968). These investigators reported a maximal concentration of 129 ppb and an average concentration of 37 ppb. Toluene was the most abundant aromatic hydrocarbon. Its concentration was more than twice that of benzene or m-xylene, the next most abundant aromatics. Comparison of toluene:benzene ratios in the atmosphere with those in auto exhausts revealed higher ratios in the atmosphere (Lonneman, et al. 1968; Pilar and Graydon, 1973). This finding suggests that a substantial amount of atmospheric toluene originates from a source other than automotive emissions, possibly from solvent losses.

Solvents are used for a variety of purposes including chemical processing, metal degreasing, dry cleaning, as thinners/vehicles in chemical products, and as surface coatings. The majority of solvents which are produced eventually evaporate into the atmosphere, either intentionally or unintentionally (NAS, 1976). A relatively small proportion enters water. In data reviewed by NAS (1976) on estimated solvent usage in the United States in 1968, toluene was the fifth most extensively utilized solvent, ranking behind only petroleum naptha (which contains toluene), tetrachloroethylene, ethanol, and trichloroethylene.

As with most other volatile hydrocarbon solvents, the most significant inhalation exposures to toluene occur in occupational and inhalant abuse settings. Typical industrial exposure environments

and their associated exposure levels are reviewed by the National Institute for Occupational Safety and Health (NIOSH, 1973) and are alluded to as they relate to potential adverse health effects and pharmacokinetics in the relevant sections of this document. Similarly, injurious effects seen in individuals who abuse toluene are discussed in the document. Inhalant abusers are unique in that they repeatedly subject themselves to extremely high vapor levels of toluene and other volatile hydrocarbons in order to become inebriated.

Dermal

Dermal exposures of significance are primarily restricted to occupational or home use settings.

PHARMACOKINETICS

Absorption

The pharmacokinetics of toluene has been extensively studied in both human and animal subjects. The majority of these studies have involved inhalation exposure to the chemical. Astrand, et al. (1972) subjected volunteers to toluene vapor at 100 ppm and 200 ppm and detected the compound in their arterial blood within 10 seconds after initiation of the exposure. The toluene concentrations in the blood increased rapidly during the first few minutes of 30- and 60-minute toluene inhalation sessions, then rose more slowly during the remainder of each session. The average arterial blood toluene levels appeared to approach equilibrium between 20 and 30 minutes of exposure time. During this relatively stable phase the blood levels were about 1 µg/ml in persons inhaling 100 ppm toluene and 2 µg/ml in persons inhaling 200 ppm toluene while at rest.

Systemic uptake of toluene was doubled by exercise. Astrand and her co-workers (1972) attributed this increase in uptake primarily to increased pulmonary ventilation. Carlsson and Lindqvist (1977) similarly observed that systemic uptake of toluene increased when subjects exercised while inhaling 100 ppm of the chemical. Furthermore, these investigators noted that obese subjects retained more toluene than did their thinner counterparts. Average uptake of toluene vapors by exercising subjects was approximately 37 percent for thin subjects versus 49 percent for obese subjects.

Relatively little attention has been devoted to delineation of the pharmacokinetics of ingested or topically applied toluene. Apparently there are no reports involving oral administration of toluene to humans. Pyykko, et al. (1977) recently published the results of a study in which the uptake of similar quantities of toluene in rats was compared upon oral versus inhalation exposure. As would be anticipated, the compound was absorbed more rapidly from the lungs than from the gastrointestinal tract. Peak toluene levels in most tissues of the rat were observed 15 to 30 minutes following a 10-minute inhalation session, but were not seen until 2 to 3 hours after gastric intubation. It should be noted that the oral dose of 0.1 ml toluene was given to fasted animals in 1.9 ml peanut oil. This volume of oil may have delayed toluene absorption. Although peak blood and tissue toluene concentrations were substantially higher in the rats that inhaled the chemical, these levels diminished rapidly after exposure and, after 2 to 3 hours, were comparable to the peak levels seen in the orally dosed animals. Toluene can be absorbed through the skin, though to a

considerably lesser degree than through the lungs or the gut. Wahlberg (1976) found that 2.0 ml of toluene applied under an impervious cover to the shaved backs of guinea pigs merely depressed body weight gain, while intraperitoneal injection of the same volume of chemical killed each test subject. Dutkiewicz and Tyras (1968) reported the rate of percutaneous toluene absorption in man to be 14 to 23 mg/cm^2/hour.

Distribution

Toluene is rapidly taken up from the bloodstream into the various body tissues according to their lipid content. The arterial blood of human subjects inhaling 100 or 200 ppm of toluene was found to contain significantly more of the solvent than venous blood, indicating ready tissue uptake (Astrand, et al. 1972). Tissue uptake of organic solvents is known to be dependent primarily upon the particular tissue's blood perfusion and fat content (Astrand, et al. 1975). Partition coefficients (tissue:blood) for toluene have been determined on the basis of a rabbit tissue experiment (Sato, et al. 1974). The partition coefficient for adipose tissue was 50 times greater than for other tissues. The partition coefficient for bone marrow was approximately 15 times greater, while that for brain and liver was roughly twice the values for lung, kidney, heart, and muscle. Because the brain is well perfused with blood and contains considerable lipid, it should rapidly and preferentially accumulate toluene upon inhalation exposure. Indeed, men exposed to high concentrations of toluene vapor experience central nervous system (CNS) depression within minutes (Longley, et al. 1967). As will be related in a subsequent section,

subtle CNS effects appear to be one of the most sensitive indices of toluene inhalation.

Ingested toluene is likely to be handled quite differently, in that the compound is absorbed more slowly and must first pass through the liver before reaching the nervous system. As will be discussed subsequently, toluene is extensively and rapidly metabolized by the liver. Thus, a dose of toluene which is sufficient to cause minimal CNS effects when inhaled will most likely have no such effect when ingested because insufficient quantities will reach the nervous system. Unfortunately, there have not been any studies to determine the lowest oral dose of toluene which will inhibit CNS function; nor are there data contrasting CNS levels of toluene immediately after oral and inhalation exposure. Pyykko, et al. (1977) did measure tissue levels over a period of 15 minutes to 24 hours after oral and inhalation administration of comparable doses. Higher tissue levels were present sooner in the animals that had inhaled the solvent. Several hours after the initial exposures, similar toluene levels were seen in both oral and inhalation test subjects' tissues. The adipose tissue was the slowest to attain its maximal toluene concentration, although it accumulated much more of the compound than any other tissue. Body fat provides an extensive reservoir for uptake of hydrocarbon solvents. This is illustrated by the observation by Bruckner and Peterson (1976) that saturation of the liver and brain of mice is not reached after three hours of inhalation of toluene concentrations as high as 4,000 ppm.

Metabolism

Toluene is believed to be converted by the mixed function oxidase (MFO) system to benzyl alcohol, which is subsequently oxidized to benzaldehyde and benzoic acid and conjugated with glycine to form hippuric acid. Ikeda and Ohtsuji (1971) demonstrated that pretreatment with phenobarbital, a classic inducer of MFO activity, resulted in a pronounced increase in urinary excretion of hippuric acid by rats given an intraperitoneal injection of 1.18 g/kg toluene. Blood levels of toluene were depressed and the benzoic acid concentration in the blood increased in the phenobarbitol-pretreated (induced) animals. Ikeda and Ohtsuji (1971) demonstrated that the rates of p-nitrobenzyl alcoholic oxidation and glycine conjugation were not affected by the phenobarbital pretreatment. The metabolism of p-nitrotoluene (an analogue of toluene) to p-nitrobenzoic acid was markedly enhanced in vitro in liver microsomes isolated from these animals. As might be expected, the duration of toluene-induced sleeping time was significantly shorter in the induced animals. Koga and Ohmiya (1978) have shown that inhibition of MFO activity by SKF 525-A or carbon tetrachloride will prolong toluene-induced narcosis and enhance toluene-induced mortality in rats. These investigators also found pyrazole to have a similar effect, which indicates the importance of alcoholic oxidation in the metabolism of toluene. The peroxidase/catalase system may also play a role in the metabolic pathway of some animals, in light of its recognized importance in metabolism of ethanol in certain species.

Toluene is rapidly and extensively metabolized to hippuric acid in experimental animals. Smith, et al. (1954) found that in

rabbits given 350 mg/kg of toluene orally, about 18 percent of the dose was eliminated in the expired air as the parent compound within 12 hours. Less than 1 percent more was exhaled over an additional 24-hour period. No glucuronide or sulfate metabolites were detected in the urine of these animals. Work in the same laboratory with rabbits given a single oral toluene dose of 275 mg/kg revealed that about 74 percent of the total dose could be accounted for as urinary hippuric acid within 24 hours of dosing (El Masry, et al. 1956). Thus, the majority of toluene is rapidly eliminated by the rabbit as the unmetabolized compound in expired air and as the glycine conjugate of benzoic acid in urine. Very little toluene metabolite is excreted into the bile of the rat (Abou-El-Makarem, et al. 1967). Bray, et al. (1951) suggested that if toluene exposure were so high that the glycine conjugation mechanism was overwhelmed, glucuronide conjugation might then occur. Bray and his colleagues did demonstrate glucuronide conjugates in the urine of rabbits given large doses of benzoic acid. It seems likely that should the normal metabolic pathway be blocked, more of the unmetabolized compound would simply be eliminated via exhalation. Bakke and Scheline (1970) administered toluene at 100 mg/kg orally to rats and found that 0.5 to 1.1 percent of the total dose was converted to p- and o-cresol, with the former predominating. These metabolites were excreted in the urine as glucuronide and apparent sulfate conjugates. Small amounts of benzyl alcohol were also detected in the rat urine.

Toluene appears to be metabolized and eliminated by humans in much the same manner as it is in animals. Ogata, et al. (1970)

subjected humans to 200 ppm toluene vapor for up to seven hours. It was found that 68 percent of the estimated amount of solvent absorbed systemically was recovered as urinary hippuric acid. This metabolite appeared in the urine soon after initiation of the exposure, an indication of rapid metabolism of toluene to this principal metabolite. Nomiyama and Nomiyama (1974) similarly observed a rapid increase in urinary excretion of hippuric acid in men and women inhaling 107 ppm toluene. Urinary hippuric acid excretion reached its maximum in the second hour of 4-hour exposures and decreased rapidly upon cessation of the exposures. Furthermore, Nomiyama and Nomiyama (1974) found an average of 18 percent of the total amount of toluene absorbed systemically by the subjects was eliminated in expired air. Urinary metabolites other than hippuric acid have not been reported in the literature. Thus, it would appear that humans metabolize toluene much the same as other species, in both a qualitative and quantitative sense.

Excretion

Toluene is rapidly excreted from the body. Most of a dose of toluene can be accounted for within the first 12 hours as the parent compound in expired air and as hippuric acid in the urine. Upon termination of inhalation sessions, toluene levels in the alveolar air and blood of human subjects drop rapidly (Astrand, et al. 1972; Nomiyama and Nomiyama, 1974; Sato, et al. 1974; Carlsson and Lindqvist, 1977). Sato, et al. (1974), after analyzing toluene desaturation data in humans, concluded that the initial rapid phase of elimination was governed primarily by the rate of alveolar ventilation, the rate of toluene metabolic clearance, and the blood/

air partition coefficient of toluene. A slower elimination rate for females than males was observed. This was attributed to the larger proportion of fatty tissue in females. In view of the greater uptake of toluene seen in obese subjects, Carlsson and Lindqvist (1977) noted that on prolonged toluene exposure, these individuals will accumulate more of the compound and will eliminate it more slowly, thereby subjecting their tissues to higher concentrations for longer periods.

Studies involving elimination of toluene in animals reveal a pattern of toluene elimination similar to that seen in man. It is possible in animal studies to monitor levels of the chemical in various bodily tissues which cannot be measured in man. Desaturation occurs more slowly in adipose tissue than in any other tissue of the rat (Pyykko, et al. 1977; Carlsson and Lindqvist, 1977). Interestingly, elimination of toluene from the bone marrow is also relatively slow, apparently the result of the lipoidal nature of the marrow. Toluene is lost quite rapidly from the brain, as is reflected physiologically by rapid recovery from CNS depression (Peterson and Bruckner, 1976; Savolainen, 1978). Peterson and Bruckner (1976), while setting up an animal model of human self-intoxication with toluene, found it necessary to re-expose mice and rats to concentrated toluene vapors at intervals of 10 to 20 minutes in order to maintain an intoxicated state in the animals.

Measurement of hippuric acid excretion in the urine has been advocated as an index of the severity of occupational toluene exposure. Ogata, et al. (1970), while evaluating human subjects exposed to vapor levels of 200 ppm, stated that the quantity of

hippuric acid excreted in the urine was proportional to total toluene exposure (i.e., exposure time X vapor concentration). Other groups of investigators, however, have observed wide interpersonal variation in hippuric acid excretion, even among control subjects not exposed to toluene (Ikeda and Ohtsuji, 1969; Engstrom, et al. 1976). Friborska (1973) found marked variations in the same individuals from day to day. Diet is undoubtedly a major source of this variation because many foods contain hippuric acid precursors such as benzaldehyde and benzoic acid. Analysis of hippuric acid levels in urine is probably of more value as a qualitative index of high-level toluene exposure than as a precise quantitative index, particularly at low exposure levels (Engstrom, et al. 1976).

EFFECTS

Acute, Subacute, and Chronic Toxicity

The primary hazard associated with acute exposure to high levels of toluene is excessive CNS depression. The 8-hour LC_{50} in mice was 5,300 ppm (Svirbely, et al. 1943). In contrast, the 8-hour LC_{50} for benzene was 10,400 ppm. Kojima and Kobayashi (1973) found 20,000 ppm toluene to be lethal to rats after 30 to 50 minutes. Death was attributed to CNS depression. Average concentrations of toluene in the tissues of the animals that succumbed were as follows: blood - 330 µg/g; liver - 700 µg/g; and brain - 890 µg/g. Wolf, et al. (1956) calculated the oral LD_{50} for young adult rats to be 7 g/kg. Kimura, et al. (1971) published a similar oral LD_{50} of 6.4 ml/kg for young adult rats. These latter investigators found newborn and 14-day-old rats to be much more susceptible to toluene poisoning than adults. The LD_{50}s were 1 ml/kg for

the newborns and 3 ml/kg for the 14-day-old animals. Kimura, et al. (1971) stated that the lowest dose at which gross signs of poisoning characterized by CNS depression were seen in the young adult rats was 2 ml/kg. They divided this dose level by a safety factor of 1,000 to derive a value of 2 µl/kg, which they felt was a reasonable maximum permissible solvent residue limit for single oral exposures.

A number of episodes of acute overexposure to toluene vapor have been reported in the medical literature. Lurie (1949) and Reisin, et al. (1975) published accounts of workers who were rendered unconscious by fumes of the chemical. Longley, et al. (1967) related the details of two episodes in which a number of men were quickly affected upon inhalation of an estimated 10,000 to 30,000 ppm toluene. Effects ranged from exhilaration and light-headedness to dizziness and unconsciousness. Recovery was quite rapid, as would be predicted, since the compound is so rapidly mobilized from the brain (Savolainen, 1978) and eliminated from the body. Little clinical evidence of tissue injury was seen in these patients. Nomiyama and Nomiyama (1978) have recently reported several fatal cases involving purposeful self-intoxication with toluene. In one instance, four persons were apparently narcotized while sniffing pure toluene in a car. Toluene is probably the most popular of a variety of volatile hydrocarbons which are inhaled intentionally for their euphoric or intoxicating effects (Press and Done, 1967; Natl. Inst. Drug Abuse, 1977). Toluene "sniffing" is a rather unique situation in that the participant repeatedly inhales high vapor concentrations in order to maintain a desired state of

altered consciousness. This practice may be continued for years, and thus affords toxicologists an opportunity to observe consequences of both acute and chronic high-level toluene exposure. The situation is often complicated by the participant's use of commercial products which consist of complex mixtures of chemicals. In such cases it is difficult to attribute toxicity to any single component.

With the increase in popularity of "glue sniffing," a situation known as "sudden sniffing death" has been brought to the attention of the medical community. Bass (1970) published an account of the sudden, unexpected deaths of 110 solvent abusers. Toluene was implicated in a number of these cases. The deaths did not appear to be due to suffocation or CNS depression, but rather to sudden cardiovascular collapse at light plane anesthesia levels. Bass speculated that cardiac arrhythmias may have resulted from a combined action of solvent, stress or physical activity, and hypoxia. Winek, et al. (1968) also published an account of such a fatality involving toluene. Chenoweth (1946) was apparently the first to demonstrate in the laboratory that toluene and a variety of other volatile hydrocarbons could sensitize the heart to catecholamines. By injecting epinephrine intravenously he was able to induce cardiac arrhythmias in dogs inhaling various hydrocarbon solvents. Taylor and Harris (1970) reported a slowed sinoatrial rate, prolonged P-R interval, and sensitization to asphyxia-induced atrioventricular block in mice subjected to either toluene or toluene-based airplane glue fumes. On the basis of these findings, it was suggested that the "sudden death" syndrome in humans may be

attributed to any one or combination of the following: sinus bradycardia, atrioventricular block, or ventricular fibrillation/failure. Taylor and Harris (1970) pointed out that not only will the stress and asphyxia often associated with solvent abuse contribute to cardiac arrhythmias, but that hydrocarbons may have direct toxic effects on the heart. Electrocardiogram analysis of rats inhaling toluene has been reported to reveal adverse effects such as disorders of repolarization and arrhythmias (Bereznyi, et al. 1975; Morvai, et al. 1976). The latter group of investigators found the effects of benzene to be much more intense. It should be emphasized here that all of the aforementioned cardiotoxic effects have been seen in humans and laboratory animals subjected to very high vapor concentrations of toluene. It would appear unlikely that low-level inhalation or oral toluene exposure would be detrimental to the cardiovascular system. Ogata, et al. (1970) did report an apparent decrease in pulse rate but no significant alteration of blood pressure in human volunteers inhaling 200 ppm toluene. No significant effect on heart rate was observed in other persons inhaling 100 to 700 ppm toluene (Astrand, et al. 1972; Gamberale and Hultengren, 1972).

Inhalation of relatively low concentrations of toluene may be somewhat irritating to mucus membranes and produce a decrement in psychophysiological functions. Several studies involving inhalation exposure of human subjects have been conducted to determine the lowest vapor level which will produce subjective complaints and objective evidence of CNS depression. Results of these studies form the basis for the NIOSH (1973) recommendation of 100 ppm for

occupational toluene exposure. Subjective complaints such as fatigue, dizziness, headache, weakness, and throat and eye irritation were made by subjects breathing toluene concentrations of 200 ppm. More objective measurements of CNS effects by Ogata, et al. (1970) and by Gamberale and Hultengren (1972) also suggest that the "minimum effect (vapor) level" is about 200 ppm. Ogata and his coworkers (1970) found a prolongation of eye-to-hand reaction time in persons inhaling 200 ppm toluene but no effect on flicker fusion. Gamberale and Hultengren (1972) noted that inhalation of 300 ppm for 20 minutes by their subjects increased reaction time, while 700 ppm of the compound was required to diminish perceptual speed. Inhalation of 100 ppm toluene for 20 minutes had no apparent effect on either index. These investigators emphasize, however, that lower vapor levels may be inhibitory on psychophysiological functions after longer periods of exposure. They also point out that substantial differences were observed in toluene uptake among individual test subjects, suggesting that CNS effects may also vary from person to person. Astrand, et al. (1972) demonstrated that exercise can double respiratory uptake of toluene. They advocated reconsideration of the current exposure limit, since the preceeding studies of impairment of performance have involved evaluation of resting subjects.

Toluene, upon acute exposure, appears to have only a limited toxicity potential, other than its capacity to inhibit CNS function and predispose subjects to cardiac arrhythmias. Even exposures to quantities of toluene sufficient to produce unconsciousness fail to produce residual organ damage in human victims (Longley, et al.

1967; Reisen, et al. 1975). Evaluations of experimental animals subjected to large doses of toluene also indicate that the chemical is relatively nontoxic. Svirbely, et al. (1943) could find no conspicuous pathologic changes in organs of mice exposed to high vapor concentrations of toluene. Bruckner and Peterson (1976) detected only slight, transient rises in serum glutamic-oxaloacetic transaminase (SGOT) activity in mice that inhaled 4,000 ppm toluene for three hours. Divincenzo and Krasavage (1974) administered toluene at 150, 300, 600, and 1,200 mg/kg to guinea pigs by intraperitoneal injection. Twenty-four hours later they measured serum ornithine-carbamyl transferase (OCT) activity and examined the livers for morphologic change. There was no alteration in OCT activity at any dose level. Only at the highest dosage was there histological evidence of lipid accumulation. Reynolds and Yee (1968) included toluene in a hepatotoxicity study because of the similarity of its lipophilic solvent properties to those of hepatotoxic aliphatic halocarbons. In contrast to other chemicals tested, administration of a 2.4 g/kg oral dose of toluene to rats had no effect after 1, 8, or 24 hours on hepatic glucose-6-phosphatase activity, calcium influx into hepatocytes, or liver morphology. In a subsequent investigation, Reynolds (1972) saw no effect on a wide battery of hepatotoxicity parameters two hours after giving 2.4 g/kg of the chemical to rats. These findings suggest that any lipophilic solvation action on hepatocyte membranes by toluene is of little toxicologic consequence. Holmberg and Malmfors (1974) provided additional evidence of the nontoxic nature of toluene by demonstrating

in vitro that concentrations as high as 100 ug/ml had no cytotoxic effect on suspensions of ascites tumor cells.

Toluene appears to have more toxicity potential on subacute exposure than it does acutely. In an effort to assess the capacity of toluene to elicit injury under conditions approximating human solvent abuse, Bruckner and Peterson (1978) subjected mice and rats five times weekly, for eight weeks, to 3-hour cycles of alternating fresh air and toluene vapor at 12,000 ppm. The concentration of toluene employed in this exposure regimen was not lethal, but did produce inebriation. A battery of standard toxicologic and histopathologic tests failed to reveal evidence of injury to the lung, liver, or kidney during the 8-week exposure period. Jenkins, et al. (1970) found that neither continuous exposure to 107 ppm toluene for 90 days nor intermittent (8 hours/day, 5 days/week) exposure to 1,085 ppm for six weeks affected body weight gain, hematologic parameters, or the morphology of a number of organs of the rat, guinea pig, dog, or monkey. Similarly, Carpenter, et al. (1976) saw no significant alteration of any of a variety of indices of toxicity in rats and dogs exposed to toluene concentrate at 988 ppm for 13 weeks via inhalation. Toluene concentrate consists of approximately 50 percent toluene, 15 percent other alkyl benzenes, 14 percent heptane, 10 percent cyclohexane, and lesser amounts of other hydrocarbons. Rhudy, et al. (1978) recently reported the results of a 90-day pilot study for a chronic toxicity study supported by the Chemical Industry Institute of Toxicology. Male and female rats were exposed by inhalation to 99.98 percent pure toluene at 30, 100, 300, or 1,000 ppm for 6 hours/day, 5 days/week

for 13 weeks. At any exposure level there was no significant alteration of a battery of test results including clinical chemistry, hematology, urinalysis, and histopathology. Animal appearance and behavior observations, food consumption, and mortality were not affected, although a slight reduction in body weight gain was exhibited by the high-dose males. Tahti, et al. (1977) exposed rats to 1,000 ppm toluene vapor eight hours daily for one week. Minimal increases in serum glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase activities, as well as apparent metabolic acidosis, were observed. This latter observation is of interest, in that Taher, et al. (1974) described two cases of metabolic acidosis in humans who had inhaled toluene for its intoxicating effects. The condition was termed renal tubular acidosis, because it was believed to be due to reversible alteration of the ability of the distal renal tubule to acidify the urine.

Short-term administration of toluene may influence the metabolic capacity of the liver. It was reported that Fabacher and Hodgson (1977) saw no modification of liver/bodyweight ratio, microsomal protein content, O- and N-demethylation, nor various spectral characteristics of cytochrome P-450 in male mice injected intraperitoneally for three consecutive days with toluene at 100 mg/kg body weight. Other methylated benzenes and a methylated napthalene increased liver weight and microsomal enzyme activity in the mice, leading the authors to speculate that such compounds were effective inducers because of their lipophilicity and persistence in the body. Apparently toluene was ineffective because it was too

readily metabolized and excreted. Ungvary, et al. (1976) attempted to design a protocol that would eliminate the problem of toluene's rapid turnover rate. They dosed rats daily by intraperitoneal (i.p.) or subcutaneous (s.c.) injection of analytical grade toluene at 0.12 to 1.0 ml/kg for 12 days to 4 weeks. Dose-dependent increases were seen in the number and total area of mitochondria per unit cytoplasmic area in the liver. Similarly, dose-dependent decreases in the average nuclear volume were also observed in hepatocytes of animals receiving i.p. injections. Subcutaneous injection was much less effective in inducing these ultrastructural alterations. The enhanced mitochondrial prominence is interesting in light of a previous report from the same laboratory (Aranka, et al. 1975) of a dose-dependent increase in succinic dehydrogenase activity and a decrease in glycogen content of livers of toluene-treated rats. The toxicological or biological significance of these findings is unclear, although the investigators have suggested that the mitochondrial changes are associated with increased microsomal xenobiotic metabolism. There is evidence that mitochondria are involved in microsomal mixed function oxidase reactions, possibly serving to transfer reducing equivalents originating from NADPH or NADH through cytochrome b_5 to cytochrome P-450 (Schenkman, et al. 1973).

Although long-term exposure to toluene is quite common in industry, there are few reports to suggest that it has produced deleterious health effects in workers. One adverse effect which has been tentatively attributed to toluene is myelotoxicity. Many of the early studies suggested this effect involved the use of toluene

contaminated with benzene (NIOSH, 1973). The preponderance of clinical/epidemiological investigations of workers routinely exposed to toluene vapor has failed to reveal any significant abnormalities of the circulating blood and/or bone marrow. Estimated toluene exposure levels in these negative studies were as follows: <200-400 ppm, Banfer (1961); 80-160 ppm, Capellini and Alessio (1971); 50-800 ppm, Friborska (1973); and 60-100 ppm, Matsushita, et al. (1975). Forni, et al. (1971) did not find a significant difference in the frequency of chromosome aberrations in peripheral blood lymphocytes between toluene-exposed workers and matched controls. In contrast, stable and unstable chromosome aberrations were significantly higher in individuals with benzene exposure. Greenburg, et al. (1942) examined 61 painters who were exposed to solvent mixtures containing largely toluene. There was a mild macrocytosis, anemia, and lymphocytosis in some of the workers, but no alteration of differential leukocyte counts, reticulocytosis, thrombocytopenia, or leukopenia. Female employees exposed to toluene and other compounds through their work with varnishes have recently been reported to exhibit decreased erythrocyte and thrombocyte indices (Syrovadko, 1977). It should be recognized here that interpretation of accounts of toxicity in occupational settings is often complicated by uncertain exposure levels, variable exposure patterns, exposure to multiple chemicals, and/or unrecognized predisposing factors.

Toluene exposures in occupational settings commonly involve relatively low-level inhalation and dermal exposure. Intentional toluene inhalation is quite a different situation in which the

participant inhales sufficient quantities to intoxicate himself. This practice may be continued for years. Despite such extreme exposure conditions and participation by large numbers of people throughout the world, hematological abnormalities in toluene abusers are uncommon. Massengale, et al. (1963) found no irregularities in the blood of 27 adolescents who sniffed toluene-based glues. The only hematologic abnormality in 16 other glue sniffers examined by Press and Done (1967) was eosinophilia in 4 of the 16. A number of persons who developed polyneuropathies upon abusing glues containing large amounts of toluene and n-hexane exhibited no evidence of hematotoxicity (Suzuki, et al. 1974; Goto, et al. 1974; Shirabe, et al. 1974; Korobkin, et al. 1975; Towfighi, et al. 1976). Powars (1965) did, however, treat six cases of aplastic anemia. Each of the victims demonstrated pre-existing sickle-cell disease and had abused a toluene-based glue.

Results of evaluations of the myelotoxic potential of toluene in laboratory animals have generally indicated that the chemical is nontoxic. Wolf, et al. (1956) have apparently conducted the only long-term toxicity study in which toluene was given orally. Female rats received toluene at 118, 354, or 590 mg/kg five times weekly for six months. Cell counts of bone marrow and circulating blood revealed no adverse effects. Takeuchi (1969) saw no alterations in peripheral blood counts in rats exposed 8 hours/day by inhalation to 200, 1,000, and 2,000 ppm of 99.9 percent pure toluene for 32 weeks. Rhudy, et al. (1978) failed to detect any hematologic abnormalities in male and female rats subjected 6 hours/day, 5 days/week for 13 weeks to 30, 100, 300, or 1,000 ppm of 99.98

percent pure toluene. This investigation served as a pilot for an ongoing 2-year inhalation exposure study (Gibson, 1979). The primary difference in experimental design between the two studies has been a change in the strain of rat and the deletion of the 1,000 ppm exposure level. Findings after 18 months of the chronic study do not indicate an adverse effect at any vapor level on the circulating blood or bone marrow of the male or female rats (Gibson, 1979). In a study of toluene-benzene interaction in mice, Andrews, et al. (1977) noted that toluene had no effect on incorporation of ^{59}Fe into developing erythrocytes. Toluene actually protected against inhibition of this process by benzene. Yushkevich and Malysheva (1975) saw no alteration in erythroblast maturation in the bone marrow of rats subjected four hours daily for four months to a topical application of toluene at 10 g/kg. This rather unusual dose regimen was said to impair leukopoiesis, as evidenced by an increase in the number of plasmic and lymphoid reticular cells in the marrow. Topical application of 1 g/kg daily was without adverse effect in this regard. Horiguchi, et al. (1976) observed leukocytosis within 10 days in mice that inhaled 1, 10, 100, or 1,000 ppm toluene 6 hours/day. Decreases in circulating erythrocytes were seen in the mice exposed to 100 and 1,000 ppm, while thrombocytopenia was said to occur in those exposed to 10, 100, and 1,000 ppm. A slight hypoplastic change was noted in the bone marrow of the group subjected to 1,000 ppm toluene. Dobrokhotov and Enikeev (1977) also observed leukocytosis accompanied by chromosome damage in the bone marrow of rats subjected four hours daily for four months to 112 ppm toluene vapor. Benzene also elicited

chromosome damage, which was additive to that of toluene when the two chemicals were administered together. One month after termination of the exposure, the leukocytosis had resolved, but the chromosome abnormalities persisted. The "positive" findings published by Yushkevich and Malysheva (1975), Horiguchi, et al. (1976), and Dobrokhotov and Enikeev (1977) should be interpreted with caution, in light of the substantial number of studies of humans and animals in which no evidence of toluene-induced myelotoxicity has been seen. It is often difficult to fully appreciate experimental conditions and protocols, to interpret data, and to judge the validity/significance of findings in translations of reports in foreign languages. For example, the purity of the toluene used in each of the three aforementioned studies is not stated. However, the findings of these investigators should not be entirely dismissed, as they may prove to be subtle, heretofore unrecognized hematopoietic responses to toluene.

Several reports have appeared in the literature which link long-term solvent exposure to altered immunocompetence. Lange and coworkers (1973a) investigated serum complement levels, serum immunoglobulin levels, and leukocyte agglutinins in persons exposed occupationally to benzene, xylene, and toluene. IgG and IgA (Lange, et al. 1973a) and complement (Smolik, et al. 1973) levels were lower in these persons than in controls. Ten of 35 solvent-exposed workers had leukocyte agglutinins (Lange, et al. 1973b). Nevertheless, it was not possible to attribute these effects to any single solvent. Capurro (1976) described in a recent letter to Lancet his observation of changes in gamma globulin fractions and

increased prevalence of colds and susceptibility to streptococcal infections in persons who worked at or lived near chemical plants which utilized large quantities of solvents. Bernshtein (1972) did report an inhibitory effect on phagocytic activity of leukocytes taken from rats exposed via inhalation to 185 ppm toluene four hours daily for six months. In contrast, Friborska (1973) noted increases in alkaline phosphatase, acid phosphatase, and lactic dehydrogenase activities in leukocytes and/or lymphocytes of workers exposed to toluene. The authors associated these alterations with increased functional capacity of the cells.

Solvent exposure has also been tentatively linked with induction of autoimmune disease. A substantial number of patients diagnosed as having glomerulonephritis were found to have had a history of intensive, long-term solvent exposure (Beirne and Brennan, 1972; Zimmerman, et al. 1975). These investigators noted that individual host susceptibility was likely to be an important factor here, since so many persons are routinely exposed to solvents without developing the disease. As was the case for the alterations seen by Lange and associates, no individual component of the complex solvent mixtures utilized by the glomerulonephritis patients could be considered the potential toxicant.

Long-term exposure of toluene appears to have little capacity to injure the liver and most other organs. The only report suggesting an adverse effect of toluene on the liver in an occupational setting was in an early paper by Greenburg, et al. (1942). They observed an increased incidence of hepatomegaly in painters exposed from two weeks to five years to solvent mixtures in which toluene

was the major component. Analyses of air samples taken from the work environment revealed exposure levels ranging from 100 to 1,100 ppm toluene. Capellini and Alessio (1971) saw no changes in liver function in 17 workers exposed for several years to approximately 125 ppm toluene. There has also been a surprisingly low incidence of hepatorenal injury in persons who purposefully inebriate themselves with toluene. Litt, et al. (1972), for example, found modest elevations of serum glutamic-pyruvic transaminase levels in only 2 percent and elevated alkaline phosphatase levels in 5 percent of a group of 982 glue sniffers. Massengale, et al. (1963) and Barman, et al. (1964) failed to detect hepatorenal injury in groups of abusers of toluene-based glues. Press and Done (1967) saw slight but transient abnormalities in urinalyses of a small percentage of the glue sniffers they examined. No evidence of liver injury was detected. These investigators concluded that should any adverse effects occur, they would be transient and would occur very soon after intensive solvent exposure. This supposition is supported by a study by Bruckner and Peterson (1976), who demonstrated that intensive inhalation exposure of mice to toluene is followed by small, reversible increases in serum levels of certain cytoplasmic enzymes. Signs of liver (Weisenberger, 1977) and kidney (Kelly, 1975) injury in toluene abusers being treated for behavioral problems cleared spontaneously during hospitalization.

Clinical findings from evaluations of solvent abusers should be interpreted with caution when considering the toxicity of specific chemicals such as toluene. Patterns and frequency of exposure may differ markedly among individuals. The commercial

products favored by many abusers are usually complex mixtures of different compounds. The formula for any given product often varies from one manufacturer to another and can be changed at any time. The abuser may use a variety of solvent-containing products, often in combination with alcohol and other drugs. Thus, chemical or drug interactions may either protect the participant or place him at increased risk. O'Brien, et al. (1971), for example, reported a case of serious hepatorenal injury in an adolescent who drank beer and inhaled a cleaner containing 80 percent toluene. A number of serious cases of polyneuropathy were seen in persons who abused products comprised largely of toluene and n-hexane. Signs of hepatorenal injury and hematotoxicity, however, were notably absent (Shirabe, et al. 1974; Suzuki, et al. 1974; Korobkin, et al. 1975; Towfighi, et al. 1976). An individual who claimed to have restricted his sniffing to pure toluene exhibited hepatomegaly and impaired liver function when hospitalized for a psychiatric disorder (Grabski, 1961). This same patient was seen at a later time when he developed severe hepatorenal toxicity from sniffing carbon tetrachloride vapor (Knox and Nelson, 1966).

Long-term animal studies have generally revealed little evidence of any residual toxic effect of toluene. Two investigations which deserve special attention at present are a 6-month oral dosing study by Wolf and his co-workers (1956) and an ongoing 2-year project (Gibson, 1979). Wolf, et al. (1956) gave female rats toluene at 118, 354, and 590 mg/kg in olive oil by stomach tube five times weekly for 193 days. Ten animals were used at each dose level. No adverse effects on growth, mortality, appearance and

behavior, organ/body weights, blood-urea nitrogen levels, bone marrow counts, peripheral blood counts, or morphology of major organs were noted. Thus, on the basis of these findings, it would be concluded that the minimum toxic oral dose of toluene must be greater than 590 mg/kg/day. After 18 months of the ongoing 2-year inhalation study, no significant effects attributable to toluene have been seen in male or female rats subjected 6 hours/day, 5 days/week to 30, 100, or 300 ppm of 99.98 percent pure toluene (Gibson, 1979). Parameters being evaluated include food consumption, body-weight gain, mortality, general appearance and behavior, peripheral blood counts, clinical chemistry indices, urinalysis indices, organ weights, and histopathology of 42 tissue specimens and of any detectable tissue mass from each animal.

Considerably more is known about the acute effects of toluene on the central nervous system (CNS) than potential adverse neurological effects of chronic exposure to the chemical. Depressant or inhibitory effects of toluene on the CNS are usually considered rapidly reversible. Their duration is dependent upon the rate of desaturation, or clearance of toluene from the CNS. Peterson and Bruckner (1976) found a high degree of correlation between the degree of performance inhibition and the toluene concentration in the brain of the mouse. Several cases of residual CNS damage have been reported involving individuals who sniffed toluene or solvent mixtures containing toluene over a period of years. One of the earliest reports was by Grabski (1961), who examined a 21-year-old male who had inhaled toluene vapor on a regular basis for two years. The patient's CNS signs were said to be consistent with

cerebellar degeneration. After several more years of toluene abuse, the same patient was reexamined by Knox and Nelson (1966), who diagnosed the man as having diffuse encephalopathy and cerebral atrophy. Satran and Dodson (1963) related the case of a man who exhibited personality changes including increased irritability and exaggerated swings in mood over a 10-year period of toluene abuse. Although his neurological exam was normal, nonspecific abnormalities were observed in his EEG. Satran and Dodson (1963) termed the condition diffuse encephalopathy. Another report of cerebellar damage was recounted by Kelly (1975). In this case a teenage girl with a past record of multiple drug and solvent abuse was found to have residual cerebellar dysfunction after 1½ years of inhaling fumes of a toluene-based paint. Two additional cases of cerebral involvement, each apparently the result of inhalation of 99 percent pure toluene, have recently been described by Boor and Hurtig (1977). One of the patients had abused toluene for 10 years before being hospitalized for ataxia. No abnormalities were evident in his EEG, but a computerized brain scan showed diffuse cerebral atrophy. An electromyogram and nerve conduction studies of all limbs showed no abnormalities of nerve or muscle. Although the condition of the patient improved significantly, the central neurological abnormalities were still evident upon examination nine months later. The second patient was exposed occupationally to toluene. He had gradually developed a number of bothersome problems, including fatigue, clumsiness of his left side, mildly slurred speech, impairment of sense of hearing and smell, and disturbance of memory and power of concentration. He showed daily

improvement and recovered completely without specific treatment. Recovery from cerebellar dysfunction, coupled with optic neuropathy, has also been described in an individual who inhaled fumes from a toluene-based paint on a daily basis for three years (Keane, 1978). On the basis of the aforementioned accounts, it would appear that prolonged, intensive inhalation of toluene may result in damage of the central nervous system, with impairment of pyramidal, cognitive, and cerebral functions. The adverse effects are largely reversible, particularly when exposure has not been too extreme. Cases such as these, however, seem to be a rare occurrence even among toluene abusers.

It has been suggested that toluene may influence the neurotoxic potential of n-hexane (Suzuki, et al. 1974) or even damage peripheral nerves (Goto, et al. 1974), since a number of persons have developed peripheral neuropathies upon sniffing mixtures of toluene and n-hexane. These neuropathies can apparently be either sensory of the "glove and stocking" type, or sensorimotor, with or without amyotrophy (Shirabe, et al. 1974). It should be recalled that the patient of Boor and Hurtig (1977) who experienced cerebral dysfunction upon intensive inhalation of 99 percent pure toluene exhibited no sensory or neuromuscular involvement. In the majority of reported cases involving hexane-toluene mixtures, the victims for years had abused products containing large amounts of toluene but no n-hexane without apparent difficulty (Shirabe, et al. 1974; Korobkin, et al. 1975; Towfighi, et al. 1976). Only a few weeks to months after switching to products containing n-hexane, they experienced progressive weakness and numbness of the extremities. No

report can be located in the literature in which peripheral neuropathy is attributed to the inhalation of toluene alone. The possible contribution of toluene to neurotoxic potential of n-hexane is discounted by findings of Suzuki, et al. (1974). These investigators administered n-hexane at 910 mg/kg alone, and in combination with toluene at 1.18 g/kg, by intraperitoneal injection to rats. The toluene had no effect on the rate of elimination of n-hexane from the blood, nor did n-hexane influence urinary excretion of toluene's major metabolite, hippuric acid. It was suggested that the two compounds do not influence one another because each is metabolized by a different enzyme system. Apparently, no one has determined experimentally whether toluene can influence the time of onset and/or magnitude of n-hexane-induced neuropathy.

In light of the apparent residual CNS effects in certain individuals who subject themselves to extreme toluene exposure, it is of interest to consider the likelihood of CNS damage occurring in an occupational setting where exposure levels are lower. Other than the transient CNS depressant effects already discussed, few reports have implicated toluene in cases of neurological impairment in industry. Matsushita, et al. (1975) did report finding abnormal tendon reflexes, reduced grasping power, and decreased agility of the fingers of 38 female shoemakers chronically exposed to solvents including 60 to 100 ppm toluene. Toluene exposure was confirmed by the finding of elevated urinary hippuric acid excretion in these subjects. Hanninen, et al. (1976) also observed moderate clumsiness of the hands of car painters exposed for years to solvents. Thorough analyses of the air in the painters' working environment

revealed the major component to be toluene (average level = 30.6 ppm), with lesser amounts of xylene, methyl isobutyl ketone, isopropanol, white spirit, and other solvents. Hanninen, et al. (1976) also observed impairments in memory, ability to concentrate, and emotional reactivity in the painters in contrast to age and intelligence-matched controls. These researchers emphasized that, while the impairments were quite modest, such effects should not be considered harmless since they may reduce one's ability to cope with the various demands of everyday life. Lindstrom (1973) conducted a similar study of 168 workers routinely exposed to hydrocarbon solvents, 51 of whom were said to be exposed primarily to toluene or toluene and xylene. Visual accuracy, psychomotor and sensorimotor speed performances of the solvent-exposed workers were inferior to performances of matched controls. Axelson, et al. (1976) recently reported the results of an epidemiologic study of workers exposed routinely to hydrocarbon solvents. These investigators concluded that such individuals had a higher risk of nonspecific neuropsychiatric disorders and that the risk increased with the number of years of exposure. Axelson, et al. (1976) emphasized that such disturbances, e.g., nervousness, irritability, insomnia, and impairment of memory and reasoning, are so nonspecific and occur in such variable patterns that they are often not recognized, nor is their etiology appreciated.

A very limited number of studies have been conducted using laboratory animals to assess CNS effects of toluene other than acute depression. Takeuchi and Hisanaga (1977) studied the influence of inhalation of 1,000, 2,000, and 4,000 ppm toluene for four

hours on the behavior and EEGs of rats with chronically implanted electrodes. An increase in rearing throughout the exposure was seen in rats inhaling 2,000 ppm. Increased rearing during the first hour was seen in rats inhaling 4,000 ppm. This early increase in activity at the highest exposure level diminished rapidly, so that the rats became ataxic from hour 2 until the end of the exposure session. In contrast, Peterson and Bruckner (1976) saw a gradual, but progressive, decrement over a 3-hour period in unconditioned reflexes/performances tested at 15-minute intervals in mice and rats inhaling 4,000 ppm toluene. The inhibitory action of toluene was rapidly reversible upon cessation of exposure in each of the aforementioned studies.

Takeuchi and Hisanaga (1977) also described EEG changes which were associated with disturbances in the sleep cycle of their toluene-exposed rats. It was suggested that these changes might be relevant to the human situation in which sleep disturbances have been attributed to toluene exposure. Although the toxicologic/physiologic significance of the EEG changes in rats is uncertain, Takeuchi and Hisanaga (1977) speculated that there could be a relationship between the sleep-related changes and abnormal EEG patterns reported in glue sniffers (Miyaska, et al. 1971) and persons with prolonged occupational exposure to organic solvents (Mabuchi, et al. 1974).

Ikeda and Miyake (1978) conducted an investigation to determine whether long-term toluene exposure, under conditions approximating those in glue sniffing, could have a detrimental effect on learning and memory. Rats were subjected two hours daily to 4,000

ppm of toluene vapor for 60 days. Several days later spontaneous activity, emotionality, and memory-learning on three different schedules were evaluated. No influence of the toluene regimen was seen on any parameter except one of the memory-learning tests. The particular test which was affected was the most complicated or difficult for the rats to perform, suggesting that higher cognitive processes may be impaired by toluene abuse. Recovery from this impairment had not occurred 80 days after the final toluene exposure. Microscopic examination of several areas of the brain of these animals did not reveal any damage. Furnas and Hine (1958) also failed to detect histopathologic damage of sections of brain, spinal cord, and sciatic nerve of rats 24 hours after they had been subjected to toluene vapor at 20,000 ppm for six consecutive 30-minute exposures. Ishikawa and Schmidt (1973) found no histopathologic lesions in brains of rats that developed a tendency to circle in their cages after inhaling high concentrations of toluene for a week. This condition, termed "forced turning," was reversible. Inoue (1975) reported that mice which inhaled 1, 10, 100, and 1,000 ppm toluene for six hours daily showed a decrease in wheel turning activity within 6 to 10 days. This finding seems questionable, in light of the lack of inhibition of spontaneous activity, such as wheel turning, in rats which inhaled 4,000 ppm toluene two hours daily for 60 days (Ikeda and Miyake, 1978).

Synergism and/or Antagonism

Toluene, in sufficient amounts, would appear to have the potential to significantly alter the metabolism and resulting bioactivity of certain other chemicals. The time at which exposure to

toluene occurs, relative to exposure to a second chemical, could be quite important. Prolonged pre-exposure to toluene may induce or stimulate mixed-function oxidase (MFO) activity, thereby enhancing metabolism of the second chemical. Should concurrent exposure occur, toluene, which is readily hydroxylated by the microsomal MFO system, would probably inhibit the metabolism of other compounds which are acted upon by this same system (Ikeda, 1974; Ikeda, et al. 1972). This phenomenon would be anticipated to result in a prolonged half-life of both toluene and the other compound. Inhibition of metabolism of a second compound may be beneficial or detrimental from the standpoint of adverse effects, depending upon the toxicity of the parent compound versus its metabolite(s). It might also be noted that toluene undergoes alcoholic oxidation and conjugation reactions subsequent to the initial hydroxylation reaction. Therefore, a substantial dose of toluene could conceivably interfere with the metabolism of compounds which undergo alcoholic oxidation and glycine conjugation.

Several animal studies have demonstrated that toluene can significantly influence the biological fate and bioeffects of other agents. Ikeda (1974) demonstrated that toluene at 430 mg/kg, given to rats by intraperitoneal injection in combination with trichloroethylene, reduced the metabolism of the trichloroethylene. Toluene's metabolism was also diminished. Ikeda, et al. (1972) found that simultaneous intraperitoneal administration of toluene and benzene to rats resulted in suppression of the metabolism of both compounds. The mutual suppression was reflected in diminution of urinary excretion of phenol and hippuric acid. Coadministration of

toluene and styrene was also shown to decrease styrene metabolism. Pretreatment of the rats with phenobarbital alleviated the suppressant effects of toluene. Andrews, et al. (1977), coadministered benzene at 440 or 880 mg/kg and toluene at 1,720 mg/kg intraperitoneally to mice and observed a marked reduction in urinary excretion of benzene metabolites, coupled with a compensatory increase in pulmonary excretion of unmetabolized benzene. It was demonstrated using liver microsomes in vitro that toluene is a competitive inhibitor of benzene metabolism. When toluene and benzene were given concomitantly by subcutaneous injection, it was determined that toluene did not significantly reduce the total amount of benzene appearing in body tissues, but markedly reduced the concentration of benzene metabolites in various tissues including bone marrow. Toluene was also found to protect against the inhibitory effect of benzene on ^{59}Fe incorporation into developing erythrocytes, suggesting that toluene may guard against benzene myelotoxicity by inhibiting benzene metabolism in bone marrow.

It has been suggested that toluene may play a role in induction of peripheral neuropathy seen in some abusers of n-hexane/toluene mixtures. However, as previously discussed, available evidence indicates that n-hexane is responsible for the neurotoxicity. Suzuki, et al. (1974) showed that n-hexane and toluene given concurrently to rats had no apparent effect on one another's metabolism elimination.

Teratogenicity

Toluene has been shown to be teratogenic in one recent study by Nawrot and Staples (1979). Toluene was administered to CD-1

mice by gavage on days 6 through 15 of gestation at levels of 0.3, 0.5, and 1.0 ml/kg body wt/dose. A significant increase in embryonic lethality occurred at all dose levels and decreased fetal weight occurred at 0.5 or 1.0 ml/kg. In the 1.0 ml/kg group, a statistically significant increase in the incidence of cleft palate was noted which did not appear to be due merely to general retardation in growth rate. The same toluene regime administered on days 12 through 15 yielded only decreased maternal weight gain. Maternal toxicity was not seen after exposure to toluene at any dose level.

Several researchers have reported that toluene is not teratogenic. Roche and Hine (1968) concluded that neither benzene nor toluene was teratogenic to the rat fetus or the chick embryo. Parameters evaluated by these investigators included body weight, bone length, and incidence of gross abnormalities. Hudak and Ungvary (1978) also concluded that benzene and toluene, as well as xylene, were not teratogens in mice and rats. These researchers assessed a battery of indices of teratogenicity. Mice exposed 24 hours/day on days 6 to 13 of pregnancy gave birth to underweight offspring. Some retardation of body weight and skeletal growth were seen in fetuses of rats exposed continuously to 399 ppm toluene on days 1 to 8 of pregnancy. No effects were noted in a variety of other indices including the incidence of external and internal malformations. Inhalation of 266 ppm toluene for eight hours each day of days 1 to 21 of pregnancy had no apparent influence on any index in the rat. Hudak and Ungvary (1978) concluded from quite limited data that toluene exposure during early

pregnancy might retard fetal development and should therefore be avoided. It was noted that toluene should readily pass the placental barrier and reach embryonal cells. Syrovadko (1977) recently reported that a group of women occupationally exposed to toluene and other solvents through the use of varnishes exhibited a relatively high incidence of menstrual disorders. The newborn children of these women were said to experience more frequent fetal asphyxia, to be more often underweight, and not to nurse as well as "normal" infants. Matsushita, et al. (1975) found dysmenorrhea to be a frequent complaint of female shoemakers exposed chronically to 60 to 100 ppm toluene. There are no accounts, however, of a teratogenic effect in humans being linked to toluene exposure.

Mutagenicity

There is no conclusive evidence that toluene is mutagenic. In a recent review of the genetic toxicology of toluene and related compounds, Dean (1978) stated that no data are available on mutagenicity testing of toluene in bacterial systems. Dean (1978) noted that since toluene is a lipophilic solvent, high concentrations could conceivably alter the penetration of other substances into cells. Lyapkalo (1973) was able to produce chromatid breaks and gaps in 11.5 percent of bone marrow cells of rats by injecting the animals with 1 g/kg of toluene daily for 12 days. Benzene, in contrast, caused chromosome damage in 57 percent of cells examined. Dobrokhotov and Enikeev (1977) found that inhalation of 112 ppm toluene four hours daily for four months resulted in leukocytosis in rats and chromosome damage in 21.6 percent of bone marrow cells. Although inhalation of benzene caused a similar incidence of

chromosome damage, leukopenia rather than leukocytosis occurred. The myelotoxic effects of toluene and benzene were found to be additive when both chemicals were inhaled together. One month post-exposure, the abnormalities in peripheral blood had resolved, but the chromosome aberrations persisted. Dobrokhotov and Enikeev (1977) estimated that toluene at 0.8 g/kg/day induced the same frequency of chromosome damage in their rats as benzene at 0.2 g/kg/day. In a study of peripheral blood lymphocytes of humans who had been exposed to an average of 200 ppm toluene for as long as 15 years, Forni, et al. (1971) did not detect any greater incidence of chromosome abnormalities than in controls. Workers with benzene exposure, however, did exhibit a significantly higher proportion of unstable and stable chromosome aberrations than did the controls. Dean (1978) concluded that in light of the apparent absence of chromosome damage in humans and the exceedingly high concentrations of toluene required to induce aberrations in animals, the exposure limit currently recommended by NIOSH of 100 ppm would most likely protect against chromosome damage in occupational exposure settings.

A significantly increased frequency of abnormal lymphocytes and chromosomal breaks has, however, been shown in recent findings on workers exposed to toluene in a rotoprinting factory and chemical laboratories (Funes-Cravioto, et al. 1977).

It seems unlikely that metabolites of toluene will induce mutations in animals exposed to toluene. Benzoic acid and hippuric acid, the principal metabolites of toluene, are rapidly excreted and generally regarded as innocuous chemicals. Cresols are

relatively minor metabolites of toluene which have been examined by Sharma and Ghosh (1965) for their ability to damage chromosomes. These investigators found that high concentrations could produce chromosomal aberrations in cells from root tips of Allium cepa bulbs. Of the three isomers, m-cresol caused the most pronounced changes. It will be recalled that urinary cresols represented only about one percent of a total dose of toluene given to rats, and that no m-cresol was detected (Bakke and Scheline, 1970).

Carcinogenicity

Toluene has not been demonstrated to be positive in any in vitro mutagenicity/carcinogenicity bioassay system, nor to be carcinogenic in animals or man. Fluck, et al. (1976) tested toluene and benzyl alcohol for their carcinogenic potential in an E. coli screening system and found both compounds to be negative. These researchers, however, discounted the applicability of the system for evaluation of lipophilic chemicals due to the chemicals' insolubility in the aqueous test medium. Toluene has been utilized extensively as a solvent for lipophilic chemicals being tested for their carcinogenic potential when applied topically to the shaved backs of animals. Poel (1963), for example, topically applied toluene throughout the lifetime of mice being used as controls and found no carcinogenic response. Doak, et al. (1976) applied toluene to the skin of mice for one year and failed to elicit skin neoplasms or an increased frequency of systemic tumors. It is not clear in these papers, however, whether the toluene was applied under an occlusive dressing or simply allowed to evaporate. Lijinsky and Garcia (1972) did report a skin papilloma in one mouse and a

skin carcinoma in a second mouse in a group of 30 animals which were subjected to topical applications of 16 to 20 µl of toluene twice a week for 72 weeks. Mazzucco (1975) found a reduction in collagen content of the skin of mice subjected to epidermal paintings with toluene three times weekly for 10 weeks. There was a shorter latency period in these animals for tumor development when toluene rather than acetone was used as the solvent for 3-methylcholanthrene. There has been no increase in tumor incidence in experimental rats as compared to controls after 18 months of a 2-year toluene inhalation study (Gibson, 1979). In this study, male and female rats have inhaled 30, 100, or 300 ppm toluene 6 hours/day, 5 days/week. Forty-two tissue specimens per animal, as well as any detectable tissue mass, are being subjected to histopathological evaluation.

There have been no accounts in the literature in which cancer in human populations has been attributed specifically to toluene. Some researchers have, however, suggested that chronic exposure to hydrocarbon solvents may predispose certain individuals to certain types of cancer. Capurro (1976) reported four cases of lymphoma and two cases of pancreatic cancer among workers and persons living near chemical plants where mixtures of hydrocarbon solvents were said to be present often. Capurro (1976) felt that both forms of cancer were so rare that it was unlikely they would have occurred in such a small population by chance. McMichael, et al. (1975) conducted an epidemiological study of rubber industry workers who were routinely exposed to a variety of solvents. The investigators found a greater than expected risk of death from cancer, with the

largest mortality excesses from lymphosarcoma, Hodgkin's disease, lymphatic leukemia, and myeloid leukemia. Upon testing the hypothesis that the excess in cancers was due to hydrocarbon solvent exposure, an association was established between duration and intensity of solvent exposure and incidence of lymphatic leukemia. Curtes, et al. (1973) reported the case history of a man who had worked with solvents, including toluene, who subsequently developed chronic myeloid leukemia. McMichael and his associates point out that benzene does not appear to cause lymphatic leukemia, but rather the hemocytoblastic and myeloblastic forms of the disease. Thus, it is suggested that another solvent or other chemical may be responsible for lymphatic leukemia and other forms of cancer seen in the study. The researchers also stress that there has been inadequate carcinogenicity testing in animals and insufficient epidemiological studies of the carcinogenic potential of many solvents generally regarded as noncarcinogenic. It should be recognized here that situations involving persons with occupational exposure to solvents are characterized by considerable job mobility and exposure to a variety of chemicals in varying patterns. Wolff, et al. (1977), for example, found toluene in combination with a number of other hydrocarbon solvents in adipose samples from workers in a styrene polymerization plant. Thus, it is quite difficult to attribute tumor induction to any single agent.

CRITERION FORMULATION

Existing Guidelines and Standards

The Occupational Safety and Health Administration (OSHA) currently limits occupational toluene exposure to 200 ppm as an 8-hour time-weighted average (TWA) concentration, with a ceiling of 300 ppm (40 CFR 1910.1000). The National Institute for Occupational Safety and Health (NIOSH, 1973) has recommended an exposure limit of 100 ppm as an 8-hour TWA with a ceiling of 200 ppm. This criterion was recommended primarily on the basis of subjective and objective signs of mucus membrane irritation and deficits in central nervous system function upon acute inhalation exposure of human subjects to 200 ppm toluene. Short-term inhalation of 100 ppm was apparently without demonstrable effect in humans. Reports reviewed by NIOSH (1973) also have failed to indicate adverse effects on the hematopoietic, hepatorenal, or other systems of workers routinely inhaling approximately 100 ppm toluene.

A review of potentially harmful effects of chemical contaminants of drinking water was undertaken by the Committee on Safe Drinking Water of the National Academy of Sciences (NAS, 1977). The recommendations of this committee were to be used by the U.S. EPA as the scientific basis for revision or ratification of the Interim Primary Drinking Water Regulations promulgated under the Safe Drinking Water Act of 1974. Toluene was one of the organic chemicals considered by the Committee. Although it was concluded that toluene and its major metabolite, benzoic acid, were relatively nontoxic, the committee felt there was insufficient toxicological data available to serve as a basis for setting a long-term

ingestion standard. It was recommended that studies be conducted to produce relevant information (NAS, 1977). Toluene has recently been considered for a second time by a reorganized Toxicology Subcommittee of the Safe Drinking Water Committee of the National Academy of Sciences. Results of the deliberations of this group have not yet been made public.

There are no Federal or State guidelines, nor standards for general atmospheric pollution by toluene.

Current Levels of Exposure

Toluene has been detected in raw water and in finished water supplies of several communities in the United States. Levels of up to 11 µg/l were found in finished water from the New Orleans area (U.S. EPA, 1975a). In a nationwide survey of water supplies from 10 cities, six were discovered to be contaminated with toluene (U.S. EPA, 1975b). Concentrations of 0.1 and 0.7 µg/l were measured in two of these water supplies. Toluene was detected in one of 111 finished drinking waters during a second nationwide survey (U.S. EPA, 1977). In a subsequent phase of this survey, toluene was found in one raw water and three finished waters out of 11 surveyed (U.S. EPA, 1977). A level of 19 µg/l measured by gas chromatography/mass spectrometry was found in one of these finished waters, and 0.5 µg/l was found in another.

There is a paucity of data available on levels of toluene in foods. Toluene was detected in fish caught from polluted waters in the proximity of petroleum and petrochemical plants in Japan (Ogata and Miyake, 1973). A concentration of 5 µg/g was measured in the muscle of one such fish. Two major metabolites of toluene,

benzaldehyde and benzoic acid, naturally occur in foods or are intentionally added. Benzaldehyde is a flavoring agent, while benzoic acid is a preservative. Benzoic acid is also given in large oral doses to humans as a clinical method for measuring liver function.

Although toluene has been detected in the atmosphere, concentrations are many times lower than vapor levels considered to be potentially harmful in occupational settings. An atmospheric concentration of 39 ppb toluene was measured in Zurich, Switzerland (Grob and Grob, 1971). An average level of 37 ppb toluene was observed in Los Angeles air in 1966 (Lonneman, et al. 1968). The maximum amount detected there was 129 ppb. Comparable levels were found upon evaluation of air in Toronto, Canada (Pilar and Graydon, 1973). The maximum concentration of toluene measured in Toronto was 188 ppb, while the average concentration was 30 ppb. The atmospheric levels of toluene in both Toronto and Los Angeles varied considerably according to the time of day and sampling location (Pilar and Graydon, 1973; Altshuller, et al. 1971). Thus, it appears that atmospheric toluene in urban areas arises primarily from automotive emissions, with solvent losses as a secondary source.

The most significant toluene inhalation exposures occur in occupational settings or via inhalant abuse. Occupational exposure levels are generally lower than the current standard of 100 ppm, although short exposures to higher vapor concentrations occur. Purposeful inhalation of toluene vapors in order to inebriate oneself is a quite different situation, since the participant may inhale extremely high concentrations repeatedly for months or

years. Toluene concentrations as high as 20,000 to 30,000 ppm can produce intoxication within minutes under such circumstances.

Special Groups at Risk

At present levels of exposure to toluene in the environment, available toxicological data do not suggest that any special group in the general population would be at risk. Exposure to levels of the chemical necessary to produce physiological or toxicological effects would be anticipated primarily in occupational or solvent abuse situations. Environmental contribution of toluene in such settings should be minimal.

Basis and Derivation of Criteria

Although acute exposure to high levels of toluene can result in marked central nervous system depression, this action is rapidly reversible upon cessation of exposure in both laboratory animals (Peterson and Bruckner, 1976) and in man (Longley, et al. 1967). When administered acutely in quite large doses to animals, toluene can alter the metabolism and bioactivity of certain chemicals which are degraded by the mixed function oxidase system. Toluene appears to have little capacity to cause residual tissue injury. There is no conclusive evidence that the parent compound or its metabolites are mutagenic, although they have apparently not been tested in an in vitro mutagenicity assay (Dean, 1978). Although toluene has not been found to be teratogenic in chickens and rats (Roche and Hine, 1968) or rats and mice (Hudak and Ungvary, 1978), one recent study by Nawrot and Staples (1979) reports teratogenic effects in mice. Toluene has not been demonstrated to be carcinogenic when applied to the skin of mice (Poel, 1963; Doak, et al. 1976) or when administered by inhalation at concentrations of up to 300 ppm for as

long as 18 months to male and female rats (Gibson, 1979). There are no accounts in the literature in which cancer in a human population is attributed specifically to toluene.

A number of investigations of the subacute and chronic toxicity of toluene have been conducted. Although the heaviest emphasis has been placed upon inhalation exposure, Wolf, et al. (1956) did conduct a long-term, oral dosing study in which female rats were given toluene at 118, 354, or 590 mg/kg in olive oil by stomach tube five times weekly for 193 days. No adverse effects on growth, appearance and behavior, mortality, organ/body weights, blood urea nitrogen levels, bone marrow counts, peripheral blood counts, or morphology of major organs were observed at any dose level. The lack of toxicity reported here is supported by findings of other groups of investigators who found no evidence of residual injury in a variety of animal species subjected to toluene vapor for varying times over periods as long as 18 months (Jenkins, et al. 1970; Carpenter, et al. 1976; Bruckner and Peterson, 1978; Rhudy, et al. 1978; Gibson, 1979).

Therefore, it seems reasonable that the highest dose utilized by Wolf, et al. (1956), namely 590 mg/kg, might serve as the basis for calculating an "Acceptable Daily Intake" for toluene. Although 590 mg/kg will be considered here as a "maximum-no-effect" dose, it should be recognized that the actual "maximum-no-effect" dose may be higher, since Wolf, et al. (1956) did not determine a "minimum-toxic-dose." Reynolds and Yee (1968) saw no effect on several parameters of hepatotoxicity in rats given a single oral dose of 2.4 g/kg toluene. The acute oral LD_{50} for toluene in young, adult

rats is reported to be 7.0 g/kg (Wolf, et al. 1956). It is possible that the actual "maximum-no-effect" dose may be lower than 590 mg/kg, should alternative indices of toxicity be evaluated. Humans may prove to be more sensitive to toluene than experimental animals. Thus, assuming a 70 kg body weight, it seems appropriate that a safety factor of 1,000 be applied in the following calculation:

$$\frac{590 \text{ mg/kg} \times 70 \text{ kg} \times 5/7 \text{ day}}{1{,}000} = 29.5 \text{ mg/day}$$

Therefore, consumption of 2 liters of water daily and 6.5 g of contaminated fish having a bioconcentration factor of 10.7, would result in, assuming 100 percent gastrointestinal absorption of toluene, a maximum permissible concentration of 14.3 mg/l for the ingested water:

$$\frac{29.5 \text{ mg/day}}{(2 \text{ l} + (10.7 \times 0.0065) \times 1.0} = 14.3 \text{ mg/l}$$

This calculation assumes that 100 percent of man's exposure comes from water. Although it is desirable to arrive at a criterion level for water based upon total exposure potential, the data base for exposures other than water is not sufficient to allow a factoring of the criterion level.

In summary, based on the use of toxicologic test data for rats, and an uncertainty factor of 1,000, the criterion level for toluene is 14.3 mg/l. Drinking water contributes 97 percent of the assumed exposure, while eating contaminated fish products accounts for 3 percent. The criterion level for toluene can alternatively be expressed as 424 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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