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Acute Toxicity of Gasoline and Some Additives

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The acute toxicity of gasoline; its components benzene, toluene, and xylene; and the additives ethanol, methanol, and methyl tertiary butyl ether are reviewed. All of these chemicals are only moderately to mildly toxic at acute doses. Because of their volatility, these compounds are not extensively absorbed dermally unless the exposed skin is occluded. Absorption through the lungs and the gastrointestinal tract is quite efficient. After ingestion, the principal danger for a number of these chemicals, particularly gasoline, is aspiration pneumonia, which occurs mainly in children. It is currently not clear whether aspiration pneumonia would still be a problem if gasoline were diluted with ethanol or methanol. During the normal use of gasoline or mixtures of gasoline and the other solvents as a fuel, exposures would be much lower than the doses that have resulted in poisoning. No acute toxic health effects would occur during the normal course of using automotive fuels.

Introduction

This paper reviews the acute toxicity of gasoline and some components that have been used as blending agents in automobile fuels. The data used to prepare this review were gleaned from laboratory animal studies, human case reports, and some human studies. In many instances the exposure levels in experimental animal studies are much higher than would be encountered by humans from evaporative emissions or from contamination of soil or groundwater. Similarly, most of the reports dealing with acute toxicity of these substances in humans are case reports where individuals either intentionally or accidentally ingested large quantities of these chemicals. Tables for each chemical provide an abbreviated list of dose levels corresponding to specific health effects. However, only limited comparisons can be made between various dose levels listed in these tables due to varying quality of the experimental data.

A basic limitation of the information on acute toxicity is that most of the available data deal with ingestion. Inhalation is an important exposure route for evaporative vehicle emissions or emissions during fueling of automobiles. The effect of aerosols on the respiratory tract has not been studied in detail. A few human case reports exist where aspiration of liquid material after ingestion has been a problem. This type of exposure where liquid material is spread throughout the lungs after aspiration is quite different from the inhalation of low concentrations of aerosols. Thus, these two types of exposure scenarios would be quite different, and no comparisons can be made.

Because in some instances the metabolism of the various blending agents, such as methanol, may be different, in different species, the toxicokinetic parameters in relation to relevant acute toxicity end points are briefly reviewed. Understanding the biotransformation of these chemicals allows identification of useful animal models for extrapolation to humans.

Discussion of treatment procedures as well as chemical interactions is not the intent of this paper. For further information on a more detailed report on clinical toxicology of methanol and hydrocarbon blends (gasoline) and methods of treatment, the reader is referred to Litovitz (*1*).

The human health effects of some chemicals (xylene, toluene, benzene, and methyl tertiary butyl ether) as well as their biotransformation are examined in isolation. However, gasoline as well as these other components are used as mixtures. Exposure to such mixtures may be to some extent at variance from exposure to individual compounds. In addition, because some components of these mixtures are more volatile than others, the proportions of the composition of vapors may be different from that of gasoline per se.

Gasoline

Gasoline is also known as petrol (Great Britain), benzin (Germany), motor spirits, and motor fuel. Gasoline is a highly flammable, mobile liquid. The boiling point of U.S. gasoline is 50–200°C (*2*). The conversion factor from parts per million in air by volume to milligrams per cubic meter is 2.967.

Gasoline is used as a fuel, diluent, finishing agent, and industrial solvent (*2*). The use of gasoline as motor fuel is

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addressed here. Automotive gasoline is a complex mixture of relatively volatile hydrocarbons with or without additives obtained by blending appropriate refinery streams. In Europe, and to a lesser extent in the United States, oxygenated compounds are also part of gasoline's components (*3*).

It has been reported that one gasoline sample, PS-6 gasoline, contained about 53% paraffins, 5% naphthenes, 36% aromatics, 6% olefins, and less than 1% unknowns by percent of weight (*4*). However, other commercial gasoline mixtures may have different compositions (*3*). According to the International Agency for Research on Cancer (IARC) (*3*), the aromatic fractions of gasoline contain benzene at a range of 0–7% volume and typically about 2–3% volume.

Ethanol and methanol may be added to commercial gasoline. Gasohol is the name given to a mixture of gasoline and ethanol and usually contains 10% ethanol (*3*); however, as much as 40% ethanol has been added (*5*). Oxygenated compounds such as methyl tertiary butyl ether (MTBE) and tertiary butyl ether (TBE) are also blended with gasoline to increase octane numbers in the United States as well as in Europe (*6*).

The composition of vapor and liquid gasoline differ. Gasoline vapor comprises mostly short-chain, low molecular weight, more volatile components (such as the C_4/C_5 chain light paraffins, which make up about 90%). The aromatics, which are larger and heavier molecules, are reduced to about 2% in the vapor phase, primarily as benzene (*7*).

Since the introduction of unleaded gasoline in the mid-1970s, the amount of leaded gasoline sold in the United States has decreased from 75% of total gasoline sales in 1975 to 25% in 1985 and to roughly 10% in 1990 (*8*). New automobiles sold after 1975 were equipped with catalytic converters, which precluded the use of leaded gasoline. Unleaded gasoline may contain some lead but never more than 0.013 g/L (*3*).

Gasoline Exposure of the General Population

Kearney and Dunham (*9*) measured gasoline vapor concentrations at a high-volume service station for 1 week. Short-term personal samples collected from self-service customers while refueling ranged from not detectable to 159 mg/m^3. The geometric mean for this range was about 23.7 mg/m^3. Other sources addressing human exposure to gasoline report similar levels and vary somewhat with activity. Based on available literature, NESCAUM (*10*) calculated that the average exposure of total hydrocarbon vapors over an unspecified time ranged from a mean of 134 ppm to 5.4 ppm by volume, depending on whether people were filling their gas tank, present in a fllling station, or lived within close proximity to a filling station. Similar levels are given by Environ (*11*). Additional information on related topics is given by Gabele (*12*), who examined the exhaust and evaporative emissions from a prototype General Motors Variable Fuel Corsica of various gasoline/methanol blends, and by Piver (*13*), who addressed methods of meeting automotive exhaust emissions standards of the 1970 Clean Air Act.

Groundwater contamination due to leaks from underground storage tanks may occur. In isolated instances this may result in additional exposure of humans from contamination of well water or evaporation of gasoline into basements. The concentrations that have been measured in well water have usually been in the parts per billion (μg/L) range by weight (*10*).

The doses or concentrations at which acute toxic effects occur in humans and animals are listed in Table 1 and are also discussed below. The exposures at which the described effects occur are much greater than any exposures that would occur through ingestion of contaminated water or the inhalation of gasoline while filling the tank of a car or spending time at a filling station. Thus, no acute toxicity would be expected from this type of exposure.

Acute Toxicity in Humans

Due to gasoline's variable composition, it is only possible to generalize about its acute toxicity. Aromatic hydrocarbons are more toxic than naphthenes, which are more toxic than paraffins (*14*). This is partly due to the more rapid absorption of aromatic hydrocarbons (*15*). In general, the irritant and toxic effects within a particular group of compounds increases with increasing molecular weight, branching, and increasing numbers of double bonds (*15*).

Inhalation and skin contact are the usual routes of exposure. Accidental ingestion may also occur. The amount of gasoline absorbed percutaneously is unknown. With normal storage and use, gasoline ingestion is an unlikely event. However, a number of cases are usually encountered by physicians every year. In adults such cases

Table 1. Acute toxicity of gasoline.

Species	Exposure route	Dose level[a]	Effect	Reference
Rat	Oral	18.85 mL/kg	LD_{50}	Weaver (*32*)
	Aspiration	0.2 mL	Instant death	Gerarde (*33*)
Mouse	Inhalation	120,000 mg/m^3/5 min	Lethal dose	Sandmeyer (*5*)
Rabbit	Dermal	5 mL/kg	0% mortality	Weaver (*32*)
Human	Oral	20–50 g	Toxic to adults	Moeschlin (*17*)
		350 g	Usual fatal dose for adults[b]	Sollman (*34*)
	Inhalation	2,250 mg/m^3/hr	No effects	Sandmeyer (*5*)
		3,680 mg/m^3/hr	Slight dizziness, irritation of eyes, nose, throat	Sandmeyer (*5*)
		8,200 mg/m^3/hr	Dizziness, mucous membranes, irritation, anesthesia	Sandmeyer (*5*)

[a]Milligrams per cubic meter are calculated based on a molecular weight of 100.
[b]Susceptibility varies.

are usually the result of siphoning, and in children it is the result of accidental ingestion from unlabeled, incorrectly labeled, or stored containers (*6*).

The principal target organ for gasoline toxicity is the central nervous system (CNS). The systemic effects of acute exposure are CNS depression and mimic those of ethanol inebriation. Exposure to gasoline concentrations results in flushing of the face, ataxia, staggering, vertigo, mental confusion, headaches, blurred vision, slurred speech, and difficulty swallowing. At high concentrations, coma and death may result in a few minutes without any accompanying respiratory struggle or postmortem signs of anoxia (*15*). The variation in susceptibility observed in the fatal oral dose range for adults (Table 1) is explained by the occurrence of respiratory aspiration. It was stated in an early extensive review of gasoline intoxication that single oral doses of approximately 7.5 g/kg or a total dose of 525 g per person for a 70-kg individual would be fatal (*16*). On the other hand, much smaller amounts, if aspirated, may lead to secondary pneumonia with a fatal outcome. This is particularly a problem in children. Moeschlin (*17*) indicates that aspiration of liquid gasoline causes pulmonary epithelial damage, hemorrhagic pneumonia, and pleurisy. Inhalation of concentrated gasoline vapors may also cause pulmonary hemorrhages, as well as early signs of pleuritic pain and pleuritic effusions.

Local effects caused by ingestion of undiluted gasoline include a burning sensation in the mouth, pharynx, and chest, gastrointestinal (GI) tract irritation, vomiting, colic, and diarrhea (*18*). Splash contact with eyes causes only slight transient corneal epithelial damage (*19*).

In humans, little information is available on a dose–response relationship. Inhalation exposure to 2250 mg/m^3 (*5*) did not result in adverse systemic health effects. In an earlier study, young male volunteers showed CNS symptoms after inhalation exposure to between 2100 and 8400 mg/m^3 for 30 min to 1 hr (*20*). Eye irritation was the only effect in another study where volunteers were exposed for 30 min to about 600, 1500, and 3000 mg/m^3 in air (*21*). Due to gasoline's varied composition, no single applicable Federal standard exists for atmospheric concentrations of gasoline. As of 1990–91, American Conference of Governmental Industrial Hygienists (ACGIH) (*22*) adopted a STEL value (short-term exposure limit) of 1480 mg/m^3 based on aromatic hydrocarbon content (*2*) and a TWA (time-weighted average) of 890 mg/m^3. In developing this TWA, the findings made by Drinker et al. (*21*) were considered, but it was determined that these studies were conducted with atomized whole gasoline rather than the more volatile fractions commonly found in gasoline vapor. It was therefore concluded that a TLV-STEL of 1480 mg/m^3 and a TWA of 890 mg/m^3 was sufficiently protective (*22,23*). However, it is not entirely clear at what concentrations the volatile fraction of gasoline would produce eye irritation. These data were also reviewed by Runion (*24*).

Gasoline Sniffing

Some people have become habituated to the inhalation of gasoline because of its initial euphoric effect. Initially, symptoms resulting from inhalation of gasoline fumes range from lightheadedness and mild confusion to a psychosislike state. However, these effects are rapidly followed by nausea, vomiting, abdominal pain, agitation, and anxiety. In addition, hypomania, collapse, and coma may result (*25*). According to Sandmeyer (*5*), gasoline can sensitize the myocardium to the effect of endogenous or exogenous adrenergics, leading to cardiac arrhythmias. This may explain the occurrence of sudden death during sniffing and the deaths of storage tank cleaners who do not use proper respiratory protection.

For leaded gasoline, organolead compounds contribute more significantly to toxic effects after a 5- to 7-day latency period. Organolead poisoning causes abnormal jaw jerk, hyperactive deep tendon reflexes, stance and gait abnormalities, and intention tremors. Symptoms of mild cases of organolead poisoning include headache, fatigue, anorexia, insomnia, and tenseness. Severe cases are marked by encephalopathy with psychosis, delirium, cerebellar ataxia, seizures, and occasionally coma and death (*26*). Inhalation abuse of leaded gasoline is also characterized by increased blood and urine lead levels.

Toxicokinetics

Inhaled gasoline is absorbed faster than ingested gasoline if aspiration does not occur (*16*). Insignificant amounts of gasoline are absorbed through the skin and are not associated with characteristic systemic effects (*15,17*). Because gasoline's components have different metabolic pathways, the biotransformation of its key components and additives are addressed individually.

Gasoline Additives. Tetraethyl lead has been used as a gasoline additive in a number of countries and is emitted in small quantities from automobile exhaust. Although it degrades quickly in the atmosphere, it can be very hazardous to gasoline sniffers. Tetraethyl lead is rapidly taken up by the nervous system. Its toxicity depends on its activation *in vivo* to trialkyl forms. Upon absorption into the body, it is converted to triethyl lead, diethyl lead, and inorganic lead (*27*).

Alternative gasoline fuel additives that may be used or have been suggested to enhance the octane number when alkyl lead is completely phased out include manganese oxide, methyl cyclopentadienyl manganese tricarbonyl (MMT), ethanol, methanol, MTBE, benzene, and toluene (*25*).

Acute Toxicity in Animals

Examples of the acute dermal, oral, and inhalation toxicity in animals are given in Table 1. The acute toxicity of a gasoline preparation (API 83-06) has been studied recently (*28*). Whole-body exposure of five young adult male and female rats to vapors of about 5 g/L of heavily catalytically reformed naphtha American Petroleum Institute (API) #83-06 in air was without adverse effects during a 4-hr exposure and subsequent 14-day observation period (*28*).

The acute oral toxicity in rats in a recent API study (*29*) resulted in an estimated oral LD_{50} in female rats of 4.82

g/kg and in male rats of 5.80 g/kg body weight when administered undiluted by gavage. The dermal LD_{50} in rabbits was > 6.0 g/kg. These results indicate that gasoline is only mildly toxic at acute doses. The primary dermal irritation index in rabbits according to the Draize test was 5.4 for rabbits when the test material was applied undiluted at 0.5 mL/area to clipped abraded and non-abraded skin, suggesting that gasoline was moderately irritating. The primary eye irritation scores were 4.7, 1.3, and 0.0, at 1, 24, and 48 hr after the exposure to 0.1 mL of undiluted material followed by immediate flushing with water, suggesting that the material was moderately irritating and that the irritation subsided completely within 48 hr. If flushing was not performed, some irritation was still noted 48 hr after exposure. The test material was not a sensitizer in guinea pigs. Nephrotoxicity has also been reported in male rats after short-term exposures; however, because of the formation of high concentrations of α_{2u}-globulins, this lesion is irrelevant for humans (*30,31*).

Recommendations and Areas for Further Research

Aspiration pneumonia after ingestion greatly influences the toxicity of gasoline. It is not clear at what concentration of gasoline in other media, such as air, water, or alcohol, this would still be a problem. Information on the effect of dilute solutions of gasoline on the lung should be obtained. Additional tests should be conducted in humans to determine whether and at what concentrations of the volatile portion of gasoline in air eye irritation is produced.

Ethyl Alcohol

Ethyl alcohol is also known as ethanol, algrain, anhydrol, ethyl hydrate, ethyl hydroxide, and grain alcohol. Ethanol is a clear, colorless, flammable liquid with a molecular formula of C_2H_5OH and a molecular weight of 46.07 g/mole, a boiling point of 78.5°C, a vapor pressure of 44 mm Hg (20°C), and a flash point (closed cup) of 13°C (*14*). The conversion factor from parts per million by volume in air to milligrams per cubic meter is 1.88. Ethanol is widely used as an industrial solvent. Gasohol is the name given to a gasoline blend with 10% ethanol (*35*). However, ethanol's consumption as a component of intoxicating beverages remains the most important cause of injury associated with ethanol use. Examples of acutely toxic doses in humans and laboratory animals are given in Table 2.

Acute Toxicity in Humans

The principal target organ for acute alcohol poisoning is the central nervous system, and the primary route of human exposure is ingestion. Ethanol vapors, even at low concentrations may cause irritation of the mucous membranes of the eyes and respiratory tract. Subjects exposed to 5000–10,000 ppm (9.4–18.8 g/m^3) experienced coughing and eye irritation, which was not noticed at concentrations below 5000 ppm. At these concentrations in air, subjects may develop stupor and pronounced sleepiness (*36*). Ethanol is a CNS depressant that induces all stages of anesthesia. For an average adult, the fatal ingested dose is approximately 1 L of 40–55% ethanol (the percentage of ethanol in whiskey, gin, rum, vodka, or brandy) consumed within a few minutes (*37*).

The relationship between symptoms and blood ethanol levels is imprecise due to widely varying physiological effects in individuals with similar blood levels. However, at approximately 0.05–0.15%, decreased inhibitions, incoordination, slow reaction time, and blurred vision are observed. Definite visual impairment, slurred speech, hypoglycemia, and staggering are associated with the blood level range 0.15–0.3% (*37*). At blood levels above 0.3%, marked incoordination, stupor, hypoglycemia, convulsions, coma, and death are observed (*37*). In adults, coma and death are more typically associated with blood levels above 0.5% (*37*). Lethal blood alcohol concentrations can vary from 0.18 to 0.6%, varying inversely with the time

Table 2. Acute toxicity of ethanol.

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral	7.8–22.5 mL/kg	LD_{50} range	Kimura (*50*)	Varies with age
	Inhalation	24,000 mg/m^3	Lethal dose	Loewy and Von der Heide (*51*)	
Mouse	Oral	5.5–7.0 mg	MLD	Weese (*52*)	By stomach tube
	Inhalation	55,000 mg/m^3	Lethal dose	Lehman and Flury (*53*)	
Dog	Oral	10–15 mL/kg	Narcosis	MacNider (*54*)	40% solution by stomach tube
Rabbit	Oral	300–400 mL	Fatal dose-adlt	Dreisbach (*39*)	Consumed < 1 hr; 100% vol
		12.5 mL/kg	Lethal dose	Munch and Schwartze (*55*)	By stomach tube
	IP injection	3.5–6.0 g/kg	MLD range	Barlow (*56*)	
	IV injection	9.4 g/kg	MLD	Lehman and Flury (*53*)	
Human	Oral	1.8–6 g/L	Lethal blood-alcohol conc. range	Kaye and Haag (*57*)	
		0.825–1.1 L/person	Fatal dose-avg. adult	Gosselin (*43*)	40–55% ethanol; within a few minutes
	Inhalation	2600 mg/m^3	Headache, stupor	Browning (*49*)	Individuals without tolerance
		9400–13,200 mg/m^3	Headache, stupor drowsiness	Browning (*49*)	Individuals with tolerance

Abbreviations: IP, intraperitoneal; IV, intravenous; MLD, minimal lethal dose.

of survival. The blood ethanol level at a particular time after ingestion depends on the rate of absorption from the gastrointestinal (GI) tract and the rate of biotransformation in the liver. A study by Jones and Jones (*40*) demonstrated that the blood ethanol concentration after equivalent oral doses is higher in women than in men, even with allowance for size differences.

Toxicokinetics

Ethanol is readily absorbed by the GI tract and the lungs (*39*), whereas percutaneous absorption is usually negligible. In two case reports, percutaneous alcohol intoxication in children was demonstrated (*41,42*); however, simultaneous inhalation cannot be totally ruled out. Ethanol is rapidly absorbed from the GI tract, particularly under fasting conditions. In the fasting state, peak blood ethanol levels are obtained in 30–60 min (*37*). Upon absorption into the bloodstream, ethanol is distributed according to the water content of tissues. Approximately 90% of administered dose is metabolized in the liver (*43*). Recent studies indicate that alcohol is also partly oxidized in the gastric mucosa.

The metabolism of ethanol in the gastrointestinal tissue is more effective in men than in women and to some extent serves as a barrier protecting against ethanol's systemic toxicity (*44*). This barrier is overcome by large doses of ingested ethanol. In addition, there appears to be a substantial amount of individual variability in the capacity for gastric alcohol oxidation. According to Frezza et al. (*45*), the capacity for local ethanol metabolism in the gastrointestinal tissue could determine how much enters systemic circulation. This hypothesis is offered as an explanation for sex-related differences in blood ethanol concentrations.

In the liver, ethanol is oxidized to acetaldehyde and then to acetic acid. The final biotransformation step involves the oxidation of acetic acid to carbon dioxide and water:

$$\underset{\text{Ethanol}}{CH_3CH_2OH} \rightarrow \underset{\text{Acetaldehyde}}{CH_3CHO} \rightarrow \underset{\text{Acetic Acid}}{CH_3COOH} \rightarrow CO_2 + H_2O$$

Several distinct enzyme-mediated pathways are involved in the oxidation of ethanol to acetaldehyde in the liver. The respective enzymes involved include alcohol dehydrogenase, catalase, and the microsomal ethanol-oxidizing system (MEOS), in particular the P450IIe2 (*38*). Acetaldehyde dehydrogenase seems to be the primary enzyme transforming acetaldehyde to acetate. In humans this enzyme is located in the cytosol of the liver; in rats it is present in the mitochondria. The resulting acetate is released from the liver and is oxidized peripherally in other tissues and in plasma. The oxidation rate of ethanol to carbon dioxide and water is 100–110 mg/kg/hr (*36*). This rate remains constant in a given individual and, within wide limits, is independent of the amount consumed.

Variation in the ethanol oxidation rate exists among different racial and ethnic groups. Omenn (*47*) and Zeiner et al. (*48*) demonstrated a more rapid conversion of ethanol to acetaldehyde in Chinese subjects than in Caucasians. These results were explained by an inherited atypical alcohol dehydrogenase in the Chinese subjects. Flushed face, tachycardia, and nausea were associated with higher blood acetaldehyde levels in this study. Vesell et al. (46) examined the effects of genetic and environmental factors on ethanol metabolism in humans. The results indicated that individual differences in rates of ethanol metabolism among 28 twins were genetically controlled and that environmental factors played a negligible role.

Ethanol inebriation in humans is rarely attributed to inhalation exposure. As with ingestion, the degree of intoxication upon inhalation varies according to degree of alcohol tolerance. For those unaccustomed to alcohol exposure, headache and slight stupor were produced by exposure to 2600 mg/m^3 after 33 min. Exposure of those with alcohol tolerance produced headaches only after a 20-min exposure to 9400 mg/m^3. Fatigue and drowsiness occurred after a 110-min exposure to 13,200 mg/m^3 (*49*).

Acute Toxicity in Animals

Examples of lethal doses by various routes of exposure are given in Table 2. In dogs, an acute ethanol dose of 3–10 g/kg produced respiratory failure and death within 12 hr. In a group of dogs given a 1.25 g/kg/hr dose, death resulted from cardiac failure and circulatory depression after a delay of 12 hr (*5*). All of these doses are comparatively large. Upon ingestion, symptoms of acute toxicity in animals include ataxia, lack of response to stimuli, absence of corneal reflex, and narcosis. Exposures by inhalation result in slight irritation of mucous membranes, excitation followed by ataxia, drowsiness, prostration, narcosis, twitching, general paralysis, dyspnea, and occasional death associated with respiratory failure (*5*). Ethanol is nonirritating to the skin of animals, and dermal absorption is poor. Ethanol is irritating and even injurious to the eyes in undiluted form, but is much less irritating when diluted (*5*).

Gasohol

Because ethanol exposure through gasohol or ethanol blended fuel exhaust would be diluted with other fuels, specifically gasoline, the actual ethanol exposure through evaporative emissions would be much lower than the amount associated with the acute toxic effects observed in experimental animal studies or in humans.

Recommendations and Areas for Further Research

It should be determined whether aspiration pneumonia after accidental ingestion of gasohol might represent as much of a problem as the ingestion of gasoline per se.

Methyl Alcohol

Methyl alcohol, also known as methanol, wood spirit, carbinal, wood alcohol, wood naphtha, methylol, Columbian spirit, and colonial spirit, is a colorless, volatile liquid with a molecular formula of CH_3OH. Its molecular weight

is 32.04 g/mole, the boiling point is 64.7°C, the flash point is 12°C, and the vapor pressure is 160 mm Hg at 30°C (*14*). The conversion factor from parts per million by volume in air to milligrams per cubic meter is 1.31. The TLV-STEL is 328 mg/m^3 (*22*).

A number of acute toxic exposures occur annually in humans through intentional or unintentional ingestion of unlabeled commercial solvents, windshield washing solutions, antifreeze, and alcoholic beverages diluted with methanol. The most recent concern for potential methanol exposure involves its possible use as a major automotive fuel in the United States.

Methanol Exposure from Vehicle Emissions

Kavet and Nauss (*58*) translate vehicle-specific emissions into ambient concentrations of methanol vapor in the following exposure scenarios: the personal garage, traffic, and public parking garage. There is substantial variation between evaporative emission concentrations for engines warming up (idling) and from hot engines being turned off.

Potential methanol exposure varies greatly between engines meeting emission standards and malfunctioning engines. For engines meeting emission standards in personal garages, the evaporative emission of methanol vapor can vary from < 2.9 mg/m^3 to > 50 mg/m^3. The estimated ambient methanol concentration among hot engines being turned off, 10% of which are malfunctioning, was projected by Gold and Moulis in 1988 to be as high as 150 mg/m^3 (*59*). Methanol concentrations for traffic situations are generally much lower (< 6 mg/m^3) than those for garages.

The final exposure scenario involves methanol refueling at service stations. The EPA estimates that the exposure concentration range for a typical 3–4 min fill-up would be 33–50 mg/m^3 methanol (*59*). However, all the data on exposure levels are based on a few measurements, and further studies are needed to elucidate these findings.

Acute Toxicity in Humans

Routes of exposure for methanol include ingestion, inhalation, and percutaneous absorption. Although the present discussion is chiefly concerned with potential inhalation exposure from vehicle emissions, acute intoxication occurs most commonly via ingestion of low-priced, adulterated, or fortified beverages (*60*).

Early manifestations of intoxication by ingestion are similar to those for ethanol. In mild cases of methanol poisoning, patients complain of headache, dizziness, nausea, lassitude, and slight abdominal pain (*60*). In more severe cases, fatigue, stupor, cyanosis, visual impairment or complete blindness, metabolic acidosis, convulsions, and circulatory collapse are noted. Furthermore, coma and/or respiratory failure and death may ensue (*61*). Visual impairment or complete blindness may be permanent. Examples of fatal doses of methanol in humans are listed in Table 3.The usual fatal dose range is 100–250 mL (*14,62*). However, the minimum dose leading to blindness in the absence of medical treatment is between 4 and 10 mL per person (*60,62*). In addition to individual susceptibility, other factors such as the amount consumed, the amount absorbed over a given time, and concomitant ethanol ingestion affect lethality.

After the initial intoxication has subsided, secondary symptoms often arise following a latent period of hours or days (*62*). During the asymptomatic latent period, methanol is transformed in the liver to formaldehyde and formic acid. Acidosis appears to trigger all late symptoms of methanol poisoning such as visual disturbances. The severity of the visual disturbances is proportional to the intensity of the delayed acidosis (*62*). Blocking methanol metabolism prevents the production of metabolites toxic to the visual system (*58*). Ethanol, which blocks methanol metabolism, is a very effective antidote and alleviates acidosis (*63*).

Table 3. Acute toxicity of methyl alcohol.

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral	7.4–13.0 mL/kg	LD_{50}	Kimura (*50*)	Methanol, undiluted, via straight needle
	Inhalation	1307 mg/m^3	Lethal dose of 16/46 animals	McCord (*77*)	Exposure time = 41 hr
Mouse	Oral	10.5–12.0 mg	MLD	Weese (*52*)	25% solution, single dose
Dog	Oral	6.3 g/kg (100%)	LD_{80}	Gilger and Potts (*66*)	Gavage, single dose
Rabbit	Oral	18 mL/kg	Lethal dose	Munch and Schwartze (*55*)	By stomach tube
Monkey	Oral	3.0 g/kg	Lowest lethal dose	Gilger and Potts (*66*)	Single dose via gavage (32–38 hr)
	Inhalation	1310 mg/m^3	Lethal to 4/11 animals	McCord (*77*)	18 hr/day; total exposure time = 41 hr
	IP injection	4 g/kg	LD_{50}	Clay et al. (*78*)	20% solution
	Dermal	5 mL/kg	Lowest reported lethal dose	McCord (*77*)	Secondary complication: edema
Human	Oral	100–250 mL	Usual fatal dose range	Budavari (*14*)	Susceptibility varies
		4 mL	Permanent blindness	Keeney and Mellinkoff (*60*)	
		0.3–1.0 g/kg	Minimum lethal dose range	Kavet and Nauss (*58*)	Untreated cases

Abbreviations: LD_{50}, lethal dose, median; MLD, minimal lethal dose; IP, intraperitoneal.

Benton and Calhoun (*64*) determined a latent period of 18–48 hr from ingestion of methanol to onset of visual disturbances. Furthermore, there appears to be no close correlation between the severity of symptoms, the quantity of methanol consumed, and blood methanol levels (*60,64*). Visual effects ranged from spots before the eyes (scotomata) to complete blindness. In serious cases, pupils are dilated and unresponsive to light (*60*). Other characteristic symptoms associated with visual disturbance include dimness of vision, hyperemia of the optic nerve head, inflammation of ganglion cells of the retina, atrophy of the optic nerve, congested, edematous retina, and blurring of optic disk edges. Without prompt treatment of the intoxication, bilateral blindness may result. Even when complete blindness is avoided, residual scotomata are characteristic. Permanent visual loss is associated with severe to moderate retinal edema. Other permanent neurologic sequelae are less frequent. These include speech difficulties, motor dysfunction with rigidity, spasticity, and hypokinesis.

The American Petroleum Institute made a rough projection of the incidence of methanol poisoning, morbidity, and mortality following the proposed widespread use of methanol fuels (85 or 100% methanol). Based on the reported 0.375% methanol mortality rate, the widespread use of methanol fuels could increase the number of methanol fatalities by 195 cases per year up from the current extrapolated 24 cases per year. Similarly, a dramatic increase in cases of blindness and neurological impairment is predicted. These considerations necessitate the development of innovative technical means to prevent siphoning and access to this material by small children as well as education of the public before methanol can be used extensively as a fuel (*65*).

Acute Toxicity in Animals

Examples of fatal doses of methanol in animals are listed in Table 3. Different animal species show a wide variation in sensitivity to methanol poisoning (*49*). Furthermore, similar to humans, animals within the same species show varying susceptibility to methanol's toxic effects (*66*). This explains the wide dose ranges for some acute toxic effects listed in Table 3.

The long latent period, relatively high toxicity, acidosis, and ocular injury observed in humans and subhuman primates are not seen after intoxication of nonprimate laboratory animals with methanol such as dogs, rabbits, rats, and mice. The rhesus and pigtail macaque are the best animal models for the evaluation of human toxicity.

A similar clinical picture in the rhesus macaque and humans was observed with respect to toxic dose levels, general clinical symptoms, ocular pathology, and acidosis. The monkeys showed no symptoms during the first 24 hr other than a mild, variable intoxication. In most animals semicoma occurred shortly before death by respiratory failure on the second day (*66*). In contrast, rodents and dogs exhibit different acute toxic effects. Their clinical picture is characterized by the early onset of symptoms such as narcosis, ataxia, hypermotility, and increased amiability proceeding to a semicomatose–comatose state and finally death. There is no latent period in these animals (*66*).

Comparison of lethal doses for nonhuman primates and other laboratory animals further establishes the nonhuman primate as a better model for human acute methanol toxicity. The lethal dose for most nonprimate laboratory animals was 6–10 times the average human lethal dose, whereas the lethal dose for nonhuman primates is within the same range (*66*). Similarly, acidosis studies indicate that nonhuman primates develop severe acidosis much more frequently than other laboratory animals (*38*). Recently attempts have been made to use small laboratory animals such as the rat and the mouse as experimental models by blocking the oxidation of formic acid (*67*).

Toxicokinetics

Methanol is readily absorbed when inhaled or ingested (*43*). Following uptake and distribution in the body, a minor portion of administered methanol is eliminated either unchanged in exhaled breath or urine. Most methanol, however, is metabolized in the liver. Metabolic clearance accounts for about 90% of initially administered low methanol doses (2 mg/kg) in both nonhuman primates and rats (*68*). Although methanol metabolism is a saturable process, Eells et al. (*69*) showed that even at very high doses (1 g/kg) administered to monkeys, 78% was recovered as exhaled CO_2.

In addition to the dominant role of metabolism in methanol clearance, metabolism is important because of the association between methanol's delayed acute toxic effects and its intermediate metabolites. Unless taken in narcotic doses, methanol itself is not considered to be the principal acute toxicant. The metabolic sequence for methanol in all mammals is as follows:

$$\text{Methanol (1)} \rightarrow \underset{\text{Formaldehyde}}{} \text{(2)} \rightarrow \text{Formate (3)} \rightarrow CO_2 + H_2O \quad (H^+)$$

In rats, rabbits, and guinea pigs, the initial oxidation of methanol to formaldehyde is mediated by a catalase-peroxidative system. However, humans and nonhuman primates oxidize methanol to formaldehyde via alcohol dehydrogenase (*38*). The rates of this initial metabolic step are similar in nonhuman primates and rats. In the second step of methanol metabolism, formaldehyde is converted to formic acid. This step is composed of two reactions. First, formaldehyde is oxidized to *S*-formylglutathione, a process that requires reduced glutathione (GSH) and is mediated by an NAD-dependent formaldehyde dehydrogenase. Second, *S*-formylglutathione is converted to formic acid, catalyzed by thiolase. It remains disputed which intermediate metabolite, formaldehyde or formic acid, is responsible for delayed effects of methanol poisoning. However, recent research shows that formate accumulation in the blood of monkeys parallels the development of ocular disturbances and acidosis, supporting the presumption that formic acid is the prime suspect for the delayed effects and the ocular toxicity (*66,67*).

A folate-dependent pathway is responsible for metabolizing formic acid in both nonhuman primates and rats. However, rats use the pathway more efficiently than nonhuman primates, thus explaining the species-dependent nature of the acute toxicity of methanol. At high methanol doses, formate enters the folate-dependent pathway in humans and nonhuman primates at rates that exceed the pathway's capacity (*58*).

In the first reaction of the folate-dependent pathway, formate forms a complex with tetrahydrofolate (THF). Subsequently, this complex is converted to 10-formyl-THF (catalyzed by formyl-THF synthetase) and then to carbon dioxide (catalyzed by formyl-THF dehydrogenase). There appears to be a strong association between the efficiency of formate metabolism and the hepatic concentration of THF. THF is derived from dietary folic acid and by its regeneration in the folate pathway. Makar and Tephly (*70*) determined that rats fed a folate-deficient diet became acidotic and accumulated formate similar to nonhuman primates. A diminished capacity to oxidize formate causes methanol toxicity in folate-deficient rats.

In addition, there is also a strong correlation between hepatic THF levels and endogenous folate regeneration. In a series of experiments, Eells et al. (*67,69,71*) blocked the folate feedback loop with nitrous oxide (N_2O), resulting in a slowed formate oxidation and increased methanol sensitivity. The extent to which N_2O slowed formate oxidation was directly related to the decrease in hepatic THF levels, demonstrating that THF concentration was the critical factor in these experiments. Subsequent research by Black et al. (*72*) showed that THF concentration in monkey livers was 59% of that in rats; the ratio of THF concentrations was similar to the ratio of their maximal formate oxidation rates. Several human studies show that even methanol exposures not saturating the folate pathway produce small amounts of formate in blood and urine (*73–75*). However, background blood formate levels varied in these studies, masking subtle differences methanol exposure may have caused. Although incremental formate accumulation may not be readily measurable against background levels, Kavet and Nauss (*58*) determined that the contribution from a single, brief methanol exposure (worst-case exposure scenario) is about 4% (0.0082 Mm) of the background formate level (0.2 Mm).

According to Kavet and Nauss (*58*), the approximate methanol dose needed to saturate the folate pathway would be 210 mg/kg for an individual with 60% body water. Given this figure, Kavet and Nauss (*58*) concluded it is unlikely that the folate pathway would be overwhelmed in the worst-case scenario described above (single exposure of 200 mg/m^3 for up to 15 min in a garage), since the estimated body burden would be less than 1 mg/kg. The same conclusion can be applied to methanol vapor exposures of 50 mg/m^3 by filling station attendants who are exposed for several minutes repeatedly throughout the day. Filling station attendants could expect an initial body burden of 0.05 mg/kg during a 5-min exposure to 50 mg/m^3 at the same ventilation. However, 8–15% of the population in the United States has a low red blood cell folate level (*76*), which may make this subpopulation more sensitive.

Recommendations/Areas for Further Research

If methanol becomes widely used in automotive fuel, exposure to methanol emissions, although not very high, would be widespread. Future research should concentrate on reducing uncertainty about health effects and about susceptible subpopulations on marginal diets or individuals who take medications that are folic acid antagonists. Further research examining the relation between formate concentration and persistence in the blood and visual impairment would be useful for predicting visual effects of vehicular methanol exposure.

Methyl Tertiary Butyl Ether

Methyl tertiary butyl ether (MTBE), or tertiary amyl ether, is a colorless, flammable liquid with a molecular weight of 88.15 g/mole and a boiling point of 55.2°C (*14*). The conversion factor from parts per million volume to milligrams per cubic meter is 3.6. MTBE is used to enhance the octane rating in unleaded gasoline. It was approved by EPA in 1979 as an octane booster in concentrations up to 11%. More recently MTBE has been used in the United States to increase the oxygen content of fuel and thereby lower carbon monoxide and other hydrocarbon emissions. Roughly 20% of the fuels now sold in the United States contain MTBE as an additive, and it is anticipated that the use of MTBE will increase. Because of this increase in use, the EPA placed MTBE on the list of chemicals for priority consideration in the promulgation of test rules. In 1987 EPA and the MTBE task force of industry negotiated a testing consent order for MTBE. Additional information on the toxicity of this compound will become available in the future.

Using a fuel with 10% MTBE, the expected amount of MTBE emitted from the tailpipe would be 2% of the volatile organic compounds. The expected ambient concentration of MTBE at service stations would be below 3.6 mg/m^3 (J. Kneiss, personal communication).

Acute Toxicity in Humans

The major exposure route for MTBE used in gasoline would be through inhalation (*79*). However, human exposure to MTBE has primarily been associated with its use as an experimental therapeutic agent dissolving gallstones in the bile duct. The local effects observed upon infusion into the gallbladder or bile duct include short-term elevation of liver enzymes, burning abdominal pain, and sedation. Systemic effects include perspiration, transient hypotension, bradycardia, and somnolence with a distinctive smell of ether in the patient's breath.

Allen et al. (*80*) indicate that MTBE can be effective in dissolving cholesterol gallstones rapidly without causing serious side effects in patients. The gall bladder concentrates MTBE with minimal systemic absorption. MTBE is a powerful lipid solvent. Allen et al. (*81*) suggest that intravascular and intrahepatic infusion of substantial amounts might produce hemolysis or necrosis. Allen et al.

(*80*) also suggest that the toxicity of MTBE is similar to that of diethyl ether, although MTBE is less volatile. The routes of exposure and the concentrations received from the use of MTBE in gasoline would be quite different. Except for providing qualitative information that suggests how humans might react to high doses of MTBE, the information of the clinical use of this material is not particularly relevant to the evaluation of the toxicity of MTBE as an additive in gasoline. For this use the routes of exposure and the doses received are very different.

Acute Toxicity in Animals

MTBE is acutely only slightly toxic (Table 4). Studying the acute toxicity of MTBE alone and in combination with gasoline in mice and rats via intravenous, intraperitoneal, subcutaneous, and inhalation routes, Snamprogetti (*81*) determined that MTBE was more toxic than gasoline, but the toxicity of gasoline was not altered by adding 10–15% MTBE. Conaway et al. (*82*) determined that although the addition of 10 or 15% (v/v) MTBE to high-octane premium gasoline did not increase the acute toxicity of gasoline in rats and mice, it did lengthen the barbiturate-induced sleeping time, reduce spontaneous motor activity, and cause slight disturbances in motor coordination.

Most animal data on MTBE concern rats, but there are some data on monkeys and mice. According to Kneiss (personal communication) concentrations of 3610 mg/m^3 can produce anesthetic effects that are reversible upon termination of exposure.

Clinical symptoms observed in rats and mice exposed to 29,000 mg/m^3 air for 6 hr over 13 consecutive days include hypoactivity, ataxia, and periocular irritation, decreased startle and pain reflexes, and decreased muscle tone. These symptoms were reversible, and no mortality was observed among the rats and mice (*79,81*). MTBE is slightly irritating to the eyes and the mucous membranes and minimally irritating to the skin (*82*).

Metabolism

After MTBE exposure, 20–70% is rapidly exhaled depending on the dose and exposure route. The remaining MTBE is excreted through the urine. In addition to the excretion of unchanged MTBE primarily via the lungs, MTBE is also metabolized. MTBE is oxidized to form formaldehyde and demethylated to form tertiary butyl alcohol (TBA). TBA is oxidized to 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid. The fraction of TBA present with MTBE in exhaled air of animals exposed to MTBE ranges from 0.6 to 4.5%. This fraction varies with the dose administered, route of exposure, and time interval after exposure. Furthermore, there appears to be an increase in the proportion of TBA in exhaled air with time (*84*). Excretion of 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid was observed in the urine of rats following inhalation, oral, and intravenous exposure to MTBE.

Brady (*85*) studied the metabolism of MTBE by rat hepatic microsomes. An 18-hr pretreatment with 1–5 mL/kg MTBE induced liver microsomal pentoxyresorufin-dealkylase activity 50-fold. In addition, pretreatment with monoclonal antibodies against the P450 isozyme P450IIE1 inhibited MTBE metabolism by 35%. Brady et al. (*85*) concluded from these results that MTBE oxidation to formaldehyde and TBA *in vivo* and possibly other biochemical effects associated with MTBE exposure are changed by agents affecting the relative quantities of cytochrome P450 isozymes.

Savolainen et al. (*86*) used MTBE to determine that the oxidation of alcohol and glycol ethers involves the breakdown of the ether bond. However, the biotransformation of TBA by the monooxygenase complex competed for the breakdown of the ether. In addition, due to TBA's slow metabolic breakdown, the alcohol conjugated with glucuronic acid. Savolainen et al. (*86*) demonstrated a linear correlation between the concentration of MTBE in the brain and the blood ether concentration. The high lipophilicity of MTBE could explain its high concentration in fat. It is not clear whether species variation in the rate of metabolism between methylation and oxidation exist among species and between high and low doses.

It appears unlikely that MTBE in fuel poses a human health hazard given calculated inhalation exposures during refueling of less than 3.6 mg/m^3.

Aromatic Hydrocarbons: Benzene, Toluene, and Xylene

Aromatic hydrocarbons are used as industrial raw materials, solvents, and components of many commercial

Table 4. Acute toxicity of methyl tertiary-butyl ether.

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral	2,963–3,865 mg/kg body weight	LD_{50}	Sivak and Murphy (*79*)	By gavage
	Inhalation	126,000 mg/m^3	LC_{50}	Conaway et al. (*82*)	4-hr exposure
		65,000 mg/m^3	LC_{50}	Sivak and Murphy (*79*)	5.6 min to death
		11,000 mg/m^3	Occasional anesthesia	Conaway et al. (*82*)	6 hr/day, 5 days/week for 9 days
		70 mg/L	No deaths occurred	ARCO (*86*)	4-hr exposure
Rabbit	Dermal	> 10 g/kg	LD_{50}	Syracuse (*83*)	
Human	Infusion via common bile duct to duodenum	15 mL	Perspiration, hypotension, bradycardia, narcosis	Geller et al. (*87*)	

Abbreviations: LD_{50}, lethal dose, median; LC_{50}, lethal concentration, 50%.

and consumer products (*5*). In this report only their use as components of gasoline will be reviewed. Small amounts of these chemicals occur naturally in blends of gasoline. In addition, aromatic rich streams containing these hydrocarbons are added as blending agents in percent concentrations to unleaded gasoline to improve the antiknock characteristics of gasoline (*88*).

These substances can enter the body through all exposure routes. However, percutaneous absorption is too slow to produce acute systemic effects. McDougal et al. (*89*) studied the dermal absorption of a number of solvents in rats and compared them to human data in the literature. In rats the absorption was generally two to four times greater than in humans. In these experiments the shaved rats were given total body exposure but inhaled fresh air through respiratory protection devices. For benzene, 0.8% of the dose was taken up. For toluene and *m*-xylene, the skin uptake was slightly greater (3.7 and 3.9%, respectively). Additional information on skin penetration of these and other chemicals is given by Grandjean (*90*).

There are few if any well-documented fatal poisoning cases in humans. Furthermore, studies suggest that liquid hydrocarbons aspirated into lungs after ingestion could cause more damage than those absorbed through the gastrointestinal (GI) tract. According to Gerarde (*33*), the oral LD_{50} may be 200 times greater than the intratracheal LD_{50}. Aspiration of a fraction of a milliliter of these liquid aromatic hydrocarbons would result in extensive pulmonary edema and hemorrhage. More study is needed on the hazards of aspirating liquid aromatic hydrocarbons (*33*).

Exposure to aromatic hydrocarbons via inhalation, ingestion, and injection produces similar systemic clinical effects. The exception is respiratory tract irritation and pulmonary edema, which result from inhalation exposure or aspiration of ingested material subsequent to regurgitation or gastric lavage (gastric lavage is no longer widely recommended) (*43*).

The principal target organ in acute intoxication is the CNS. The clinical picture after acute administration of benzene, toluene, or xylene is essentially the same and occurs in about the same dosage range. At acute doses, these compounds are only moderately toxic. Although studies with mixtures of these chemicals have not been conducted, it is possible that if given as a mixture in comparable amounts the acute toxicity of the mixture would not differ. The symptoms reported resemble those occurring with ethanol inebriation (*43*). These symptoms, which follow lower inhalation or oral exposure levels, include dizziness, weakness, euphoria, headache, nausea, vomiting, tightness in the chest, and staggering (*38*). More severe exposures result in visual blurring, tremors, shallow and rapid respiration, ventricular fibrillation, paralysis, unconsciousness, and convulsions (*39*). In contrast to aliphatic hydrocarbons where coma is associated with depressed reflexes, benzene induces states of unconsciousness that are associated with hyperactive reflexes such as tremors, motor restlessness, hypertonia, and jerking or twitching movements (*43*).

Direct skin contact with liquids promotes defatting of the keratin layer, which causes vasodilation, erythema, and dry and scaly dermatitis (*5*). Xylenes are more potent skin irritants than benzene or toluene. Direct eye contact with liquid or solid aromatic hydrocarbons causes itching, lacrimation, and irritation. Conjunctivitis and corneal burns have also been reported (*33*). Liquid toluene splashed into the eyes causes corneal burns if untreated (*33*). Toluene and benzene vapors irritate the mucous membranes of the respiratory tract. The irritant action of toluene on skin and mucous membranes is stronger than that of benzene. For all three aromatic hydrocarbons, the degree of irritation depends on the concentration and duration of exposure.

The acutely toxic doses of aromatic hydrocarbons are listed in Tables 5–7. All of these chemicals have a low order of toxicity unless they are aspirated following ingestion and vomiting. Humans appear to be more susceptible than rodents to the acute oral toxicity of aromatic hydrocarbons. According to the Agency for Toxic Substances and Disease Registry (ATSDR) (*91*), the dose of benzene expected to cause death in humans is 100 mg/kg/day (for a period of up to 14 days) compared to 1000 mg/kg/day for animals (Table 5).

Acute Toxicity of Specific Compounds

Benzene. The molecular formula for benzene is C_6H_6, the molecular weight is 78.11 g/mole, the boiling point is 80.1° C, the vapor pressure is 100 mm Hg at 26.1° C, and the flash point is −11°C (*14*). The conversion factor from parts per million volume to milligrams per cubic meter is 3.19.

Although the major effect of high chronic benzene exposure is hematopoietic toxicity with resulting anemia, leukopenia, thrombocytopenia, and ultimately leukemia in some individuals, the most sensitive target organ for acute benzene toxicity is the CNS. The acutely toxic doses are listed in Table 5. The primary signs of mild benzene intoxication include dizziness, weakness, headache, euphoria, nausea, vomiting, tightness in the chest, and staggering (*33*). Benzene intoxication also produces dyspnea, vertigo and tinnitus, inebriation, and delirium. More severe exposure results in visual blurring, tremors, ventricular fibrillation, paralysis, unconsciousness, convulsions, and deep anesthesia (*5,62,91*).

TOXICOKINETICS. Because benzene is highly volatile, the most prevalent route of exposure is by inhalation. In humans, at concentrations of 160–320 mg/m^3 in air for several hours, 50% is absorbed by the lungs. Benzene inhaled by human subjects at a concentration of 0.340 mg/L for 5 hr resulted in 33–65% body retention, 3.8–27.8% exhaled unchanged through the lungs, and 0.1–0.2% excreted in the urine (*5*). A study of respiratory retention and uptake in humans as a function of time during the exposure period revealed that absorption was greatest in the first 5 min, decreasing to a constant level after 30 min. Respiratory retention represents the difference between respiratory uptake and excretion. Schrenk et al. (*93*) determined that benzene was rapidly absorbed in the lungs of dogs. Similar to humans, most absorption occurred early in the exposure period (during the first 30 min), and equilibrium was established after several hours. In addi-

Table 5. Acute toxicity of benzene.[a]

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral	1.0–5 g/kg	LD_{50} range	Kimura (*50*)	Varies by age and strain
		930 mg/kg	Lowest lethal dose	ATSDR (*91*)	
	Inhalation	43,800 mg/m^3	Lowest lethal dose	Drew and Fouts (*96*)	4-hr exposure
	Instillation, lung	0.25 mL	Cardiac arrest	Gerarde (*33*)	
Mouse	Oral	4.7 g/kg	LD_{50}	Savchenko (*97*)	
	Inhalation	33,000 mg/m^3	LC_{50}	Svirbely et al. (*98*)	
		77 mg/L	Lethal dose	Sandmeyer (*5*)	Death in 50 min
	IP injection	0.47 g/kg	LD_{50}	Sandmeyer (*5*)	
Dog	Inhalation	146,000 mg/m^3	Lethal dose	Sandmeyer (*5*)	
Rabbit	Inhalation	112,000–1,100,000 mg/m^3	Lethal dose	Carpenter et al. (*99*)	Death in 36 min
	SC injection	0.10 mL	Moderate irritant, conjunctiva; transient corneal injury	Wolf et al. (*100*)	
Human	Oral	128–428 mg/kg	Lethal dose range	ATSDR (*91*)	70-kg adult
	Inhalation	61,000–64,000 mg/m^3	Potentially fatal	Gerarde (*33*)	5–10 min
		9,600 mg/m^3	Tolerable for 30 min–1 hr	Gerarde	

Abbreviations: LD_{50}, lethal dose, median; LC_{50}, lethal concentration, 50%; IP, intraperitoneal; SC, subcutaneous.
[a]No data were found for benzene lethality by dermal exposure in humans or animals.

tion, recent animal studies with rats and mice indicate that uptake is inversely proportional to exposure concentrations (*91*), suggesting that at higher concentrations less of the chemical is absorbed.

Although no definitive scientific data exist on oral absorption of benzene in humans, case studies show that benzene is readily and rapidly absorbed by this route. In addition, animal studies indicate that almost all of the ingested benzene is absorbed (*91*). Parke and Williams (*93*) demonstrated that about 90% of ^{14}C-labeled benzene administered orally to rabbits was eliminated in exhaled air and urine.

According to ATSDR (*91*), information on the acute dermal toxicity of benzene from dermal exposure is not available. Dempster et al. (*94*) investigated the time–effect relationship of behavioral and hematological changes resulting from benzene inhalation by mice. Although benzene itself is thought to be responsible for neurotoxic effects, its hematologic effects are thought to be caused by metabolites. However, in this experiment, hematological and specific behavioral changes followed the same time course upon 6-hr inhalation exposure to 320 mg/m^3 benzene. This suggests that benzene metabolites may be involved in behavioral changes observed in mice. After a 6-hr exposure to 3195–9584 mg/m^3, Dempster et al. (*94*) also observed changes in neuromuscular function in mice. The short time period between exposure and effect suggests either a direct effect of benzene or rapid conversion to a sufficient concentration of metabolites.

The liver is the primary site of benzene metabolism; conversion of benzene occurs by mixed-function oxidases there. Retained benzene is oxidized to phenol, 1,2-dihydroxybenzene, 1,4-dihydroxybenzene, or 1,2,4-trihydroxybenzene, cresols, mercapturic, or muconic acids and conjugated to sulfate or glucuronide (*5*). Benzene oxide is also formed and in turn is transformed to phenol. Hydroquinone and/or catechol are formed by the introduction of a second hydroxyl group. Finally, the addition of a third hydroxyl group produces 1,2,4-trihydroxybenzene or glucuronides and sulfate esters through conjugation reactions. Hydroxylated benzene metabolites may be converted to their corresponding quinones or semiquinones (*95*).

Benzene appears to stimulate its own metabolism, increasing the rate of toxic metabolite formation (*91*). In contrast, excess phenol accumulation inhibits microsomal activity by feedback inhibition (*5*). In addition, pretreatment with other compounds alters the rate of benzene metabolism. Benzene metabolism, mediated largely by mixed-function oxidases in hepatic microsomes, is increased by 40% in rats and 70% in mice upon phenobarbital pretreatment. Pretreatment with toluene inhibits benzene metabolism. Benzene metabolism is enhanced by ethanol ingestion and dietary factors such as food deprivation and carbohydrate restriction (*91*). The metabolism and elimination of benzene appears to be similar in humans and animals. According to Sandmeyer (*5*), metabolism and elimination of benzene is more rapid in humans than in dogs.

Toluene. Toluene has a molecular formula of C_7H_8, a molecular weight of 92.14 g/mole, a boiling point of 110.62°C, a vapor pressure of 22 mm Hg at 20°C, and a flash point of 4.4°C (closed cup) (*14*). The conversion factor from parts per million volume to milligrams per cubic meter is 3.76. The TLV-STEL is 565 mg/m^3 (*22*).

The acutely toxic doses in different species are listed in Table 6. The oral LD_{50} in rats has been reported to be about 5 g/kg (range 2.6–7 g/kg body weight) depending on age and strain (*50,100,101*). The reported LC_{50} for mice is about 20,040 mg/m^3, compared to 32,800 mg/m^3 for rats (*98*). Toluene is only slightly irritating to the skin and eyes of rabbits (*102*). In humans, in addition to the systemic effects already discussed, exposure to toluene at low concentrations produces anorexia and prolonged reaction time. At high concentrations, purpura, paresthesia, visual disturbances, metabolic acidosis, coma followed by pulmonary edema, and post-narcotic nervous disturbances have been reported (*17,101*). Acute exposures to amounts of toluene sufficient to produce unconsciousness fail to produce residual organ damage (*33*).

Table 6. Acute toxicity of toluene.

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral	5500–6500 mg/kg	LD_{50} range for the adult rat[a]	Kimura (*50*)	1 week observed; undiluted; one dose, straight needle
	Inhalation	32,800 mg/m^3	LC_{50}	Carpenter et al. (*110*)	4-hr exposure
	IP injection	800–1,640 mg/kg	LD_{50} range	Sandmeyer (*5*)	Undiluted
Mouse	Inhalation	20,040 mg/m^3	LC_{50}	Svirbely et al. (*98*)	Exposure time not reported
Dog	Inhalation	2860 mg/m^3	No discomfort	Carpenter et al. (*110*)	6 hr
Rabbit	Inhalation	132,000–170,000 mg/m^3	Lethal dose	Carpenter et al. (*110*)	40 min to death
	Dermal	14 g/kg	LD_{50}	Sandmeyer (*5*)	
Human	Inhalation	376.7 mg/m^3	LOAEL; eye irritant	Andersson et al. (*111*)	6-hr exposure
		380 mg/m^3	NOAEL	Von Oettingen et al. (*18*)	8-hr exposure
		750 mg/m^3	Uncoordination; reaction time impaired	Von Oettingen et al. (*18*)	
	Dermal	753.4 mg/m^3	Paresthesias	Von Oettingen et al. (*18*)	8-hr exposure
	Eye	376.7–1883.4 mg/m^3	Range for irritant	Sandmeyer (*5*)	

Abbreviations: LD_{50}, lethal dose median; LC_{50}, lethal concentration, 50%; IP, intraperitoneal; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level.

[a]Effect may be age-dependent; LD_{50} for 14-day-old rats was much lower.

HABITUATION. Toluene abuse and addiction have been observed in the general population. Addiction may result from inhaling glues, paint thinners, fingernail polish removers, and cleaning fluids (*43*). Few studies have examined the acute effects of toluene exposure on tolerant individuals. Garriott and Petty (*103*) exposed habituated subjects to air levels greater than 30 mg/L, which is above the reported fatal concentration range of 10–28 mg/L. Garriott and Petty (*103*) observed that these individuals exhibited no distress and only moderate signs of intoxication such as slurred speech, impaired ability to concentrate, and slow, unsteady movements. However, Garriott and Petty (*103*) attribute this effect only partially to established tolerance and suggest that the reported fatal dose range be reexamined. Exposure to toluene through solvent abuse and glue sniffing usually involves exposures to a mixture of compounds (*91*).

TOXICOKINETICS. Human studies indicate that toluene is readily absorbed after inhalation (*104*). Ovrum et al. (*105*) demonstrated a high correlation between alveolar and arterial concentrations of toluene during and after exposure of humans to 300 mg/m^3. Pyykko (*106*) showed that toluene is absorbed more rapidly via inhalation exposure than from oral exposure (15–20 min compared to 3 hr). Dermal absorption is much slower than absorption from either inhalation or oral exposure. The amount absorbed in human forearm skin per hour was 14–23 mg/cm^2/hr (*104*). In addition, the dermal LD_{50} value of 14 g/kg for rabbits demonstrates negligible dermal absorption through intact skin of animals (Table 6) (*5*).

It is not possible to correlate health effects to toluene levels in tissues after absorption. However, data show that toluene is distributed to lipoidal and highly vascular tissues such as the brain, liver, kidneys, and blood (*104*). Benignus et al. (*107*), who studied toluene levels in the blood and brain of rats during and after exposure to 2167 mg/m^3 toluene for up to 4 hr, showed that toluene levels in the blood and brain of rats upon inhalation exposure reached 95% of the estimated peak levels in 53 and 58 min, respectively. Although brain and blood toluene levels did not rise at significantly different rates, the brain level fell significantly more rapidly than the blood level. No studies were found in which toluene distribution in humans or animals after oral or dermal exposure were reported.

Microsomal liver enzymes control the first step of toluene metabolism and its initial conversion to benzyl alcohol. Pyykko (*106*) demonstrated that continuous toluene inhalation of 7,500 mg/m^3 in adult male rats increased the level of these enzymes significantly after 12–24 hr. After exposure, enzyme activity and concentration of cytochromes returned to control levels in 1–4 days. This finding is consistent with time courses of induction after single-dose exposures to other drugs such as phenobarbital.

A study by Geller et al. (*108*) suggests that the extent of detoxification of toluene is sex dependent. In male and female Sprague-Dawley rats acutely exposed to high concentrations of toluene (45,000–136,000 mg/m^3), hepatic levels of alcohol dehydrogenase were significantly increased in the females. Alcohol dehydrogenase catalyzes the conversion of benzyl alcohol, an intermediate metabolite of toluene, to benzaldehyde. Benzaldehyde is eventually converted to hippuric acid, the major urinary metabolite of toluene (*109*). Female rats do have an increased capacity to biotransform toluene (*104*).

Toluene per se is excreted through exhaled air, and metabolites are primarily excreted in urine. Two metabolites, hippuric acid and to a lesser extent *ortho*-cresol in urine are used to monitor exposure in workers (*110*). In nonfatal cases, effects of short-term exposure generally resolve completely after exposure (*104*).

Xylene. The molecular formula of xylene is C_8H_{10}, the molecular weight is 106.17 g/mole, the boiling point is 138.3°C, the vapor pressure is 6 mm Hg at 20°C, and the flash point is 25–27°C (*14*). The conversion factor from parts per million volume to milligrams per cubic meter is 4.33.

There are three forms of xylene: *ortho*-, *meta*-, and *para*-xylene. Mixed xylene is a mixture of these three

forms with small amounts of other chemicals as well. Both human and animal data suggest that mixed xylene and *o*-, *m*-, and *p*-xylene produce similar effects, although not necessarily with equal potency.

The acutely toxic doses of xylene are listed in Table 7. According to Hodge and Sterner's (*112*) classification system of toxicity, the data on acute oral exposure and inhalation of xylenes show them to be slightly toxic by these exposure routes (*113*) (Table 7). Effects specific to xylene inhalation exposure in humans include nose and throat irritation, severe lung congestion, pulmonary hemorrhages, and edema. Animal data provide evidence for respiratory irritation as well.

Neurological deficits associated with acute xylene inhalation exposure in humans include impaired short-term memory and alteration in equilibrium or body balance. In addition, there are cases of xylene producing a variety of other symptoms including epileptic seizures, amnesia, cerebral hemorrhage, and unconsciousness. In instances of solvent abuse, the instant death that results may be caused by sensitization of the myocardium to epinephrine. When this occurs, endogenous hormones precipitate sudden and fatal ventricular fibrillation or respiratory arrest and consequent asphyxia. Clinical findings from acute exposures of workers (not necessarily involving solvent abuse) to xylene suggest that females are more susceptible to solvent effects (*114*).

According to Sandmeyer (*5*), the visual disturbances observed in humans upon acute xylene exposure are comparable to the exaggerated rotary and positional nystagmus in the rabbit. Furthermore, xylene may produce turbidity and severe irritation of the conjunctiva, with lacrimation and edema.

The neurological effects of xylene are not well understood. Human studies indicate that the first observable neurological effect is seen in the central vestibular system, which controls equilibrium and body balance. Savolainen et al. (*115*) determined that the mean venous blood xylene concentration in which body balance was impaired in six human subjects was 29.1 ± 3.2 μmole/L. Experimental studies often use rabbits to model body balance effects in humans. Alternatively, xylene may produce clinical symptoms by altering nerve conductivity (*113*).

Most volunteers exposed to 2000 mg/m^3 technical-grade xylene for 15 min had eye irritation and irritation of the upper airways (*115*). Ingestion of xylene may lead to irritation of the gastric mucosa (*43*). Skin contact with xylene may cause a burning sensation and reversible erythema (*116*), and prolonged exposure may lead to contact dermatitis (*117*). In addition, effects on the kidneys and liver have been reported in humans after acute exposure to high levels (*119,120*).

TOXICOKINETICS. Xylene absorption by the lungs and the stomach is rapid. However, although absorption after ingestion is complete, retention by the lungs ranges from 50 to 75%. Physical exercise as well as higher concentrations can increase the amount of xylene absorbed through the lungs. Experimental studies on humans indicate that *m*-xylene in the vapor or liquid form is absorbed through the skin. However, dermal absorption of xylene is only a small fraction of that absorbed after inhalation (*113*). More specifically, Riihimaki and Pfaffli (*120*) showed that percutaneous exposure to 2610 mg/m^3 xylene vapor for 3.5 hr corresponded to an inhalation exposure of less than 43 mg/m^3 for the same time period.

Once absorbed, xylene's biotransformation takes place in the liver or the lungs. The metabolism of xylene is independent of the exposure route, the specific isomer, the administered dose, or the exposure duration. The first step consists essentially of the oxidation of a side-chain methyl group by microsomal liver enzymes to toluic acids (methylbenzoic acids). There is agreement among animal and human studies that xylene induces liver microsomal cytochrome P450 similar to phenobarbital. The second

Table 7. Acute toxicity of xylene.

Species	Exposure route	Dose level	Effect	Reference	Notes
Rat	Oral (gavage)	3500–8600 mg/kg	LD_{50}	NTP (*122*), ATSDR (*113*)	Mixed xylene, in corn oil and undiluted
	Inhalation	28,000–29,000 mg/m^3	LC_{50}	ATSDR (*113*), Carpenter et al. (*114*)	For mixed xylene, 4 hr
		21,000 mg/m^3	LC_{50}	Harper et al. (*123*)	For *p*-xylene, 4 hr
Mouse	Oral (gavage)	5,300–5,600 mg/kg	LD_{50}	NTP (*122*)	Sex dependent
	Inhalation	23,000 mg/m^3	LC_{50}	Bonnet et al. (*124*)	For *m*-xylene, 6 hr
		20,000 mg/m^3	LD_{50}	Bonnet et al. (*124*)	For *o*-xylene, 6 hr
		17,000 mg/m^3	LC_{50}	Bonnet et al. (*124*)	For *p*-xylene, 6 hr
	Eye	1.8 mL/kg	LD_{50}	Schumacher (*125*)	
Rabbit	Dermal	14.1 mL/kg	LD_{50}	Sandmeyer (*5*)	For *m*-xylene
	Eye	13.8 mg	Irritation; corneal injury	Sandmeyer (*5*)	
Human	Oral	15 mL	Potential lethal dose	Bonnichsen (*126*)	
	Inhalation	860 mg/m^3	Irritant-eyes, nose, throat	Nelson et al. (*127*)	3–5-min exposure
		>870 mg/m^3	Nausea, vomiting, dizziness, incoordination, mucous membrane irritation	Browning (*128*)	
		43,000 mg/m^3	Unconscious, potentially fatal	Morley (*118*)	

Abbreviations: LD_{50}, lethal dose, median; LC_{50}, lethal concentration, 50%.

step involves the conjugation of toluic acids with glycine to form toluric acids (methylhippuric acids), the primary urinary end product. The majority of xylene metabolites are readily excreted through urine and are indicators of worker exposure. Much of the xylene taken into the body is excreted within 18 hr after exposure. The shortest reported time for appearance of metabolites in urine is 2 hr. The amount of methyl hippuric acid excreted in urine increases with time, reaching a maximum at the end of the exposure (*104*).

The metabolism of xylene in humans and animals produces the same end products but in different quantities. The quantitative difference occurs in the metabolism of methylbenzoic acid or toluic acid. In humans, methylhippuric acid accounts for more than 90% of the absorbed dose, but in rats given *m*- or *p*-xylene by IP injection, the respective amounts of *m*- and *p*-methylhippuric acid excreted in urine ranged from 49% to 62.6% and 64% to 75% of the administered dose. Likewise, the proportion of administered doses excreted in rabbits as methylhippuric acids was substantially less than that in humans. The remaining portion is accounted for by production of glucuronic acid derivatives formed from conjugation with glucuronic acid (instead of glycine) or the production of xylenols by aromatic hydroxylation. Sedivec and Flek (*121*) showed that humans given 19 mg/kg xylene excreted only methylhippuric acid, whereas rabbits given 600 mg/kg excreted both methylhippuric acid and glucuronic acid derivatives. These quantitative differences may be explained by larger doses administered to the rabbits. Furthermore, the formation of an excess amount of glucuronic acid derivatives in rabbits may represent a secondary alternative pathway activated when the amount of glycine available for conjugation is limited or has been depleted. This would suggest that the second step conjugation of toluic acid is the rate-limiting step in humans (*113*).

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