Environmental Health Criteria 52

TOLUENE

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR TOLUENE

The WHO Task Group on the Environmental Health Criteria
for Toluene met in Geneva from 3 to 7 September 1984. Dr M.
Mercier, Manager, IPCS, opened the meeting and welcomed the
participants on behalf of the heads of the three IPCS
co-sponsoring organizations (UNEP/ILO/WHO). The Group
reviewed and revised the draft criteria document for toluene
and made an evaluation of the risks for human health and the
environment from exposure to toluene.
DR M. GREENBERG, of the US ENVIRONMENTAL PROTECTION
AGENCY, was responsible for the preparation of the first
draft, and DR G.J. VAN ESCH, of Bilthoven, The Netherlands,
was responsible for the final technical editing.
The efforts of all who helped in the preparation and
finalization of the document are gratefully acknowledged.

* * *

1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 Identity and analytical methods

Toluene is the common name for methylbenzene. It is a clear, colourless liquid that is volatile (vapour pressure of 3.82 kPa), flammable, and explosive in air. The technical product may contain small amounts of benzene. Toluene will not react with dilute acids or bases and is not corrosive. In the atmosphere, it reacts rapidly with hydroxyl radicals to form a variety of oxidation products.

Adequate analytical methods have been developed to measure toluene in air, water, biological tissues and fluids, and food products, using gas chromatography with conventional flame ionization detectors. The detection limit for toluene depends on sampling procedures and matrices, but is of the order of 1 $\mu g/m^3$ or 1 $\mu g/kg$ or even lower.

1.1.2 Production, uses, and sources of exposure

Toluene is a commercially-important intermediate chemical produced throughout the world in enormous quantities (0.5 – 1 x 10^7 tonnes). It is produced both in the isolated form and as a component of mixtures. Toluene produced in the form of a mixture is used to back-blend gasoline. Isolated toluene, on the other hand, is used in: (a) the production of other chemicals; (b) as a solvent carrier in paints, thinners, adhesives, inks, and pharmaceutical products; and (c) as an additive in cosmetic products. Purified toluene usually contains less than 0.01% benzene, but the industrial grade may contain up to 25% benzene.

The primary man-made sources of toluene released into the environment are:

(a) indavertent sources (65%), i.e., emission from motor vehicles and aircraft exhaust, and losses during gasoline marketing activities, spills, and cigarette smoke;

(b) processes in which toluene is used (33%); and

(c) toluene production (2%).

The significance of each of these sources is expected to vary widely from country to country. On the basis of available data and estimates, 86% of the toluene produced is

eventually released into the biosphere (predominantly the troposphere). The life-time of toluene ranges from several days to several months.

In urban areas, a toluene level in ambient air of 0.0001 - 0.204 mg/m^3 has been detected. Background levels monitored at sites throughout the world indicate that the general population is exposed to trace levels (0.00075 mg toluene/m^3). Toluene has been detected in drinking-water (0 - 0.027 mg/litre), well water (0.005 - 0.1 mg/litre), and in raw water (0.001 - 0.015 mg/litre).

The general population is exposed to toluene mainly through inhalation of vapour in ambient air, cigarette smoking, and, to a minor extent, by ingestion of food or water contaminated with toluene.

Certain groups of individuals are exposed to high levels of toluene occupationally. Permissible levels of occupational exposure established in various countries range from 200 to 750 mg/m^3 as a time-weighted average (TWA) for an 8-h day and a 40-h week. A maximum allowable concentration (MAC) of 50 - 100 mg/m^3 has been adopted by other countries.

A special group exposed to toluene includes individuals who intentionally abuse solvent mixtures containing toluene (e.g., "glue-sniffers") and those who are exposed to toluene accidentally. Solvent abuse is a world-wide problem, and long-term abusers are routinely exposed to concentrations exceeding 3750 mg/m^3.

1.1.3 Kinetics, biotransformation, and biological monitoring

Studies on laboratory animals and human beings have shown that toluene is readily absorbed from the respiratory tract with an uptake of 40 - 60% in human beings. Liquid toluene is also rapidly absorbed through the skin (14 - 23 mg/cm^2 per h), but absorption from the gastrointestinal tract appears to be slower.

Following absorption, toluene is rapidly distributed, with highest levels observed in adipose tissue followed by bone marrow, adrenals, kidneys, liver, brain, and blood. A calculated brain/blood ratio of 1.56 was reported in rats exposed via inhalation for 3 h. Controlled studies on volunteers revealed that the higher the relative uptake of toluene the lower the alveolar concentration of the solvent. The relationship between arterial blood and alveolar air concentration was linear and closely correlated. After exposure at rest for 30 min to 300 mg toluene/m^3, the relative uptake averaged 52%, the alveolar concentration was 28% of the inspired air concentration, and the arterial concentration mounted to 0.7 mg/litre of blood. Thus, by measuring the toluene concentration in alveolar air during

exposure, it is possible to estimate the arterial blood concentration.

Some 60 - 75% of absorbed toluene is metabolized to benzoic acid by the microsomal mixed-function oxidase system, with subsequent conjugation with glycine to form hippuric acid. It is eliminated in this form through the kidneys. About 10 - 20% of the absorbed toluene is excreted as benzoyl glucuronide. Small amounts of toluene undergo ring hydroxylation to form o-, m-, and p-cresol, which are excreted in the urine as sulfate or glucuronide conjugates. A proportion of the absorbed toluene (20 - 40%) is eliminated unchanged in expired air. After a single exposure, the elimination of toluene and its metabolites is almost complete in 24 h. The half-life of toluene in subcutaneous adipose tissue has been estimated to be between 0.5 and 2.7 days.

Analysis of expired air and/or blood during exposure reflects current intake. The determination of the average hippuric acid concentration in urine collected at the end of the workshift appears to be the most practical method of evaluating the overall occupational exposure of workers to toluene levels of more than 375 mg/m^3 (100 ppm). An average level of hippuric acid of less than 2 g/litre (specific gravity = 1016) or per g creatinine suggests that the atmosphere was probably contaminated by less than 375 mg/m^3. The o-cresol assay in urine should be further investigated for determining exposures to low levels of toluene.

1.1.4 Effects on experimental animals

Acute inhalation data indicate that the species sensitivity decreases as follows: rabbit, guinea-pig, mouse, and rat. Inhalation LC$_{50}$ values have been reported in the range of approximately 20 0000 - 26 000 mg/m^3 for mice and approximately 45 000 mg/m^3 for rats. The oral LD$_{50}$ in the rat is between 2.6 and 7.5 g/kg body weight, depending on the strain, age, and differences in sex. Toluene is a slight dermal and a moderate eye irritant in animals and man. Acute dermal toxicity appears to be quite low (rabbit: LD$_{50}$ 14.1 ml/kg body weight).

In short- and long-term inhalation studies on experimental animals, no effect was seen with exposure to 375 mg toluene/m^3 for 24 months. In oral studies, administration of 590 mg toluene/kg body weight, per day, for 6 months did not produce any effects. At low dose levels, in rats, the target organs seem to be the kidneys and testes, while at high dose levels, liver changes and effects on the central nervous system are predominantly seen. Reversible functional and/or morphological changes are dose-related.

Numerous studies using pure toluene have failed to demonstrate haematopoietic effects. Toluene does not cause permanent pathological effects on the heart, but high doses (> 4000 mg/m³) may induce cardiac arrhythmia.

Contradictory results are reported in the existing literature regarding the pathological effects of toluene on the respiratory and urinary tracts of dogs, guinea-pigs, and rats.

Toluene primarily affects the central nervous system (CNS). A biphasic response to toluene exposure, which is typical of a narcotic drug, has been found with initial excitability followed by a depression in response. In most studies, behavioural effects have been observed with exposures in excess of 1875 mg/m³. Progressive narcosis and seizures have been seen at high exposure levels (15 000 mg/m³, 4 h/day). Initial depression of cortical activity resulting in coma was induced in cats at 26 250 mg/m³, 10 min/day, for 40 days. Exposure at 7500 mg/m³, for 24 weeks, caused interruption of the sleep cycle in the rat. Toluene has not been shown to cause peripheral neuropathy.

Skin-painting studies on mice, where toluene was used as a vehicle control, and one inhalation study on rats exposed to pure toluene (112.5 - 1125 mg/m³, 6 h/day, 5 days/week, for 24 months) did not reveal any carcinogenic effects.

The results of studies on the mutagenic effects of toluene in microbial, mammalian-cell, or whole-organism test systems have, in most cases, been negative. Positive findings were reported in 5 studies using in vivo mammalian assays. In these studies, however, the purity of the toluene used was not always stated.

Toluene does not appear to be teratogenic in mice, rats, or rabbits, but embryotoxic/fetotoxic effects were seen in rats at a dose that was non-toxic for the dams exposed to toluene concentrations of 1000 mg/m³ air, and spontaneous abortion occurred in rabbits exposed to 1000 mg/m³ during the entire period of organogenesis. However, orally administered toluene was reported to be teratogenic in CD-1 mice. Exposure to 870 mg/kg body weight on days 6 - 15 significantly increased the incidence of cleft palate. A level of 430 mg/kg body weight was without effect.

The ability of toluene to interfere with biotransformation and alter the toxic effects of several solvents has been documented by several investigators. For example, toluene decreased n-hexane metabolism and neurotoxicity, and also benzene metabolism and effects on the haematopoietic system. However, it increased the hepatotoxicity of carbon tetrachloride.

1.1.5   Effects on human beings

Toxicity studies on human beings have primarily involved individuals exposed to toluene via inhalation either in experimental or occupational settings or during episodes of intentional abuse of solvent mixtures containing toluene.

The primary effect of toluene is on the central nervous system (CNS). The effect may be depressant or excitatory, with euphoria in the induction phase followed by disorient-ation, tremulousness, mood lability, tinnitus, diplopia, hallucinations, dysarthria, ataxia, convulsions, and coma.

Acute controlled and occupational exposures to toluene in the range of 750 - 5625 mg/m^3 (200 - 1500 ppm) caused dose-related CNS effects. Acute exposure to high levels of toluene (e.g., 37 500 mg/m^3 or higher for a few min) during industrial accidents was characterized by initial CNS excitative effects (e.g., exhilaration, euphoria, hallucina-tions) followed by progressive impairment of consciousness, eventually resulting in seizures and coma.

Single, short-term exposures to toluene (750 mg/m^3 for 8 h) have reportedly caused transient eye and respiratory tract irritation with lachrymation at 1500 mg/m^3.

Repeated occupational exposures to toluene over a period of years at levels of 750 - 1500 mg/m^3 (200 - 400 ppm) have resulted in some evidence of neurological effects.

Toluene-containing mixtures have been implicated in the causation of peripheral neuropathy but, in most cases, known neurotoxins such as n-hexane or methylethylketone have been present, and the role of toluene is not clear.

Irreversible neurological sequelae, such as encephalo-pathy, optic atrophy, and equilibrium disorders have been described in adult chronic toluene abusers. Toluene inhalation was reported to be an important cause of encephalo-pathy in children (aged 8 - 14 years) and may lead to permanent neurological damage.

Transient abnormalities of hepatic enzyme activities have been found in abusers of toluene mixtures, but significant permanent hepatic damage does not occur. Occasional reports of renal damage in glue-sniffers have appeared, characterized by a form of distal tubular acidosis. There is no evidence that toluene damages the haematopoietic tissues or the heart.

No adequate epidemiological studies on human beings exist.

The results of 3 studies indicated an increased frequency of chromosome damage in the cultured blood lymphocytes of rotogravure workers occupationally exposed to toluene, but, in 3 other similar studies, no effects were found. However, in most cases, the number of subjects studied was small. Moreover, the extent of exposure differed among the 6 studies

and exposure to other, possibly mutagenic agents, such as benzene and tobacco smoke, had usually not been adequately considered.

Data on human beings are not adequate for the evaluation of the teratogenicity of toluene. Subjective complaints of dysmenorrhoea and disturbances in menstruation have been reported in female workers exposed concurrently to toluene, benzene, xylene, and other unspecified solvents. The limited data available do not, however, specifically associate occupational exposure to toluene with reproductive effects in female and male workers.

1.1.6   Effects on aquatic and terrestrial organisms in the environment

Available data indicate that the production and use of toluene do not adversely affect aquatic and terrestrial ecosystems. The acute toxicity levels for fish and aquatic invertebrates (LC_{50}) range from 3.7 to 1180 mg/litre, but most organisms show an LC_{50} in the order of 15 - 30 mg/litre. Photosynthesis and respiration by marine phytoplankton communities are inhibited by toluene at 34 mg/litre. No adverse effects were seen in long-term studies on 3 species of freshwater and marine fish at concentrations ranging from approximately 1.4 to 7.7 mg/litre. Spawning fish may detect and avoid waters containing toluene at 2 mg/litre. The effects of sublethal exposure to toluene are reversible, and toluene residues do not accumulate in fish or aquatic food-chains.

Toluene concentrations in industrial waste waters were reported to range from 0.010 to 20 mg/litre. The biodegradability of toluene by microorganisms ranged from 63 to 86% after up to 20 days.

The adverse impact of toluene spills will be limited to the immediate spill area, because of its fast degradation under aerobic conditions.

The volatility and biodegradability of toluene suggest that it would have a short half-life on soil surfaces.

Photolysis of toluene in the air, which also contains other pollutants such as nitrous oxides and ozone, may contribute to smog production.

1.2   Conclusions and Recommendations

1.2.1   Conclusions

The available data indicate that exposure of the general population and environment to toluene does not present any health and/or environmental hazards, at present. However,

long-term occupational exposure and solvent abuse may be associated with permanent pathological changes and further investigations are justified.

1.2.2 Recommendations

(a) Environmental monitoring data

Data are needed on the magnitude, frequency, duration, and extent of exposure(s) to toluene in the general population.

(b) Biological monitoring data

(i) Further investigations are required on the possibility of using determinations of toluene concentrations in exhaled air and blood in the evaluation of the integrated exposure during the previous 24 h; and

(ii) There is a need for a comparative study of the validity of hippuric acid and cresol determinations in urine.

(c) Human reproductive effects

Information on the possible reproductive effects of toluene in males and females is not adequate. Research in this field is therefore recommended. The similarity of the effects reported on human fetal growth and those observed in animals draws attention to the need for further studies on women exposed to toluene. Both experimental animal and human case studies give information on the supposed role of toluene in causing teratogenic effects through toxicokinetic or toxicodynamic interaction. These reports should stimulate further research on laboratory animals.

(d) Respiratory defence mechanisms

There is a need for further evaluation of the potential effects of volatile organic substances such as toluene on respiratory defence mechanisms.

(e) Neurobehavioural toxicity

(i) There is a paucity of data regarding the behavioural and neurological effects of pure toluene at low levels (i.e., below 375 - 750 mg/m^3). In particular, the extent and nature (including permanence) of neurobehavioural effects and the threshold of exposure to

toluene, below which there are no-observed-adverse effects, need to be determined to properly evaluate the potential risks.

(ii) There is a need for further research to define and refine the tests that are most relevant for neuropsychological investigations.

(iii)   Toluene inhalation is a cause of encephalopathy in children and may lead to permanent neurological damage. Diagnosis is most important if further damage due to continued abuse is to be prevented, and sensitive assays should be further investigated (e.g., toluene levels in expired air and in blood).

(f) Human studies on the significance of the reported hepatomegaly and induction and inhibition of microsomal enzyme systems for the detoxification or metabolic activation of other chemicals are indicated.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Toluene is a common name for the chemical formed when one hydrogen atom of the benzene molecule is replaced with a methyl group.

Chemical structure: $C_6H_5-CH_3$
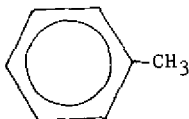
Chemical formula: C_7H_8

Relative molecular mass: 92.13

CAS chemical name: phenylmethane

CAS registry number: 108-88-3

RTECS registry number: XS 5250000 (Tatken &
                                     Lewis, 1983)

Common synonyms: methylbenzene

Common trade names: Methacide, Methylben-
                                     zol, Toluol

Technical products in which toluene is the principal ingredient are commonly formed from petroleum in which petroleum fractions containing methylcyclohexane are catalytically dehydrogenated. The purification of toluene products may include azeotropic distillation with paraffinic hydrocarbons, naphthenic hydrocarbons, or alcohols. Because of the variety of methods used to produce toluene, the range of impurities varies widely. Benzene is an important common impurity in technical grades of toluene. Highly-purified toluene (reagent grade and nitration grade) contains less than 0.01% benzene, while industrial grade and 90/120 grade toluene contain a significant quantity of benzene. The 90/120 grade contains as much as 25% (US NIOSH, 1973).

2.2 Physical and Chemical Properties

Toluene is a volatile liquid that is flammable and explosive. Some physical and chemical properties of toluene under standard conditions are presented in Table 1.

Table 1 Physical and chemical properties of toluene

Melting point	-95 °C	Weast (1977)
Boiling point (760 mm Hg)	110.6 °C	Weast (1977)
Density (g/ml, 20 °C)	0.8669	Weast (1977)
Specific gravity (20 °C)	0.8623	Weast (1977)
Vapour pressure (25 °C)	28.7 mm Hg	Weast (1977)
Vapour density (air = 1)	3.20	Weast (1977)
Log partition coefficient (octanol/water)	2.69	Tute (1971)
Surface tension (20 °C)	28.53 dynes/cm	Walker (1976)
Liquid viscosity (20 °C)	0.6 cp	Walker (1976)
Refractive index (20 °C)	1.4969	Cier (1969)
Percent in saturated air (760 mm, 26 °C)	3.94	Walker (1976)
Density of saturated air-vapour mixture (760 mm; air = 1, 26 °C)	1.09	Walker (1976)
Flammable limits (percent by volume in air)	1.17 - 7.10	Walker (1976)
Flash point (closed cup)	4.4 °C	Walker (1976)
Autoignition temperature	552 °C	Walker (1976)
Solubility in:		
Fresh water (25 °C)	535 mg/litre	Sutton & Calder
Sea water (25 °C)	380 mg/litre	(1975)
Saturation in:		
Air (25 °C)	112 g/m^3	Sutton & Calder (1975)

2.3 Organoleptic Properties

Toluene is a clear, colourless liquid at ambient temperature and has a benzene-like odour. The odour threshold for toluene in air has been determined to be 9.4 mg/m^3. The sensory threshold (the concentration at which volunteers, when exposed for 15-min inhalation periods, had olfactory fatigue, mild eye irritation, "tasting something", "light-headed", and

headache, but, nevertheless, were willing to work for 8 h) was 700 mg/m^3 (section 9.1.2.) (Carpenter et al., 1976a,b).

2.4 Conversion Factors

In air (1 atm), at 25 °C: 1 ppm (V/V) = 3.75 mg/m^3 = 0.0407 mmol/m^3;

1 mg/m^3 = 0.266 ppm (Katz, 1969)

2.5 Analytical Methods

Many methods have been used to determine the concentration of toluene in air, water, and soil.

Toluene exhibits characteristic UV, IR, NMR, and mass spectra, which are useful in many specific control and analytical problems. Analytical methods have included colorimetry, involving nitration followed by reaction with various ketones, spectrophotometry, direct estimation by means of colorimetric indicator tubes, and gas chromatography (Maffett et al., 1956; Dambrauskas & Cook, 1963; Whitman & Johnston, 1964; Williams, 1965; Kolekovsky, 1967; Reid, 1968). Gas chromatography (GC) offers the greatest specificity and sensitivity of the numerous methods of analysis. Both packed columns using silica gel and capillary columns have been used to separate toluene from interfering substances (Fett et al., 1968). Photoionization detectors provide better selectivity and sensitivity for toluene measurements than flame ionization detectors (Federal Register, 1979). Nevertheless, the flame ionization detector is the most common detector used in volatile hydrocarbon analyses; the use of gas chromatography interfaced with computerized mass spectrometry has been developed for samples containing toluene (Jermini et al., 1976; Lingg et al., 1977; Dowty et al., 1979; Rasmussen & Khalil, 1983). The detection limit for toluene in the environment depends on sampling procedures and preparations, but is low, of the order of 1 µg/m^3 or 1 µg/litre or even less.

2.5.1 Sampling procedures

2.5.1.1 Air

When concentrations of toluene are large enough, air samples can be collected as grab samples using aluminized plastic bags, Tedler bags, or glass containers (Neligan et al., 1965; Lonneman et al., 1968; Altshuller et al., 1971; Pilar & Graydon, 1973; Schneider et al., 1978). When smaller

concentrations of toluene are to be measured, it is quantitatively adsorbed on various large surface area materials, such as charcoal, through which the air is passed (Reid & Haplin, 1968; White et al., 1970). Tenax GC®, Porapak Q®, and a variety of molecular sieves have been used as sorbents for toluene. The sorbent is heated and the enriched toluene sample is flushed with an inert gas directly into a high-resolution glass or fused capillary tube for characterization and measurement by gas chromatography/mass spectrometry/computer techniques (Krost et al., 1982). Passive air sampling using charcoal as a sorbent has been designed specifically for the long-term sampling of indoor and ambient air (Seifert & Abraham, 1982, 1983). If equipment for the thermal desorption of toluene from sorbents is not available, toluene can be extracted from the sorbent using carbon disulfide (Reid & Halpin, 1968; Fraser & Rappaport, 1976; Esposito & Jacobb, 1977; Fracchia et al., 1977).

The detection limit for toluene in air depends on the volume of air passed through the sorbent, but is approximately $0.1 \mu g/m^3$ (Holzer et al., 1977). For the passive collection methods, detection limits of approximately $1 \mu g/m^3$ are obtained for ambient air monitoring (Hester & Meyer, 1979).

Cigarette smoke, a source of toluene for human beings, requires a special sampling method (Dalhamn et al., 1968b).

2.5.1.2 Water

Other methods, apart from direct aqueous injection and dichloromethane extraction, have been used to determine toluene in industrial waste waters (Jungclaus et al., 1976, 1978). The three most commonly used methods for the determination of toluene in aqueous media are the purge and trap, headspace, and sorption on solid sorbents (including different variations of these methods, concerning the temperature of the purging system, the stripping rate, the duration of stripping, etc).

Purge and trap

The most widely used method for the determination of toluene in drinking-water, waste water, and rain-water is the purge and trap method (Bertsch et al., 1975; Grob & Zurcher, 1976; Lingg et al., 1977; Bellar & Lichtenberg, 1979; Dowty et al., 1979). The detection limit is generally 1 µg/litre.

Headspace analysis

This method has not been applied frequently for the analysis of environmental samples; however, the method was

standardized with water samples spiked with model compounds.
Toluene concentrations of the order of 0.1 - 1.0 µg/litre
can be determined by this method (Vitenberg et al., 1977;
Drozd et al., 1978).

Sorption on solid sorbents

This method, which is rarely used, is used for monitoring
toluene in drinking-water (Ryan & Fritz, 1978).

2.5.1.3 Soils and sediments

The purge and trap method has been modified for the
determination of volatile organic compounds in soil and
sediment samples. In general, the recovery of toluene from
these samples is low. A detection limit of approximately
0.2 µg/kg can be attained.

2.5.2 Biological monitoring of toluene exposure

A number of biological tests have been investigated for
evaluating human exposure to toluene: toluene in expired air
and/or in blood and human breast milk; hippuric acid in urine
and/or blood; and benzoic acid, and o-cresol in urine (section
7.4). *The time of sampling of biological material is very*
critical in all cases, because of the rapid metabolism of
toluene. In addition, the possibility that toluene metabolism
might be modified by the presence of other chemicals must be
considered (Waldron et al., 1983).

2.5.2.1 Blood, expired air, body fluids, and tissues

Toluene in blood has been determined by the GC analysis of
headspace samples (detection limit: 10 µg/litre) (Premel-
Cabic et al., 1974; Anthony et al., 1978; Radzikowska-Kintzi &
Jakubowski, 1981; Oliver, 1982). A direct injection method
applicable to GC in the determination of toluene in whole
blood has been reported by Aikawa et al. (1982).

Cocheo et al. (1982) have developed a purge and trap
method for the detection of toluene in blood in which the
detection limit is estimated to be less than 7.5 µg/litre.
Bellanca et al. (1982) described a similar method using GC-FID
for detecting toluene and other organic compounds in tissues
and body fluids.

The concentration of toluene in alveolar air samples,
collected during exposure, is related to the intensity of the
exposure (Astrand et al., 1972; Brugnone et al., 1976, 1980;
Carlsson, 1982,a,b; Astrand, 1983).

Under steady-state conditions, a constant relationship
between the uptake rate of toluene and toluene concentrations
in venous blood has been observed. Under non-steady-state
conditions, however, no simple relation exists between uptake
and the venous blood concentration of toluene.

Direct measurements confirmed a previous hypothesis that
the concentration of toluene in arterial blood during and
after exposure could be estimated from concentrations in
alveolar air.

While there is no unanimity, it can be concluded that
analysis of expired air and/or blood reflects actual intake
and may be a useful indicator of exposure to toluene (King et
al., 1981).

2.5.2.2 Urine

Toluene

Trace amounts of absorbed toluene, excreted in the urine,
can be analysed by one of the methods outlined in section
2.5.1.2.

Metabolites of toluene

The major metabolite, hippuric acid, is eliminated in the
urine. It can be determined by a number of methods including
colorimetry, UV spectrometry, and thin-layer chromatography
(TLC) (Umberger & Fiorese, 1963; Pagnotto & Lieberman, 1967;
Bieniek & Wilczok, 1981; Bieniek et al., 1982). The
sensitivity of the TLC method is 6 mg hippuric acid/litre
urine. Another sensitive method for estimating hippuric acid
in urine was developed by Caperos & Fernandez (1977). In this
method, the hippuric acid in urine is extracted, methylated,
and quantified by GC-FID. The sensitivity of the method was
determined to be 5 mg/litre urine.

Bergert et al. (1982), Hansen & Dossing (1982), and Poggi
et al. (1982) determined the levels of urinary-hippuric acid
and other metabolites of toluene by a high-performance liquid
chromatographic (HPLC) method.

Hippuric acid is a normal constituent of urine,
originating mainly from food containing benzoic acid or
benzoates. For the occurrence of hippuric acid in the urine
of unexposed compared with that in toluene-exposed persons,
see Table 6 (p. 55). The mean urinary-hippuric acid excretion
is higher in females than in males.

Unexposed persons excreted a mean concentration of
< 1.0 g hippuric acid/litre, while workers exposed to
toluene excreted hippuric acid concentrations that were at
least 2 - 6 times higher, depending on exposure levels.

Taking into account the levels of hippuric acid in urine observed for unexposed persons and the individual variation in these levels, separation between exposed and unexposed workers cannot be done on an individual basis. On a group basis, however, the methods are sufficiently sensitive.

At present, the determination of the average hippuric acid concentration in urine collected at the end of workshift appears to be the most practical method for evaluating overall occupational exposure to toluene levels exceeding 375 mg/m³ air. A group average of less than 2 g/litre (specific gravity = 1.016) or g creatinine suggests that the atmosphere was probably contaminated by less than 375 mg/m³ (100 ppm) toluene. The possibility of using the determination of toluene in expired air and/or blood and o-cresol in urine, particularly for exposure to low levels of toluene, should be further investigated.

Sufficient data are not available to give an opinion about the measurement of other metabolites such as benzoic acid or o-cresol in urine to estimate exposure to toluene in the air.

2.5.2.3 Human breast milk

Toluene in human breast milk can be determined by the purge and trap method, followed by thermal desorption and capillary GC-MS analysis (Pellizzari et al., 1982).

2.5.3 Foods and food containers

A headspace GC technique for quantification, and a GC-MS technique for confirmation, were used to determine trace amounts of toluene in plastic containers. Toluene present in the μg/kg range can be determined by this method (Hollifield et al., 1980).

2.5.4 Detection of marketed toluene purity

Toluene is marketed in different purity grades. The purity as well as the number, concentrations, and identity of other components can be determined by HPLC, GC, and GC-FID methods (Fett et al., 1968; Grizzle & Thomson, 1982). The toluene content of high purity samples can be accurately measured by determining the freezing point (Hoff, 1983).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural Occurrence

Some types of vegetation are natural sources of toluene in the environment (US NRC, 1980).

3.2 Man-Made Sources

3.2.1 Production levels, processes, and uses

3.2.1.1 Production

Production of toluene as a by-product of the carbonization of coal was the major source of toluene during the latter part of the 19th century. Since the second World War, the manufacture of toluene from petroleum sources has steadily increased, and that from coke and coal-tar products has decreased. At present, toluene is principally produced (87%) by the catalytic reforming of refinery streams (Hoff, 1983). An additional 9% is separated from pyrolysis gasoline produced in steam crackers during the manufacture of ethylene and propylene. The other 4% originates as a by-product of other processes.

3.2.1.2 World production figures

World production figures for toluene are summarized in Table 2, according to different geographical areas, for the years 1979-81. From Table 2, it is clear that, in 1981, the world production of toluene was more than 10 000 metric tonnes.

3.2.1.3 Manufacturing processes

Loss into the environment during normal production and handling

The three primary man-made sources of toluene released into the environment are:

(a) production sources; toluene can be released into the environment during its production as process losses, fugitive emissions, and storage losses (approximately 2%);

(b) toluene when used as a solvent; toluene is released into the ambient air, as a result of evaporation (approximately 34%);

Table 2. World-wide annual toluene production in metric tonnes

Geographical area	Total toluene production		
	1979[a]	1980[a]	1981[b]
Africa			43
Canada	941		
Europe (western)	1179	913	1666
Israel			63
Japan	962		> 2193
Oceania			46
South America			382
Thailand	21[c]		16[c]
USA	3273	5104[b]	6234
USSR			> 1179[d]

[a] From: Chemical Industry (1980).
[b] From: World Petrochemicals (1982) (as cited by Hoff, 1983).
[c] From IRPTC (1984) (special inquiry).
[d] Includes capacity data for three USSR toluene plants, which may not have been completed.

(c) inadvertent sources; the emission of toluene through its use in gasoline can occur from three distinct sources including; evaporative losses from automobile service stations; evaporation from marketing activities (handling and transfer of bulk quantities); and emissions from motor vehicles and aircraft (approximately 65%).

Other inadvertent sources of toluene emissions into the environment include other manufacturing processes, by-product formation, and cigarette smoke (Anderson et al., 1980). There is substantial contamination of the environment from seepage in the oceans, on land, and from the weathering of exposed coal strata.

3.2.2 Uses

Toluene is of great importance as a chemical intermediate and solvent.

Up to 95% of the annually-produced toluene in the USA is blended directly into the gasoline pool as a component to increase the pyrolysis of gasoline (to increase the octane number) (Hoff, 1983).

Isolated toluene is much more important as a solvent than either benzene or xylene. Approximately two-thirds of its use as a solvent is in paints, inks, thinners, coatings, adhesives, degreasers, and other formulated products requiring a solvent carrier (Kumai et al., 1983; Inoue et al., 1983).

Furthermore, toluene is used as a raw material in the organic synthesis of a large number of chemicals such as toluene diisocyanate, benzoic acid, benzaldehyde, xylene, toluene-sulfonylchloride (the o-isomer is converted to saccharin), other derivatives of toluene used as dye intermediates, resin modifiers, germicides, etc. Lastly, toluene is used as a denaturant in specially-denatured alcohol.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport and Distribution Between Media

4.1.1 Air

Toluene released into the environment mainly enters the atmosphere (because of its high vapour pressure) and surface waters. Transport from the water (low solubility) to the atmosphere is rapid. MacKay & Wolkoff (1973) and Mackay & Leiononen (1975) reported the calculated evaporation half-life for toluene from 1 m deep water to be approximately 5 h; in a state of equilibrium, only 26% of toluene would be present in the gaseous phase above sea water (US NRC, 1980).

Atmospheric oxidation of toluene removes 50% of the compound in less than 2 days (half-life was estimated to be 12.8 h). Because of this rapid removal, toluene will most probably not remain in the atmosphere long enough to be removed by air to surface transfer mechanisms, such as dry deposition or precipitation (US EPA, 1980).

Toluene has been detected in rain water at levels of 0.13 - 0.7 µg/litre (Lahmann et al., 1977).

Toluene does not absorb radiation at wavelengths longer than 295 nm. Although it absorbs insignificant amounts of sunlight in the lower atmosphere, a charge-transfer complex between toluene and molecular oxygen absorbs radiation of wavelengths up to 354 nm. According to Wei & Adelman (1969), it is the photolysis of this complex that may be responsible for some of the observed photochemical reactions of toluene related to smog production. Photolysis of toluene in air that also contains nitrous oxides yields ozone, peroxyacetyl-nitrate, and peroxybenzoylnitrate.

Toluene is removed from the atmosphere primarily through free radical chain processes, of which reactions with hydroxy radicals are the most important processes (Brown et al., 1975; Perry et al., 1977). In the atmosphere, there are several free radicals that are likely to combine with toluene, including hydroxyl radicals (OH), atomic oxygen (O), and peroxy radicals (RO_2), where R is an alkyl or aryl group, and also ozone (O_3). The tropospheric lifetime of toluene at high latitudes during summer has been estimated to be about 4 days; in winter, the lifetimes may be of the order of months. At tropical latitudes, the lifetimes are short (days to weeks) and do not vary with season. The average concentrations of toluene found in different regions of the world vary between 0 and approximately 0.75 µg/m³ air (Rasmussen & Khalil, 1983).

4.1.2   Water

Sauer et al. (1978) concluded, from their studies of the coastal waters of the Gulf of Mexico, that toluene and other alkyl benzenes are present at low levels in the marine environment.

The presence of toluene in surface water in the USA has been monitored by the US EPA STORET system (US EPA, 1980). Only 17% of all surface waters monitored contained toluene at concentrations higher than 10 µg/litre.   Factors affecting toluene levels in surface water and groundwater include volatilization, solubility, and, where groundwater is concerned, degradation and/or adsorption of toluene during percolation through soils. Toluene was detected in 85% of the 39 wells tested in 1978.   The toluene concentration in these well waters was below 10 µg/litre.   Toluene has been detected in raw water and in finished water supplies (up to 19 µg/litre) in several communities in the USA (US EPA, 1975a,b, 1977).   It has been suggested that toluene may be chlorinated during the chlorination process of waste water (Carlson et al., 1975). However, this could not be confirmed in laboratory experiments, and it was concluded that chlorine added to waste water would not bind with toluene (US EPA, 1980).

4.1.3   Soil

Toluene probably exists in soils in the adsorbed state. The adsorption of toluene by clay minerals (bentonite and kaolinite) was found to follow Freundlich's adsorption isotherm and the adsorption capacity increased as the pH value decreased (El-Dib et al., 1978).   It can be anticipated, therefore, that a portion of toluene in soil will be transferred to air and water. The part that stays in soil may participate in chemical reactions (including photochemical reactions) and biological degradation and transformation.

The results of 2 laboratory experiments (US EPA, 1980; Wilson et al., 1981) showed that, about 40 - 80% of toluene applied to the surface of sandy soils at 0.9 and 0.2 mg/litre, respectively, volatilized into the air (estimated half-life of 4.9 h). The volatilization rate is, for instance, dependent on the nature and organic content of the soil, and the laboratory studies showed that toluene moved through sandy soils with low organic carbon content.   The transfer of toluene from soil to groundwaters is of importance with regard to the contamination of these sources of drinking-water.

4.1.4   Entry into the food chain

In 59 samples of edible fish (not specified), 95% showed toluene concentrations of less than 1 mg/kg (w/w) (US EPA, 1980). Toluene was also detected in fish caught from polluted waters in the proximity of petroleum and petrochemical plants in Japan (Ogata & Miyake, 1973, 1978).

4.2 Biotransformation

4.2.1   Biodegradation

Toluene is easily degraded by activated sludge in sewage plants (Malaney & McKinney, 1966; Matsui et al., 1975) and by bacteria in estuarine and marine environments (Walker & Colwell, 1976; Tabak et al., 1981). It is also biodegraded by a variety of soil microorganisms using toluene (up to 0.1%) as the sole source of carbon (Tausson, 1929; Kaplan & Hartenstein, 1979; Wilson et al., 1981).

Biodegradation of toluene accounted for 0.31, 4.81, 0.36, 0.09, and 18.47% of the total toluene loss in oligotrophic lakes, eutrophic lakes, clean rivers, turbid rivers, and ponds, respectively. Using the standard dilution method and a settled domestic filtered waste-water effluent as the seed to determine the biochemical oxygen demand, the biodegradability of toluene (percent bio-oxidized) ranged from 63% to 86% after up to 20 days (Price et al., 1974; Bridié et al., 1979; Davis et al., 1981).

The degradation of toluene has also been studied in mixed cultures of bacteria (predominantly Pseudomonas). Chambers et al. (1963), using these phenol-adapted bacteria, reported 38% degradation of toluene after 180 min. In another study, Dechev & Damyanova (1977) grew sludge cultures using phenol, xylene, or toluene as the sole carbon source and found that phenol-adapted bacteria proved less able to degrade xylene and toluene, while toluene-adapted microorganisms showed greater versatility in their ability to oxidize phenol and xylene. For information on the metabolism of toluene by various types of microorganisms, see Gibson (1971), Smith & Rosazza (1974), Subramanian et al. (1978), and Kaplan & Hartenstein (1979).

4.2.2   Bioaccumulation

The quantities of organic chemicals that accumulate in aquatic organisms depends on uptake, excretion, and metabolism (Hansen et al., 1978).

Bioaccumulation of toluene has not been studied adequately. The log octanol/water partition coefficient is

2.69, a value that indicates that slight to moderate accumulation takes place.

Roubal et al. (1978) did not find any toluene, while higher homologues of toluene were present, in the tissues of Coho salmon (Oncorhynchus kisutch). Berry (1980) detected only small quantities of ^{14}C activity in different tissues of bluegills (Lepomis machrochirus). Mean concentrations of 12.4 mg/kg muscle tissue and 1.5 mg/kg liver tissue were found in eels (Anguilla japonica) kept in sea water containing 16.1 mg toluene/litre (Ogata & Miyake, 1978). They showed that the half-life of toluene was 1.4 days. Berry & Fisher (1979) determined that ^{14}C-toluene in 4th-instar mosquito larvae was transferred to the bluegill stomach and intestine, but that levels of toluene residues in other organs and tissues were indistinguishable from those in the controls. Consequently, it is unlikely that toluene accumulates in an ecosystem food chain.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

5.1.1. Air

The reported concentrations of toluene in air reflect, undoubtedly, the regional differences in terms of production, use, and emission patterns, the effects of meteorological processes affecting transport and fate, sample siting and averaging times, and differences in sampling, analysis, and detection. The toluene concentrations in the vicinity of industrial sources of toluene may represent a burden for the general population in such areas (Smoyer et al., 1971; Mayrsohn, et at., 1976). Sexton & Westberg (1980) carried out an ambient air monitoring programme near an automotive painting plant. Toluene concentrations downwind within 1.6, 6, and 16.5 km of the plant were 0.600, 0.075, and 0.055 mg/m³, respectively. The background toluene concentration at a distance of 1.6 km upwind of the plant was 0.0055 mg/m³.

In the period between 1971 and 1980, atmospheric concentrations of toluene were estimated in Canada, Europe, and the USA. The average concentrations found varied widely. In rural areas, the levels were low whereas, in cities and airports, very high concentrations were found. The average concentrations ranged from 0.0005 to 1.31 mg/m³. The highest level found was 5.5 mg/m³ (Altshuller et al., 1971; Grob & Grob, 1971; Pilar & Graydon, 1973; Leonard et al., 1976; Lahmann et al., 1977; Johansson, 1978; Pellizzari, 1979; Arnts & Meeks, 1981; Häsänen et al., 1981; Brodzinsky & Singh, 1982; Tsani-Bazaca et al., 1982; Wathne, 1983).

Rainwater from a residential area, an airport, and a busy traffic intersection in Berlin (FRG) showed toluene concentrations of 0.00013, 0.0007, and 0.00025 mg/m³, respectively (Lahmann et al., 1977).

5.1.2 Water

Toluene has been detected in the drinking-water supplies of several communities. The average and maximum concentrations of toluene in treated Canadian water were reported to be 0.002 mg/litre and 0.027 mg/litre, respectively, with a frequency of 20% during the months of August and September. The corresponding values for the raw water were < 0.001 mg/litre and 0.015 mg/litre, respectively. The frequency of occurrence and the concentration of toluene in water showed seasonal variation,

the summer-time values being higher than the winter-time
values (Otsun et al., 1980).

In a nation-wide survey of water supplies from 17 cities
in the USA, 7 were discovered to be contaminated with toluene
(0.0008 up to 0.011 mg/litre) (US EPA, 1975a,b). Saunders and
colleagues (1975) found that the concentration of the various
contaminants including toluene in tap water fluctuated from
week to week, but that the chemical composition remained the
same.

Toluene was detected in well water at 0.005 - 0.1 mg/litre.

The concentration of toluene in a variety of industrial
wastewaters was reported to be in the range of 0.01 up to 10
mg/litre (Jungclaus et al., 1976; Yamaoka & Tanimoto, 1977;
Rawlings & Samfield, 1979; US EPA, 1980).

5.2   General Population Exposure

Human exposure to toluene through the inhalation of urban
air and oral intake is summarized in Table 3. The air intake
estimate is based on a breathing rate of 1.2 m^3/h for an
adult during waking hours and 0.4 m^3/h during sleep (8
h/day). The average drinking-water intake and fish
consumption have also been considered. It should be
remembered that Table 3 shows estimates of the toluene uptake
per week by human beings under certain conditions of exposure
and not the amount observed. Only 40 - 60% of inhaled toluene
is absorbed by human organs. Also, part of the absorbed
toluene is rapidly excreted from the body (sections 7.1, 7.4).

Rasmussen & Khalil (1983) suggested that 0.75 μg/m^3
could be regarded as an upper background level to which all
populations are exposed. Inferences from the total air
monitoring data base (Brodzinsky & Singh, 1982) suggest that
urban residents throughout the world are likely to be exposed
to considerably higher levels (Table 3).

The three most likely sources that may lead to dermal
exposure to toluene in the general population are the use of
vehicular fuels, toluene-containing solvents, and cosmetic
products. Although cosmetic products may involve smaller
exposures compared with the other two sources, the population
exposed is large (Anderson et al., 1980).

5.3   Occupational Exposure During Manufacture, Formulation, or Use

Available information suggests that particular occupa-
tional subgroups are likely to be exposed to considerably
higher levels than the general population. Such subgroups
include, printers, shoemakers, and those associated with the
production of toluene and/or toluene-containing products.

Table 3. Toluene exposure estimates under different conditions of exposure

Exposure conditions	Observed range of concentrations	Frequency of exposure	Total volume of exposure or amount consumed per week	Inhalation or ingestion rate (mg/week)
General population				
Inhalation				
Urban areas	0.1 - 204 µg/m³	168 h/week	156.8 m³	0.02 - 32
Rural and remote areas	trace to 3.8 µg/m³	168 h/week	156.8 m³	trace to 0.6
Areas near manufacturing and user sites	0.1 - 600 µg/m³	168 h/week	156.8 m³	0.02 - 94
Ingestion				
Drinking-water	0 - 19 µg/litre	2 litre/day	14 litre	0 - 0.3
Food (fish only)	0 - 1 mg/kg	6.5 g/day	45.5 g	0 - 0.45
Occupational group				
Inhalation	377 mg/m³ [a]	40 h/week	48 m³	18 100
Dermal	0 - 170 µg/litre [b]	0 - 30 min/week	5.9 litre	0 - 1.0
Cigarette smokers				
Inhalation	0.1 mg/cigarette [c]	20 cigarettes/day	140 cigarettes	14

[a] This value is similar to permissible standards in various countries and represents the worst-case estimate. In some industries, the exposure level rarely exceeds 37.5 mg/m³.

[b] This value represents exposure to blood due to dermal contact and represents absorbed levels.

[c] From: Dalhamn et al. (1968a); toluene content may be higher depending on tobacco type.

Atmospheric levels such as those cited in Table 4 can reflect only the conditions prevailing at the time of an investigation. They do not represent the peak exposures to which workers may be subjected during such incidents as breakdown or leakage of process equipment, transfer operations, etc. However, the adoption of lower exposure limits in several countries is likely to have decreased actual exposure to toluene at the work-place.

Table 4. Concentrations of toluene in the air at work places

Occupation/work-place	Toluene concentration (mg/m³)		Reference
	Range	Average	
24 workers in paint and pharmaceutical industry	750 - 3000; 560 - 7100		Parmeggiani & Sassi (1954)
rotogravure printers and helpers	750 - 1500		Banfer (1961)
11 workshops in 8 factories (rotary processes for rotogravure printers)	15 - 828		Ikeda & Ohtsuji (1969)
39 workers in: rotogravure plant 1954/56 1957/1965 CTR of room near fold machine between machine 1967 near fold machine between machine	0 - 900 525 - 896 210 - 1039 1148 - 3090	761 761 1 616 585 994	Forni et al. (1971)
rotogravure printer	68 - 1875		Szadkowski et al. (1976)
rotogravure printer	200 - 300	3000	Szilard et al. (1978)
11 leather-finishing plants -finish area -washing & topping operations	71 - 319 109 - 731	199 420	Pagnotto & Lieberman (1967)
rubber coating plants (< 1% benzene)	128 - 450	274	

Table 4 (contd).

Occupation/work-place	Toluene concentration (mg/m³)		Reference
	Range	Average	
19 workers in V belts for industrial machine plants			Capellini & Allessio (1971)
(1)	300 - 600	468.8	
(2)	788 - 1125	937.5	
rotogravure printer	50 - 615		Ovrum et al. (1978)
24 workers in rotogravure printer	81 - 706		Veulemans et al. (1979)
32 workers in rotogravure printer	26 - 420		Mäki-Paakkanen et al. (1980)
500 women/leather and rubber shoe factory		250	Michon (1965)
53 women/leather factory		250	Kowal-Gierczak (1969)
1000 workers/vapour commercial toluene			Wilson (1943)
1 - 3 weeks exposure	188 - 5625		
(1)	188 - 750		
(2)	750 - 1875		
(3)	1875 - 5625		
29 workers spraying merchant ship	approximately 37 500 - 112 500		Longley et al. (1967)
2 h after incident	18 750 - 37 500		

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

The atmosphere is a major reservoir of toluene emissions and photochemical reactions are capable of rapidly degrading it. Toluene discharged into natural waters and soils is removed by volatization and biodegradation. This section reviews the effects of toluene on organisms in the aquatic and terrestrial environments.

6.1 Microorganisms

Microorganisms capable of degrading toluene are widely distributed in the environment (Gibson, 1971; Subramanian et al., 1978; Bridié et al., 1979; Wilson et al., 1981). Although toluene can be toxic for microorganisms, microorganisms are of great importance for the degradation of toluene in natural waters and soils. The metabolism of toluene in microorganisms is similar to that in mammals, except that ring hydroxylation to cresols is more prevalent (Gibson, 1971). In addition, the metabolic pathway involves oxidation of the benzyl carbon to form benzoic acid, which is further metabolized as a carbon source.

Bridié et al. (1979) showed that toluene has a biological oxygen demand (BOD) in conventional waste-water treatment of 69% (expressed as a percentage of the theoretical demand — ThoD) in a standard 5-day test. BOD values greater than 50% are indicative of a readily-degradable chemical that can be adequately treated by municipal and industrial waste-treatment facilities. Moreover, toluene spilled in the environment would be expected to be degraded under aerobic conditions.

6.2 Aquatic Organisms

The threshold for the acute effects of toluene in aquatic biota is 1 mg/litre. Aquatic organisms are exposed to toluene via respiration, resulting in changes in gill permeability and internal carbon dioxide (CO_2) poisoning.

Data on environmental factors affecting the toxicity of toluene are not extensive, but neither temperature nor water hardness have been found to have any significant effects (US EPA, 1980).

As in mammals, toluene causes adverse effects in aquatic organisms through the mechanism of narcosis. Symptoms in aquatic organisms progress from mild stimulation, to lethargy, loss of equilibrium accompanied by shallow breathing and slowed heart rate, anaesthesia, and death (Bakke & Skjoldal, 1979; Maynard & Weber, 1981; Veith et al., 1983). The effects are largely reversible except for residual CNS effects as

evidenced by alteration of schooling behaviour for longer
periods after near lethal exposure. Narcosis is expected to
occur at concentrations of 11 mg/litre in fresh water and 8
mg/litre in seawater.

A summary of aquatic toxicity data for fish and
invertebrates from fresh water and marine environments is
presented in Table 5. Because of the high volatility of
toluene, only flow-through tests and static tests with
measured concentrations are included. The acute LC_{50} for
freshwater organisms varies from 21.5 mg/litre for mosquito
larvae to 29 and 26 mg/litre for day-old fry and juvenile
fathead minnows, respectively. The results of long-term
studies have shown the no-observed-adverse-effect concen-
tration for the early life stage of fathead minnow to be 4 -
6 mg/litre.

The acute LC_{50} for marine organisms varies from 3.7
mg/litre in bay shrimp to 28 mg/litre in the Dungeness crab.
However, the mosquito fish had an LC_{50} of 1180 mg/litre.
Newly-hatched fry from Coho salmon and pink salmon were
slightly less sensitive to toluene than the bay shrimp with
96-h LC_{50} values of 5.5 mg/litre and 7.0 mg/litre,
respectively. Long-term effects of toluene in marine
organisms were measured in the sheepshead minnow and Coho
salmon. The 28-day no-observed-adverse-effect concentration
for the minnow was between 3.2 and 7.7 mg/litre. The 40-day
no-observed-adverse-effect concentration for the early
life-stage of salmon was between 1.4 and 2.8 mg/litre.

Potera (1975) studied the effects of toluene on marine
phytoplankton. Photosynthesis was inhibited at toluene
concentrations of 34 mg/litre. The same concentration caused
a 62% inhibition in respiration.

An important long-term effect of chemicals on fish
reproduction is the avoidance response in spawning areas.
Maynard & Weber (1981) found that Coho salmon could avoid
water containing toluene at concentrations greater than 2
mg/litre.

6.3 Terrestrial Organisms

Data on the toxicity of toluene for terrestrial organisms
are not available.

6.4 Population and Ecosytem Effects

The Task Group was unaware of studies of effects of
toluene on ecosystems within natural populations.

Table 5. Toxicity of toluene for fish and aquatic invertebrates

Species	Duration (h)	Effect	Concentration (mg/litre)	Reference
Mosquito larvae (Aedes aegypti)	24	LC50	21.5	Berry & Brammer (1977)
Zebrafish (Brachydanio rerio)	48	LC50	25	Sloof (1979)
Goldfish (Carassius auratus)	96	LC50	23a; 58b	Brenniman et al. (1976)
Fathead minnow (Pimephales promelas)	96	LC50	63 (embryos)	Devlin et al. (1982)
	96	LC50	29 (1-day fry)	
	96	LC50	26 (juvenile)	
	32 days	no effect	4 - 6	
Sheepshead minnow (Cyprinodon variegatus)	96	LC50	13 (juvenile)	Ward et al. (1981)
	28 days	no effect	3.2 - 7.7	Ward et al. (1981)
Coho salmon (Oncorhynchus kisutch)	96	LC50	5.5 (fry)	Moles et al. (1981)
	40 days	no effect	1.4 - 2.8	Maynard & Weber (1981)
		avoidance no effect	2.0	
Pink salmon (Oncorhynchus gorbuscha)	96	LC50	7.0 (fry)	Korn et al. (1979)
	24	LC50	5.4	Thomas & Rice (1979)
Guppy (Poecilia reticulata)	96	LC50	59.3	US EPA (1980)
Bluegill (Lepomis machrochirus)	96	LC50	24	US EPA (1980)
Mosquito fish (Gambusia affinis)	96	LC50	1180	US EPA (1980)

Table 5 (contd).

Species	Duration (h)	Effect	Concentration (mg/litre)	Reference
Daphnia magna	?	LC$_{50}$	313	US EPA (1980)
Striped bass (Morone saxatilis)	96	LC$_{50}$	7.3	Benville & Korn (1977)
Grass shrimp (Palaemonetes pugio)	24 24	LC$_{50}$ LC$_{50}$	17.2 (adult) 25.8 (larvae)	Potera (1975)
Dungeness crab (Cancer magister)	96 48	LC$_{50}$ LC$_{50}$	28 170	Caldwell et al. (1976) US EPA (1980)
Bay shrimp (Crago franciscorum)	96	LC$_{50}$	3.7	Benville & Korn (1977)
Brine shrimp (Artemia salina)	24	LC$_{50}$	33	US EPA (1980)
Copepode (Nitocra spinipes)	24	LC$_{50}$	24.2 – 74.2	US EPA (1980)
Marine algae[c]				
Chlorella vulgaris	24	EC$_{50}$	245	US EPA (1980)
Selenastrum capri cornutum	96	EC$_{50}$	> 433	US EPA (1980)

[a] Flow-through system.
[b] Static system.
[c] Besides these 2 algae, at least 5 other marine algae were tested, and all had a low sensitivity.

6.5 Effects on the Abiotic Environment

The primary effect of toluene on the abiotic environment is in contributing to irritating reaction products in the atmosphere. However, there are no studies reporting the specific contributions of toluene to smog formation.

7. KINETICS AND METABOLISM

7.1 Absorption

7.1.1 Inhalation

7.1.1.1 Rat

In rats exposed to 2156 mg toluene/m^3 for up to 240 min, the estimated asymptotic value of toluene for blood was 10.5 mg/litre and, for brain, 18 mg/kg tissue. To reach the 95% level during uptake required 53 min for blood and 58 min for brain (Benignus et al., 1981).

7.1.1.2 Dog

The respiratory retention of inhaled toluene was studied in dogs, at concentrations of 400 - 600 mg/m^3. Retention in the total respiratory tract was found to be approximately 90% of the inhaled toluene. Varying the ventilation rate, tidal volume, or the concentration of toluene up to 825 mg/m^3 did not have any effect on the respiratory retention (Egle & Gochberg, 1976).

7.1.1.3 Human volunteers

In human studies, uptake of toluene has been estimated by different authors to be 40 - 60% of the total amount inhaled (Nomiyama & Nomiyama, 1974a; Astrand, 1975; Carlsson & Lindqvist, 1977; WHO, 1981; Carlsson, 1982a).

Nomiyama & Nomiyama (1974a) measured pulmonary uptake in volunteers exposed to 431 mg toluene/m^3 for 4 h. Uptake at the end of 1 h was approximately 52% and decreased to 37% at the end of 2 h, remaining constant at that level for the remaining 2 h. This was later confirmed by Carlsson (1982a) and Astrand (1983).

The asymptote during uptake of toluene was estimated by different authors. Because of the differences in the methods and designs used, these data are not comparable, but the values ranged from 10 - 80 min (Astrand et al., 1972; Gamberale & Hultengren, 1972; Veulemans & Masschelein, 1978a).

Carlsson (1982a) investigated the effects of physical exercise on the rate of toluene uptake. Twelve male volunteers were exposed to 300 mg toluene/m^3 during 4 consecutive 30-min work-loads at 150 watts (W), 100 W, 50 W, and at rest. During the initial 30-min period at 150 W, the mean relative uptake declined from about 55% initially to 29% at the end of the period. During continued exposure at 100 W, 50 W, and rest for 2 h, the relative uptake averaged 32, 36, and 39%,

respectively (Carlsson, 1982a). Consequently, there was an increase in the relative uptake (from 29 to 39%) with decreasing work-loads during exposure. These findings were confirmed by Astrand (1983). Astrand also found that doubling the concentration of toluene in inspired air gave a 2-fold uptake, which is in agreement with the results of Veulemans & Masschelein (1978b).

7.1.2 Dermal

7.1.2.1 Guinea-pig

Jakobson et al. (1982) monitored the concentration of toluene in the arterial blood of anesthetized guinea-pigs following epicutaneous exposure. In this study, a 3.1 cm² area of clipped back skin was continuously exposed to liquid toluene by means of a sealed glass ring. Toluene in the blood increased rapidly within 1 h to a concentration of 1.3 mg/litre, and then decreased, in spite of continuing exposure, to a plateau concentration of 0.5 mg/litre after 6 h.

7.1.2.2 Human volunteers

In human volunteer studies, Dutkiewicz & Tyras (1968a,b) showed that absorption through the skin occurred following exposure to liquid toluene (rate of absorption 14 - 23 mg/cm² per h), and, to a much lesser extent, following exposure to saturated aqueous solutions (rate of absorption 0.16 - 0.6 mg/cm² per h).
Sato & Nakajima (1978) reported that a maximum toluene concentration in the blood of 0.17 mg/litre was found when the skin of volunteers was immersed in liquid toluene for 30 min. In studies conducted by Riihimäki & Pfäffli (1978), volunteers, wearing light, loose-fitting clothing and respiratory protection, were exposed to 2250 mg toluene/m³ for 3.5 h. The authors estimated, on the basis of toluene measured in expired air, that uptake through the skin was approximately 1% of the theoretical uptake through the respiratory system. Similar conclusions were reached by Piotrowski (1967).

7.1.3 Oral

Oral absorption appears to occur more slowly than that through the respiratory tract. On the basis of measurements of toluene excreted unchanged in the expired air (18%) and levels of hippuric acid in the urine of rabbits, toluene appears to be completely absorbed from the gastrointestinal tract (Smith et al., 1954; El Masry et al., 1956).

7.2 Distribution

7.2.1 Inhalation

The dynamic distribution in the body of any organic solvent vapour, e.g., toluene, is determined by its solubility in the body fluids and tissues. Determination of the solubility of toluene in various body fluids, tissues, and tissue components has been carried·out in mammals. The solubility was expressed in terms of partition coefficients, which numerically equal the Ostwald solubility coefficients (Sato et al., 1974a,b; Sherwood, 1976; Sato & Nakajima, 1979a).

7.2.1.1 Mouse

The concentrations of toluene in the liver, brain, and blood of mice exposed to 15 000 mg toluene/m^3 for 3 h rose continuously throughout the exposure period, to 625 mg/kg in liver, 420 mg/kg in brain, and 200 mg/kg in blood, at the end of exposure. Intermittent exposure to about 40 000 mg/m^3 in cycles of 5 min on, 10 min off, or 10 min on, 20 min off, for a total of 3 h, produced tissue and blood levels approximately 3 times higher than those produced by a single 10-min exposure and similar to those produced by the 3-h exposure (Peterson & Bruckner, 1978; Bruckner & Peterson, 1981a).

Whole-body autoradiography techniques were used to study the distribution and fate of toluene and its metabolites, and covalently bound reactive intermediates in mice exposed to methyl-^{14}C-toluene by inhalation. High levels of radioactivity were observed in adipose tissue, bone marrow, spinal nerves, spinal cord, and the white matter of the brain. Radioactivity was also registered in the blood, liver, and kidneys (particularly in the medullary region). Since the radioactivity in the central nervous system (CNS), spinal nerves, and adipose tissues was volatile, it was proposed that it was probably toluene itself. All radioactivity in the nervous tissues had disappeared by 1 h after exposure. Toluene was still present in body fat 2 h after exposure but had been almost cleared from fatty tissues in 4 h. Four hours after inhalation, only traces of non-volatile radioactivity remained in the liver; after 24 h, all radioactivity had disappeared from the body (Bergman, 1978, 1979, 1983).

7.2.1.2 Rat

Benignus et al. (1984a) developed a log-log model relating venous-blood and brain levels of toluene to inspired air levels. Groups of 15 Long-Evans hooded rats were exposed to

188, 375, 1875, or 3750 mg toluene/m^3 for 3 h. The data showed that a 3-h exposure was sufficient to produce toluene levels in both blood and brain that were close to asymptote. The calculated brain/blood toluene ratio in rats was estimated to be 1.56. Values reported by, or that could be estimated from, others compare well, considering the various exposure times: 1.27 in rats (Pyykkö et al., 1977); 2.50 in rats (Pryor et al., 1978); 1.26 in mice (Ogata et al., 1974); 2.05 mice (Bruckner & Peterson, 1981a). Benignus et al. (1984b) reported that blood-toluene concentrations rose at a rate that was independent of dose level (50 - 1000 mg/kg body weight, sc), and that blood levels fell at different rates, depending on dose level.

After adult male rats were exposed for 1 h through inhalation to ^{14}C-labelled toluene (1950 mg/m^3), the highest concentrations of radioactivity were found in the adipose tissue and were up to 2 orders of magnitude higher than those found in blood. The next highest concentration of radioactivity occurred in the adrenals and kidneys, followed by liver, cerebrum, and cerebellum. Loss of radioactivity from adipose tissue and bone marrow during the following 6 h appeared to occur more slowly than the loss from the other tissues (Carlsson & Lindqvist, 1977; Pyykkö et al., 1977).

Pregnant CFY rats were exposed for 24 h (on days 10 - 13 of gestation) to 1375 or 2700 mg toluene/m^3 (Ungváry, 1984). Toluene concentrations in maternal blood, 2 h after exposure, were 6.44 and 13.69 mg/litre, at the lower and higher exposure, respectively. In fetal blood, the concentrations were about 76% of the maternal levels, and the concentrations of toluene in amniotic fluid were 0.24 and 0.96 mg/litre. Toluene concentrations, 4 and 6 h after exposure, were similiar to those measured after 2 h.

7.2.1.3 Human volunteers

Male volunteers (19 - 43 years of age) were exposed to a toluene concentration of 300 mg/m^3 for four 30-min periods at rest and/or during stepwise-increased work-load (50 W, 100 W, 150 W). The relative uptake averaged 52% at rest, and 49%, 40%, and 29% at 50-, 100-, and 150-W work-load, respectively, at the end of 30 min of exposure (section 7.1.1). The corresponding alveolar concentrations were 29, 39, 53, and 69% of the inspired concentrations. The arterial concentration amounted to 0.7 mg/litre blood at rest and 3.3 mg/litre blood at 150-W work-load for 30 min (Carlsson, 1982b). Consequently, the arterial concentration increased, not only when the concentration of the inspired solvent increased, but also with increasing work-loads, when the concentration in the inspired air was constant (Astrand, 1983).

The relationship between the relative uptake and the alveolar concentration (as a percentage of the concentration in inspired air) was linear and in close agreement with the ratio found by other investigators (Astrand, 1975). The higher the relative uptake, the lower the alveolar concentration of the solvent. The relationship between arterial-blood and alveolar-air concentrations for toluene was linear and thus the arterial-blood concentrations were closely correlated with the alveolar-air concentration. Thus, by measuring the concentration of toluene in alveolar air during exposure, it is possible to estimate the arterial-blood concentration (Piotrowski, 1967; Carlsson & Lindqvist, 1977; Ovrum et al., 1978; Carlsson, 1982a,b; Astrand, 1983).

In the study carried out with male subjects described above, Carlsson and co-workers also estimated the toluene concentrations in subcutaneous fat. At rest, the peak concentration in the fat was approximately 2 mg/kg. After exercise, the toluene concentration was 5 - 10 times higher than at rest. Subjects with the least amount of adipose tissue showed the smallest accumulation of toluene in body fat and those that were overweight showed a high accumulation.

In a male subject with about 12% body fat, the estimated quantity of toluene in this fat amounted to 5% of the total uptake, after 2 h exposure at rest. After 2 h of exposure at 50 W, it amounted to 20%. The elimination half-life for toluene in subcutaneous adipose tissue ranged between 0.5 and 2.7 days, and increased with increasing amounts of body fat.

The quotients between the concentrations of toluene in subcutaneous adipose tissue and arterial blood ranged from 1.2 after exposure at rest to 4.7 after exposure combined with a 50-W work-load. It took about 2 days of continuous exposure to toluene, at rest, for the concentration in the subcutaneous adipose tissue to reach 63% of the solvent partial pressure in the arterial blood.

During prolonged exposure, persons with a high body fat content may be exposed to a more prolonged effect of toluene on the central nervous system than thin persons, since toluene disappears more slowly from the adipose tissue and blood.

By increasing the blood circulation, physical exercise produces conditions favouring a high uptake in the skeletal muscles, heart, CNS (especially the brain), and adipose tissues. Consequently, there is a decrease in the toluene concentration in the liver, kidneys, and gastrointestinal tract (Carlsson & Lindquist, 1977; Carlsson, 1982a,b).

7.2.2   Oral

7.2.2.1   Rat

Oral administration of 4-^{3}H-toluene (100 µl toluene in
400 µl peanut oil by intubation) to adult male rats produced
a pattern of tissue distribution similar to that produced with
inhalation exposure. Distribution appeared to be delayed,
because of the time needed for absorption from the digestive
tract. Maximum tissue concentrations occurred 2 - 3 h after
administration for most tissues and 5-h after administration
for adipose tissue (Pyykkö et al., 1977).

7.2.3   Intraperitoneal

7.2.3.1   Rat

Savolainen (1978) observed that after ip injection of rats
with 500 µmol methyl-^{14}C-toluene, the concentration of
radioactivity in the CNS was highest in the cerebrum. Toluene
was rapidly removed from the CNS and was almost undetectable
after 24 h.

7.3 Metabolic Transformation

7.3.1   Oral

The initial step in the metabolic transformation of
toluene to benzoic acid, after oral administration, appears to
be hydroxylation of toluene to benzyl alcohol (Fig. 1) by the
microsomal mixed-function oxidase system. In rats, rabbits,
and man, approximately 20% of the dose is excreted unchanged
via the lungs, while approximately 80% is converted to benzoic
acid and excreted in the urine unchanged or as its glycine
conjugate, hippuric acid. Furthermore, it has been found that
toluene is excreted as benzylmercapturic acid in smaller
quantities in rats. Small amounts of benzoic acid may be
conjugated with glucuronic acid and excreted as benzoyl
glucuronic acid in the urine. Minor amounts (less than 1%) of
toluene undergo ring hydroxylation to form o-, m, and
p-cresol, which are excreted in the urine as sulfate or
glucuronide conjugates (Smith et al., 1954; El Masry et al.,
1956; Daly et al., 1968; Bakke & Scheline, 1970; Angerer,
1976, 1979; Pfäffli et al, 1979; Van Doorn et al., 1980;
Woiwode & Drysch, 1981).
Ikeda & Ohtsuji (1971) demonstrated that the induction of
hepatic mixed-function oxidases, by pretreatment of adult
female rats for 4 days with phenobarbital, increased the
metabolism of toluene when administered ip. A clear (3-fold)

4

CONHCH$_2$COOH

HIPPURIC ACID

Glycine

COOH

CH$_2$OH

EXHALED
UNCHANGED

25-40%   60-75%   BENZYL ALCOHOL   BENZOIC ACID

CH$_3$

10-20%   Glucuronic
acid

TOLUENE   CH$_3$
OH   BENZOYL GLUCURONIDE

~0.1%

o-CRESOL

~1%   GLUCURONIDE AND
SULFATE CONJUGATES

CH$_3$ CH$_3$
OH   OH

m-CRESOL   p-CRESOL
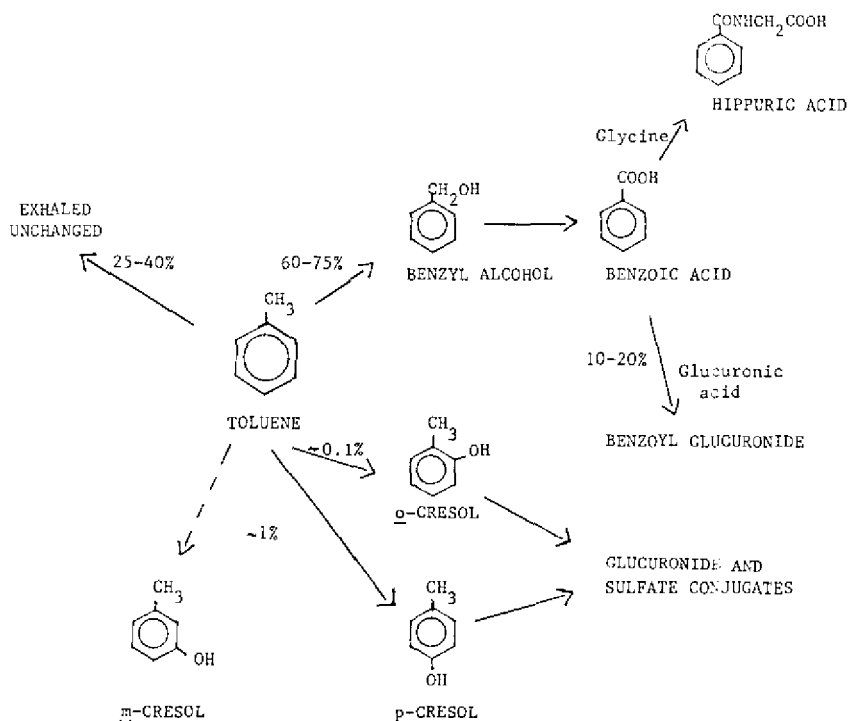
Fig. 1. Metabolism of toluene in human beings and animals.

increase in hippuric acid levels in urine was already found
after 2 h in comparison with levels in rats administered only
toluene. High levels of benzoic acid were found in the blood
compared with none in non-induced rats. Treatment of rats
with phenobarbital enhanced the in vivo metabolism of toluene
and resulted in increased tolerance in the rats to the
narcotic action of toluene. No effects of the pretreatment
was observed on the rates of oxidation of aromatic alcohol to
the corresponding acid, phenolic sulfatation, or on the
glucuronidation or glycine conjugation of benzoic acid. Rapid
disappearance of toluene from the blood because of enhanced
metabolism, together with reduced sensitivity of the central
nervous system, could explain the shortened sleeping time
after the ip injection of toluene.

7.3.2   Inhalation

7.3.2.1   Human beings

Toluene is metabolized in human beings by the pathway outlined in Fig. 1. The excretion of hippuric acid in the urine was elevated within 30 min of the initiation of inhalation exposure, indicating that the metabolism of toluene is rapid. The urinary hippuric acid levels reached a steady-state level after 4 h of continuous exposure (mean toluene concentration in air of 350 mg/m^3) under a moderate energy load (Ogata et al., 1970; Nomiyama & Nomiyama, 1978; Veulemans & Masschelein, 1979). The maximum rate of transformation of benzoic acid to hippuric acid seemed to be limited by the availability of glycine (Quick, 1931; Amsel & Levy, 1969).

During the inhalation of toluene, the rate of uptake was estimated to equal the full conjugating capacity at toluene concentrations of about 2950 mg/m^3, at rest, or about 1015 mg/m^3 during moderately-heavy work (Riihimäki, 1979).

o-Cresol was identified in the urine of workers exposed to 5 - 420 mg toluene/m^3 (Angerer, 1979; Pfäffli et al., 1979; Apostoli et al., 1982; Hansen & Dossing, 1982; Kawai et al., 1984). p-Cresol may also be a metabolite of toluene as it was present in higher concentrations in the urine of workers exposed to toluene than in the urine of unexposed workers (Angerer, 1979). The difference, however, was not significant. Apostoli et al. (1982) and Woiwode et al. (1979) reported finding m-cresol and p-cresol in addition to o-cresol in the urine of workers exposed to 1050 mg toluene/m^3. No m-cresol was detected in the urine of unexposed workers.

3.3   In vitro studies

Toluene has been shown to produce a Type I binding spectrum with cytochrome P 450 (EC 1.14.14.1) from rats and hamsters (Canady et al., 1974; Al-Gailany et al., 1978).

Incubation of toluene with rat or rabbit liver microsomes resulted in the production of small amounts of o-cresol and p-cresol. The migration of deuterium, when toluene was labelled in the 4-position, and a comparison of the rearrangement products of arene oxides of toluene with the cresols obtained by microsomal metabolism of toluene suggest that arene oxides are intermediates in the metabolism of toluene to o- and p-cresols (Daly et al., 1968; Kaubisch et al., 1972).

7.4   Elimination and Excretion in Expired Air, Faeces, and Urine

7.4.1   Toluene

7.4.1.1 Laboratory animals

Toluene is rapidly exhaled as the unchanged compound (approximately 20 - 40% of the absorbed toluene). Only trace amounts of toluene (about 0.06%) are excreted unchanged in urine. Whole-body autoradiography of laboratory animals, including mice, showed that excretion of toluene metabolites took place mainly via the kidneys. Most of the absorbed toluene was excreted within 12 h of the end of exposure (Bergman, 1978, 1979, 1983).

Mice exposed to a high initial concentration of methyl-^{14}C-toluene in a closed chamber for 10 min excreted ≃ 10% of the absorbed dose as volatile material in the exhaled air and about 68% of the radioactivity in the urine within 8 h (Bergman, 1979).

Rates of urinary hippuric acid excretion in rabbits exposed to toluene vapour at 1313 mg/m^3 for 100 min or 16 835 mg/m^3 for 10 min increased to reach maximum values 1.5 h after exposure (Nomiyama & Nomiyama, 1978). Excretion rates returned to baseline levels, 7 h after the initiation of exposure to the lower dose level, and 3 h after exposure to the higher dose level.

Rats given 50 mg ^{14}C-toluene/kg body weight, ip, excreted less than 2% of the administered radioactivity in the bile within 24 h (Abou-El-Markarem et al., 1967). Bergman (1979) showed excretion of toluene metabolites (benzoic acid) via bile into the intestinal tract in mice after inhalation of toluene.

In a study in rats, methyl-^{14}C-toluene was administered, sc, in a dose of 184 mg/kg body weight (Gut, 1983). About 20% of the radioactivity had been excreted in the urine after 8 h and 50% after 48 h.

7.4.1.2 Human beings

Human beings exposed through inhalation to toluene (concentrations ranging from 350 to 700 mg/m^3) exhaled 5 - 20% of the absorbed toluene after exposure was terminated (Srbova & Teisinger, 1952, 1953; Nomiyama & Nomiyama, 1974a,b). Alterations in physical activity influenced the elimination rate. Astrand (1983) reported that the elimination rate was doubled under conditions of a light work-load at 50 W compared with resting conditions. The

concentrations of toluene in the alveolar air, and arterial and venous blood of human subjects declined rapidly, immediately after the end of exposure and then the rate of decline gradually decreased (Astrand et al., 1972; Sato et al., 1974b; Carlsson & Lindqvist, 1977; Ovrum et al., 1978; Veulemans & Masschelein, 1979; Carlsson, 1982a,b).

In the desaturation period, male and female volunteers expired 17.6 and 9.4%, respectively, of the total amount of toluene calculated to have been absorbed during exposure (Nomiyama & Nomiyama, 1974b). They reported rate coefficients for the rapid phase of 5.10/h ($t_{1/2}$ = 8.16 min) for men and 3.22/h ($t_{1/2}$ = 12.9 min) for women; the rate coefficient for the slow phase was 0.335/h ($t_{1/2}$ = 124 min) for both sexes. Toluene retained in the body fat is eliminated by pulmonary ventilation and by biotransformation. The half-time for toluene was 0.5 - 3 days (Carlsson, 1982a, Astrand, 1983). There was a correlation between the half-time and the individual's content of body fat (section 7.2.1.3).

Brugnone et al. (1983) reported the cases of 2 workers who were admitted to a hospital because of coma due to an accidental high-level occupational exposure to a mixture of solvents; the levels of toluene were, respectively, 823 - 1122 µg/litre in the blood and 52 - 38 µg/litre in the alveolar air, on the second day of admission (36 h after the accidental exposure). At 112 h after exposure, the alveolar-toluene concentration was 1 - 3 µg/litre. The blood-toluene concentrations at 112 h were 45 and 120 µg/litre, respectively. The mean decline rate of toluene, expressed as half-life, was calculated to be between 19 and 21 h both in the alveolar air and in the blood. During the first 2 days, the lung clearance of toluene was of the order of 350 ml/min in the first worker and 270 ml/min in the second worker.

Dermal exposure of human subjects to toluene liquid or vapour resulted in the appearance of toluene in the expired air. When exposure ceased, a rapid decrease in toluene levels in alveolar air was noticed (Guillemin et al., 1974; Riihimäki & Pfäffli, 1978). The excretion of toluene in the expired air appeared to consist of at least 2 exponential phases (Riihimäki & Pfäffli, 1978).

7.4.2   Excretion of metabolites

7.4.2.1 Human beings

Volunteers inhaling toluene at concentrations of approximately 200 - 550 mg/m^3, for 3 - 4 h, excreted 60 - 70% of the absorbed dose as hippuric acid in the urine (Ogata et al., 1970; Veulemans & Masschelein, 1979).

A relatively wide range of hippuric acid excretion levels has been reported for groups of workers exposed to toluene during different operations (Table 6). For example, Pagnotto & Lieberman (1967) found a range of 2.75 — 6.80 g/litre urine (mean, 3.66 g/litre) for spreaders in the rubber-coating industry exposed to 274 mg toluene/m^3. Ikeda & Ohtsuji (1969) reported a range of 2.28 — 3.54 g/litre (mean, 2.84 g/litre) for 8 workers exposed to 469 mg toluene/m^3. In a control group of 17 unexposed workers, a mean level of 0.95 g/litre (range 0.55 — 1.6 g/litre) was recorded by Capellini & Alessio (1971).

From the studies carried out by Pagnotto & Lieberman (1967), Ikeda & Ohtsuji (1969), Ogata et al. (1971), and Apostoli et al. (1982), it is concluded that the urinary levels of hippuric acid are proportional to the concentrations of toluene in the air, though within wide variations.

Ogata et al. (1970) carried out a study on human volunteers and found that the quantity of hippuric acid excreted was proportional to the total exposure (mg/m^3 x h). In descending order of precision, the following were also related to exposure: rate of excretion during the exposure period; concentrations of hippuric acid in urine corrected to constant urine density; and concentrations in urine uncorrected for density. With the exception of the latter, these variables could be used in screening tests to show whether workers could have been exposed to concentrations greater than the maximum allowable concentration.

Apostoli et al. (1982) found that, besides a good correlation between urinary-hippuric acid levels and air levels of toluene, there was also a good correlation between urinary-o-cresol and blood-toluene concentrations and toluene concentrations in the air.

Table 6. Hippuric acid excretion levels

Number of workers and/or operation	Toluene concentration (mg/m³)		Hippuric acid excretion levels (g/litre urine)		Reference
	Mean	Range	Mean	Range	
Spreaders in rubber industry	73	34 - 120	3.66	2.75 - 6.80	Pagnotto & Lieberman (1967)
Leather-finishing industry:					
automatic spraying	53	19 - 85	2.38	1.50 - 3.66	Pagnotto & Lieberman (1967)
washing and tapping	112	29 - 195	4.48	2.15 - 5.85	Pagnotto & Lieberman (1967)
unexposed workers			0.8	0.4 - 1.4	Pagnotto & Lieberman (1967)
31 unexposed			0.35	0.20 - 0.62	Ikeda & Ohtsuji (1969)
118 exposed workers	356	15 - 900	3.25	0.45 - 6.48	Ikeda & Ohtsuji (1969)
18 exposed workers	469	300 - 600	2.1 ± 0.83		Capellini & Alessio (1971)
17 unexposed			0.95 ± 0.33	0.55 - 1.6	Capellini & Alessio (1971)
23 male volunteers (3-h exposure)	375		2.55 ± 0.55		Ogata et al. (1970)
	750		5.99 ± 1.20		Ogata et al. (1970)
53 exposed workers	101		2.04		Angerer (1976)
30 unexposed			0.79		Angerer (1976)
20 workers in art-furniture industry		15 - 164	approximately 0.75	0.21 - 2.2	Apostoli et al. (1982)

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Single Exposures

The acute toxicity of toluene by various routes of exposure is summarized in Table 7.

In all species studied, the symptoms found with increasing dose were irritation of the mucous membranes, incoordination, mydriasis, narcosis, tremors, prostration, anaesthesia, and death. From the acute toxicity studies, especially the inhalation studies, there is some indication that sensitivity differed between the species tested. However, it should be kept in mind that the studies are hardly comparable.

From the oral and inhalation studies, there is evidence that there is a difference in sensitivity between the rat strains used and also at different ages.

8.1.1 Inhalation

Bruckner & Peterson (1981a,b) found an age-dependent sensitivity in outbred male rats (ARS/Sprague Dawley) and male IRC mice. Animals of 4 weeks of age were found to be more susceptible to toluene narcosis, when exposed to toluene vapour at 9750 mg/m^3 for 3 h, than 8- and 12-week-old animals. In contrast, Cameron et al. (1938) stated that very young Wister rats (9-day-old) were less sensitive to toluene exposure than adults.

von Oettingen et al. (1942b) observed that 6 dogs showed an increase in respiratory rate and a decrease in respiratory volume after 1 h of exposure to 3188 mg toluene/m^3 (containing only 0.01% benzene).

8.1.2 Oral

Immature 14-day-old Sprague Dawley rats were more sensitive to ingested toluene (analytical grade) than juvenile or adult males (Table 7).

8.1.3 Intraperitoneal and intravenous injection

Batchelor (1927) and Cameron et al. (1938) reported the ip lethal dose for rats and mice to be approximately 1.7 g/kg body weight. Female mice were less sensitive to toluene than males (Ikeda & Ohtsuji, 1971).

Keplinger et al. (1959) determined the ip LD_{50} of toluene in rats of both sexes at three different environmental temperatures. It was found that the LD_{50} was 800 mg/kg body weight at 26 °C, 530 mg/kg at 8 °C, and 225 mg/kg at 36 °C.

Table 7. Acute toxicity of toluene

Route/species	Dose	Duration (h)	Effect	Reference
Inhalation				
Rat	45 750 mg/m³	6.5	LC_{50}	Cameron et al. (1938)
Rat	15 000 mg/m³	4	16% mortality	Smyth et al. (1969a)
Mouse	45 750 mg/m³	6.5	100% mortality	Cameron et al. (1938)
Mouse (Swiss)	19 950 mg/m³	7	LC_{50}	Svirbely et al. (1943)
Mouse	26 033 mg/m³	6	LC_{50}	Bonnet et al. (1979)
Dog	3188 mg/m³	1	no mortality	von Oettingen et al. (1942b)
Oral				
Rat	7.53 g/kg body weight		LD_{50}	Smyth et al. (1969a)
Rat (CFY males)	5.90 g/kg body weight		LD_{50}	Ungváry et al. (1979)
Rat (Sprague Dawley) (male)	5.58 g/kg body weight		LD_{50}	Withey & Hall (1975)
14-day-old (both sexes)	2.6 g/kg body weight		LD_{50}	Kimura et al. (1971)
juvenile (male)	5.5 g/kg body weight		LD_{50}	
adults (male)	6.4 g/kg body weight		LD_{50}	
Dermal				
Rabbit	14.1 mg/kg body weight		LD_{50}	Smyth et al. (1969a)
Intraperitoneal				
Rat (female)	1.64 g/kg body weight		LD_{50}	Ikeda & Ohtsuji (1971)

Paksy et al. (1982) demonstrated that ip administration of 553 or 1843 mg toluene/kg body weight caused muscular weakness and equilibrium disturbances in male rats, within 30 min of exposure.

Toluene administered iv as a 2 - 5% infusion (2.75 mg/kg body weight per min) in Intralapid®, for 1 h, caused vestibular disturbances in female rats (Tham et al., 1982).

8.1.4   Subcutaneous injection

Quantities of 1.1 - 1.25 g/kg body weight and 4.3 - 8.7 g/kg have been found to cause death in rats and mice, respectively, when injected sc (Batchelor, 1927; Cameron et al., 1938). Braier (1973) reported that all rabbits injected with 3.46 g/kg body weight died by the end of the second day.

8.2   Short-Term Exposures

8.2.1   Inhalation

8.2.1.1   Mouse

Mice exposed to 3750 mg/m^3 for 20 days did not show histological damage to the lungs and kidneys. However, leukocytosis, and decreased thrombocyte count and RBC count were seen, particularly at the highest dose level. There was some evidence of hypoplasia in bone marrow (Horiguchi & Inoue, 1977). The same was found by Bruckner & Peterson (1981b) in mice exposed to 15 000 mg/m^3 for 8 weeks.

Effects were found in mice with exposure to 45 000 mg toluene (99.9% pure)/m^3, in cycles of 10 min inhalation exposure with 20-min recovery periods for 7 cycles/day, 5 days/week, for 8 weeks. These included a depression in body weight gain (food intake was not measured). The animals became ataxic with blood-toluene levels of between 40 - 70 g/litre, immobile with levels of 75 - 125 g/litre, drowsy and difficult to arouse with levels of 125 - 150 g/litre, and unconscious with levels exceeding 150 g/litre. Blood-urea nitrogen (BUN) levels were consistently reduced during the exposure period. Recovery occurred 2 weeks after exposure. No detectable histopathological effects were seen in the brain, lungs, liver, heart, or kidneys, though decreases in kidney, brain, and lung weights were found. Substantial

toluene residues were found in the brain, 1 h after exposure
(Bruckner & Peterson, 1981a,b).

8.2.1.2 Rat

von Oettingen et al. (1942b) reported increasing numbers
of casts in the collecting tubules of rat kidneys during
inhalation of 99.9% pure toluene at concentrations of 750,
2250, 9375, and 18 750 mg/m³ for 5 or 15 weeks (7 h/day, 5
days/week). There was no clear influence on the composition
of the blood, with the exception of a temporary decrease in
WBC count at the highest dose level. A few casts in the
kidneys were seen after the third week of exposure at 2250
mg/m³ and earlier at the higher dose levels.

Furnas & Hine (1958) reported on the neurotoxicity of
toluene (pure product) in rats. An initial exposure to 18 750
mg/m³ proved to be ineffective in producing CNS changes.
Exposures were increased to 37 500 mg/m³ for 20 min and then
to 75 000 mg/m³ for 1 h. At the highest level, there was
decreased mobility but no quivering or twitching and no
hyperresponse to auditory stimuli.

A significant depression was observed in the relative
adrenal weight in Donryu strain rats exposed to 99% pure
toluene at 750, 3750, or 7500 mg/m³ during 8-h daily
exposures, for 32 weeks (Takeuchi, 1969). No influence on
blood composition was found. Histologically, the zona
glomerulosa of the adrenal cortex of toluene-exposed rats was
thicker, while the zona fasciculata and zona reticularis were
reduced. The author suggested that toluene affected the
hypothalamo-pituitary-adrenal system. In another study, it
was noted that exposure of male Sprague Dawley rats to 3750 mg
toluene/m³, for 8 h daily for 4 weeks, significantly
increased adrenal weight after 2 weeks and that the weight
remained higher after 4 weeks. Eosinophile count increased
and, after 4 weeks, it was significantly greater than in the
controls (Takeuchi et al., 1972).

Matsumoto et al. (1971) found degeneration of germinal
cells in the testes in 4 out of 12 Donryu male rats exposed by
inhalation to 750 mg toluene/m³, for 8 h/day, 6 days/week,
for 1 year. Absolute testicular weight at 1 year was lower in
rats exposed to 375 and 750 mg/m³ in comparison with
controls, and there was a trend toward a decrease in the
relative testes weight.

In the studies of Matsumoto et al. (1971), exposure of
rats through inhalation to toluene concentrations of 375, 750,
or 7500 mg/m³ for 8 h/day, 6 days/week, for 43 weeks,
produced hyaline droplets in renal tubules. There was an
absolute and relative increase in kidney weight. No change in
the morphological blood picture was found.

Exposure of rats to 4095 mg toluene/m³ for 6 weeks or to 15 000 mg/m³ for 8 weeks did not induce histological changes in the liver or changes in blood composition (Jenkins et al., 1970; Bruckner & Peterson, 1981b).

Dose-dependant effects were found in rats with high-level intermittent exposure to 45 000 mg/m³ (toluene 99.9% pure), in cycles of 10 min inhalation exposure with 20-min recovery periods for 7 cycles/day, 5 days/week, for 8 weeks (Bruckner & Peterson, 1981a). After several cycles of exposure, progressive deterioration in performance was noted in rats after each exposure. A depression in body weight gain was seen in rats during the 8 weeks of intermittent toluene exposure. Food intake was not measured. An increase in aspartate aminotransferase (SGOT) (EC 2.6.1.1) levels was noted in rats. An increase in lactate dehydrogenase (LDH) (EC 1.1.1.27) was also seen. Recovery occurred 2 weeks after exposure. There were no detectable histopathological changes in brain, lung, liver, heart, or kidneys, though a decrease in organ weights (kidneys, brain, and lung) was noted in treated rats (Bruckner & Peterson, 1981b). Substantial toluene residues were found in the brain, 1 h after exposure. Previous work by these authors showed that performance was inversely correlated with the toluene concentration in brain tissue.

A group of rats was exposed to 4000 mg toluene/m³ through inhalation, for 6 h/day, 5 days/week, for 4 weeks. The toluene increased myocardial vascular resistance and reduced cerebral nutritive blood flow. It did not change the ECG, blood pressure, cardiac output, distribution of cardiac output to the organs, nutritive blood flow, the circulatory resistance of other organs, and the histological structure of the heart (Morvai & Ungváry, 1979).

Pyykkö (1983a) reported that inhalation of 7500 mg toluene vapour/m³ for 8 h/day for 1-16 days, caused insignificant changes in rat kidney microsomes. After discontinuation of exposure, the activities of enzymes and the concentration of cytochromes returned to the control level in 1 - 4 days. A decrease in the activities of monooxygenases and the concentration of cytochrome P-450 (EC 1.14.14.1) of adult male rat lung microsomes after 6 - 24 h toluene exposure was found, but those of cytochrome-b₅ (EC 1.6.2.2) and NADPH-cytochrome c reductase (EC 1.6.2.4) were not changed (Pyykkö, 1983a).

Gut (1983) demonstrated a post-inhalation, dose-related increase in cytochrome P-450 content in rats exposed to levels up to 4000 mg/m³ for 24 h. When rats from this exposure group were pre-treated with phenobarbital prior to toluene exposure, a decreased induction of cytochrome P-450 was seen.

Korpela et al. (1983) found an increase in the haemolytic resistance of the rat erythrocyte in hypotonic medium, in in vitro studies and in in vivo studies, when animals were

exposed to a toluene concentration of 7500 mg/m^3. In vitro dose levels of 200 - 500 mg/litre were tested for the antihaemolytic effect. A maximum was reached with 300 mg/litre.

8.2.1.3 Dog

Appreciable fat in the convoluted tubules and hyaline casts in the collecting tubules of the kidneys and congestion in the lungs were observed in dogs exposed through inhalation to 750, 1500, or 2250 mg/m^3 for approximately 20 daily 8-h exposures, then for 7 h/day, 5 days/week for 1 week, and finally to 3188 mg/m^3 for 1 h (von Oettingen et al., 1942b).

At autopsy, hyperaemic renal glomeruli and albuminuria were observed, but no effects on the bone marrow, in 2 dogs exposed to 7500 mg/m^3 (8 h/day, 6 days/week, for 4 months), then 9975 mg/m^3 (8 h/day, 6 days/week, for 2 months) (Fabre et al., 1955).

8.2.2   Other animal species and routes

Neither continuous exposure to 389 mg/m^3 toluene for 90 days nor repeated exposure to 4095 mg/m^3 for 6 weeks (8 h/day, 5 days/week) affected the liver, kidneys, lung, spleen, heart, or blood composition in 30 rats, 30 guinea-pigs, 4 dogs, or 6 monkeys, as assessed by histopathological examination. In addition, no effects of treatment were seen in the brain or the spinal cord of dogs or monkeys. No significant changes were observed in any of the haematological parameters (haemoglobin, haematocrit, or leukocyte count). All except 2 of 30 treated rats survived exposure, and all animals in the study gained body weight with the exception of the monkeys (Jenkins et al., 1970).

Guinea-pigs exposed to toluene at 4688 mg/m^3 for 4 h/day, 6 days/week, survived 3 weeks of exposure, though they were severely affected. At 3750 mg/m^3, guinea-pigs were not affected even after 35 exposures, though there was evidence of degenerative changes in the liver and kidneys (Smyth & Smyth, 1928).

Reversible morphological changes in the liver were noted when toluene was injected via the sc and ip routes in CFY male rats. The dose levels were 1 ml/kg body weight ip for 12 days or sc for 3 weeks, 0.5 ml/kg body weight ip or sc for 3 weeks, and 0.25 or 0.125 ml/kg body weight ip or sc for 4 weeks (Ungváry et al., 1976). The same changes were observed when

toluene was given orally to guinea-pigs (Divincenzo & Krasavage, 1974).

Subcutaneous injection of rats with toluene at 0.87 g/kg body weight, twice daily, for 6 months, elicited repolarization disorders, atrial fibrillation, and in some of the animals, ventricular extrasystoles. Intravenous injection of 0.4 mg toluene/kg body weight in rats reduced arterial blood pressure; however, injection of the same dosage by the ip or sc route did not have any effects on blood pressure (Morvai et al., 1976).

Rabbits administered sc 300 mg toluene/kg body weight for 6 weeks or 700 mg/kg body weight for 9 weeks in rabbits did not show any effects on DNA synthesis in bone-marrow cells or peripheral blood elements (Speck & Moeschlin, 1968). Braier (1973) found a transient slight granulopenia followed by granulocytosis in rabbits given 865 mg toluene/kg body weight, sc, for 6 days. No changes in bone marrow were seen.

8.2.3   Oral

8.2.3.1 Rat

In a short-term oral study, female rats fed up to 590 mg toluene/kg body weight by intubation, for periods of up to 6 months, did not exhibit toxicological effects as determined by gross appearance, growth, blood counts, analysis for blood-urea nitrogen, final body and organ weights, bone-marrow counts, or histopathological examination of adrenals, pancreas, lungs, heart, liver, kidneys, spleen, and testes (Wolf et al., 1956).

8.3   Skin and Eye Irritation; Sensitization

8.3.1   Skin

Repeated (10 - 20) applications of undiluted solvent to the rabbit ear or the shaved skin of the abdomen, for 2 - 4 weeks, produced slight to moderate irritation (Wolf et al., 1956; Smyth et al., 1969a) and increased capillary permeability locally (Delaunay et al., 1950). Cutaneous contact (1 ml as skin depot) in the guinea-pig resulted in histopathological changes, such as karyopyknosis, karyolysis, spongiosis, and cellular infiltration in the dermis, within 16 h (Kronevi et al., 1979).

8.3.2   Eye

Depending on the dose level and the duration of the application, slight to severe irritation of the conjunctival

membrane was reported following direct application of toluene
to the rabbit eye (Carpenter & Smyth, 1946; Wolf et al., 1956;
Smyth et al., 1969a).

The results of the different studies are summarized in
more detail in Table 8.

8.4 Long-Term Exposures

8.4.1 Inhalation

8.4.1.1 Rat

The long-term toxicity of inhaled toluene was studied in
Fisher-344 rats. Four groups of 120 male and 120 female rats
were exposed to 0, 112, 375, and 1125 mg/m^3, for 6 h/day, 5
times per week, for 24 months. All animals were examined for
clinical changes throughout the course of the study and
selected animals were used for ophthalmological,
haematological and clinical chemistry studies, and
urinalysis. A slight, but significant reduction in
haematocrit was observed among female rats exposed to 375 or
1125 mg/m^3. Among the 1125 mg/m^3 group only, the mean
corpuscular haemoglobin concentration was slightly, but
significantly, increased. No histopathological changes were
found in liver, kidneys, lungs, or other organ systems
including spleen and bone marrow (Gibson & Hardisty, 1983).

8.5 Reproduction, Embryotoxicity, and Teratogenicity

8.5.1 Reproduction

No data are available.

8.5.2 Embryotoxicity and Teratogenicity

A number of studies have been carried out on the chicken
embryo (McLaughlin et al., 1964; Elovaara et al., 1979), but
the test is not considered a suitable test for teratogenicity
and thus, the results have not been recorded in this document.

8.5.2.1 Inhalation

(a) Rat

Hudák et al. (1977) exposed CFY female rats to 6000 mg
toluene/m^3 for 24 h/day during days 1 - 8, 9 - 14, or 9 - 21
of pregnancy. No teratogenic effects were found. However, a
definite embryotoxic effect, which was related to the duration
of the exposure was noted. Seventeen percent of implants died

Table 8. Acute effects of toluene on skin and eyes

Route/species	Dose	Duration (h)	Effect	Reference
Skin				
Rabbit	435 mg	72	mild irritation (well-defined erythema and slight oedema)	RTECS (1984)
Rabbit	500 mg	72	moderate-to-severe erythema and moderate oedema	RTECS (1984)
Guinea-pig	1 ml	16	karyopyknosis, karolysis, perinuclear oedema, spongiosis, junctional separation, cellular infiltration in dermis; no liver or kidney damage	Kronevi et al. (1979)
Guinea-pig	2 ml, covered		completely absorbed by 5th - 7th day; no mortality up to 4 weeks; weight less than controls for weeks 1 - 3; no differences at week 4	Wahlberg (1976)
Eye				
Rabbit	0.005 ml		moderately severe injury	Smyth et al. (1969a)
Rabbit	100 mg	30 sec (then rinsed)	mild eye irritation	RTECS (1984)
Rabbit	870 μg	72	mild eye irritation	RTECS (1984)
Rabbit	2 mg	24 h	severe eye irritation	RTECS (1984)

or were resorbed in the group exposed between 7 and 14 days and, in the group exposed during days 9 - 21 of pregnancy, fetal and placental weights were decreased and the bone development was retarded.

In a follow-up study, Hudák & Ungváry (1978) exposed rats to 1000 mg toluene/m^3 for 8 h/day on days 1 - 21 of pregnancy, or to 1500 mg toluene/m^3 for 8 h/day on days 1 - 8 or 9 - 14 of pregnancy. There were no signs of maternal toxicity at 1000 mg/m^3. There were no significant effects in toluene-exposed groups on implants/dam, live fetuses/dam, dead or resorbed fetuses/dam or malformations. Fetal body weight was signficiantly reduced by 13% when dams were exposed to 1000 mg/m^3 throughout pregnancy, but not in the 1500 mg/m^3 groups exposed in early or mid-pregnancy. There was a signficant increase in retarded ossification in the 1000 mg/m^3 groups exposed throughout pregnancy and in the 1500 mg/m^3 group exposed on days 1 - 8 of pregnancy. Signficiant increases were also seen in fused and extra ribs in the fetuses, when dams were exposed to 1500 mg/m^3 on days 9 - 14 of pregnancy.

(b) Mouse

Hudák & Ungváry (1978) concluded from their study that toluene administered via inhalation at 500 mg/m^3, for 24 h/day, from day 6 to 13 of pregnancy, was not teratogenic in mice.

Shigeta et al. (1982) investigated the effects of maternal exposure to toluene at a concentration of 375 or 3750 mg/m^3, for 6 h/day, from the first to the 17th day of gestation, on mouse embryos, fetuses, and postnatal growth. No significant differences compared with controls were found. There was a slight increase in the incidence of resorbed fetuses and rudimentary 14th ribs, and an increase in the incidence of extra 14th ribs after exposure to 3750 mg toluene/m^3 (32.6% compared with a mean incidence in the control litter of 19.2%).

(c) Rabbit

In a study by Ungváry & Tätrai (1984), New Zealand rabbits were exposed to 500 or 1000 mg toluene/m^3, for 24 h/day, on days 6 - 20 of pregnancy. The toluene caused spontaneous abortions at 1000 mg/m^3, but no teratogenic effects were found at either concentration.

8.5.2.2 Oral

Toluene was administered, by gavage, to CD-1 mice from days 6 to 15 of gestation at doses of 260, 430, or 870 mg/kg

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body weight per day and from days 12 to 15 at 870 mg/kg body weight per day. The vehicle used was cottonseed oil (0.5% of maternal body weight per dose). A significant increase in embryonic lethality occurred at all dose levels, when toluene was administered on days 6 - 15, and a significant reduction in fetal weight was measured in the 430 and 870 mg/kg groups. Exposure to 870 mg toluene/kg on days 6 to 15 also significantly increased the incidence of cleft palate; this effect reportedly did not appear to be due merely to a general retardation in growth rate. When toluene was administered at 870 mg/kg on days 12 - 15, however, decreased maternal weight gain was the only effect observed. Maternal toxicity was not noted after exposure to toluene on days 6 - 15 at any dose level (Nawrot & Staples, 1979).

Kostas & Hotchin (1981) studied the effects of toluene in the drinking-water on mice exposed prenatally, postnatally, or continuously. The test animals were the offspring of dams given drinking-water containing 16, 80, or 400 mg toluene/litre during pregnancy and lactation. After weaning, the test mice were exposed to the same toluene concentrations as the dams. No effects of toluene exposure were seen on maternal fluid consumption, offspring mortality rate, development of eye or ear opening, or surface-righting response. At 35 days of age, the offspring exposed to 400 mg toluene/litre showed decreased habituation of open-field activity. Rotorod performance measured at 45 - 55 days of age was depressed in all exposed groups. Postnatal exposure alone did not produce similar results.

Although it is generally accepted that toluene readily crosses the placenta, it does not appear to be teratogenic in mice, rats, or rabbits (Hudák et al., 1977; Hudák & Ungváry, 1978, Litton Bionetics, Inc., 1978b; Tätrai et al., 1980; Shigeta et al., 1982; Ungváry et al., 1983; Ungváry, 1984; Ungváry & Tätrai, 1984). It is fetotoxic, causing a reduction in fetal weight in mice and rats and retarded ossification with some increase in minor skeletal anomalies at doses that are below those toxic for the dam as well as at toxic doses (Hudák & Ungváry, 1978; Nawrot & Staples, 1979).

8.6 Mutagenicity and Related End-Points

The genetic activity of toluene has been tested in an array of microbial, isolated mammalian cell, and whole organism test systems. The results have usually been negative. In the few studies in which a positive result was found, the purity of the toluene was not stated.

8.6.1   DNA damage

The ability of toluene to induce DNA damage was evaluated
in 2 studies by comparing its differential toxicity for
wild-type and DNA repair-deficient E. coli and S. typhimurium
(Matsushita et al., 1971; Fluck et al., 1976; Mortelmans &
Riccio, 1980). Toluene did not produce any differential
toxicity in these tests.

8.6.2   Mutation

Toluene has been reported to be non-mutagenic in the Ames
Salmonella assay when tested with strains TA 1535, TA 1537,
TA 1538, TA 98, and TA 100 (Litton Bionetics, Inc., 1978a;
Mortelmans & Riccio, 1980; Nestmann et al., 1980; Bos et al.,
1981; Snow et al., 1981), and in the E. coli WP2 reversion to
trp$^+$ prototrophy assay (Mortelmans & Riccio, 1980).
Toluene (0.05 - 0.30 µl/ml, with and without mouse liver
S-9 activation) failed to induce specific locus forward
mutations in the L5178y Thymidine Kinase (TK) mouse lymphoma
cell assay (Litton Bionetics, Inc., 1978a).
Toluene, with and without metabolic activation, was
tested for its ability to induce reversions to isoleucine
independence in S. cerevisiae strain D7 (Mortelmans & Riccio,
1980), mitotic gene conversion to tryptophan independence in
strains D4 (Litton Bionetics, Inc., 1978a) and D7 (Mortelmans
& Riccio, 1980), and mitotic crossing over at the ade2 locus
in strain D7 (Mortelmans & Riccio, 1980). Toluene did not
elicit a positive mutagenic response in any of these tests.
Donner et al. (1981) reported that pure liquid toluene in
doses of 500 and 1000 mg/kg fed to Drosophila melanogaster
males (white strain), for 24 h, did not induce recessive
lethal mutations.

8.6.3   Chromosomal effects

Evans & Mitchell (1980) concluded that toluene did not
alter sister chromatid exchange (SCE) frequencies in cultured
Chinese hamster ovary (CHO) cells. In this study, CHO cells
without rat liver S-9 activation were exposed to 0.0025 -
0.04% toluene for 21.4 h, and CHO cells with activation were
exposed to 0.0125 - 0.21% for 2 h.
In an analysis of 720 metaphases from the bone marrow of 5
male rats that had been injected sc with 0.8 g toluene/kg body
weight per day, for 12 days, chromosomal aberrations were
observed in 13% of the preparations. Sixty-six percent of the
aberrations were chromatid breaks, 24% were chromatid
"fractures", 7% were chromosome "fractures", and 3% involved
multiple injuries. The frequency of spontaneous aberrations

in 600 marrow metaphases from 5 control rats injected with vegetable oil averaged 4.16% (34.2% were chromatid aberrations; 65.8% were breaks); no chromosomal "fractures" or multiple injuries were recorded. The significance of the positive clastogenic effects attributed to toluene is difficult to assess, however, because the purity of the sample employed was not stated, and because the distinction between chromatid breaks and "fractures" was not clear (Dobrokhotov, 1972).

Lyapkalo (1973) administered 1 g toluene/kg body weight per day to 6 rats, by sc injection, for 12 days. Treatment with toluene resulted in chromosome aberrations in 11.5% of the bone-marrow cells examined (84 aberrant metaphases/724 cells) compared with 3.87% (40/1033) in olive oil-injected controls. The types of aberrations that were found consisted of "gaps" (60.47%), chromatid breaks (38.37%), and isochromatid breaks (1.16%). The purity of the toluene used in this study was not stated.

Dobrokhotov & Enikeev (1976) exposed rats to 610 mg toluene/m^3 via inhalation, for 4 h daily (presumably 6 days/week). After 4 months of exposure, damaged metaphase chromosomes were seen in 21.6% of the bone-marrow cells analysed. The percentage of metaphases with damaged chromosomes in bone-marrow cells from control rats was 4.02%. Chromosome damage was observed in the group with toluene 1, 2.5, and 4 months after the initial exposure. However, Donner et al. (1981) did not find an increased frequency of chromosome aberrations in the bone-marrow cells of male Wistar rats following inhalation exposure to toluene at 1125 mg/m^3, for 6 h/day, 5 days/week for 15 weeks. The frequency of SCEs was significantly increased in rats exposed for 11 and 13 weeks, but the frequency was in the control range after 15 weeks of exposure.

Pure toluene injected ip into Charles River rats, did not induce bone-marrow chromosomal aberrations (Litton Bionetics, Inc., 1978b). Toluene was injected at dosages of 22, 71, and 214 mg/kg body weight in 2 different studies. In one study, 5 rats were sacrificed at 6, 24, and 48 h following injection of each dose; in a second study, 5 rats were dosed daily at each level for 5 days, and the rats were sacrificed 6 h after injection of the last dose. Approximately 50 cells per animal were scored for damage. Dimethyl sulfoxide (the vehicle) was administered ip at 0.65 mg/kg body weight per rat and served as a negative control, while triethylenemelamine (TEM) in saline administered at 0.3 mg/kg body weight was used as a positive control.

Gad-El-Karim et al. (1984) treated 5 male and 5 female CD-1 mice with 1720 mg toluene/kg body weight by oral gavage. An equal number of control animals was treated with olive

oil. The mice were killed 30 h after dosing. Toluene did not cause any clastogenic effects (micronuclei or chromosome aberrations) in the bone marrow of the animals.

Feldt & Zhurkov (1984) studied the clastogenic effect in bone-marrow cells and the inducibility of dominant lethal mutations in germ cells of randomly bred SHR male mice treated with different doses of toluene by gavage. They found a dose-related increase in the rate of polychromatophilic erythrocytes with micronuclei. The minimum effective dose was 200 mg toluene/kg body weight. Toluene did not induce chromosome aberrations in bone-marrow cells or dominant lethal mutations in germ cells.

The ip administration of toluene to male Swiss mice did not cause an increase in micronucleated polychromatophilic erythrocytes in the bone marrow (Kirkhart, 1980). Two doses (separated by 24 h) of 250, 500, or 1000 mg/kg body weight were administered to groups of 32 mice. The animals were sacrificed at 30, 48, and 72 h after the first dose (8 mice/time interval). Five hundred polychromatic erythocytes per animal were evaluated for the presence of micronuclei.

Toluene was evaluated for its ability to induce dominant lethal mutations in the sperm cells of CD-1 male mice (Litton Bionetics, Inc., 1981). Test mice were exposed, via inhalation, to exposure levels of 375 and 1500 mg/m^3 for 6 h/day, 5 days/week, for 8 weeks. Following treatment, the males were mated sequentially with 2 females/week for each of 2 weeks. Toluene did not cause any significant reduction in the fertility of the treated males, and did not cause increases in either pre- or post-implantation loss of embryos, compared with the controls. A significant induction of dominant lethal mutations was observed in the positive control mice that received triethylene melamine (TEM).

8.7   Carcinogenicity

8.7.1   Inhalation

The carcinogenicity of inhaled toluene (purity 99.98%) was assessed in Fisher-344 rats (Gibson & Hardisty, 1983). Groups of 120 males and 120 females were exposed to toluene at concentrations of 112.5, 375, or 1125 mg/m^3 for 6 h/day, 5 days/week, for 24 months. No increased incidence of neoplastic lesions was observed in males or females. Neoplasms were observed in the lungs and liver, endocrine organs, lympho-reticular system, mammary glands, skin, testes, and uterus, but the lesions occurred with equal frequency in both control and treated groups. There were no differences in mortality between the groups.

8.7.2   Oral

Preliminary results of a study that is still in progress were reported by Maltoni et al. (1983). Groups of 40 male and 40 female 7-week-old Sprague Dawley rats were given 500 mg toluene/kg body weight (98.34% purity) by stomach tube in olive oil, 4 - 5 days/week, for 2 years. Results were reported after 92 weeks and indicated no increase in the incidence of Zymbal-gland, oral-cavity, nasal-cavity, liver, or mammary-gland tumours, compared with controls.
Carcinogenicity studies on mice and rats are in progress in which toluene is being administered orally. The studies fall within the US National Toxicology Program (no details are available).

8.7.3   Dermal

Toluene has been used as a solvent for lipophilic chemicals such as polycyclic aromatic hydrocarbons, in tests for their carcinogenic potential, when applied topically to the shaved skin of animals. The results in mice have been mainly negative for toluene itself (Poel, 1963; Coombs et al., 1973; Doak et al., 1976).
Lijinsky & Garcia (1972) reported a skin papilloma in one mouse and a skin carcinoma in a second mouse from a group of 30 animals subjected to topical applications of 16 - 20 µl of toluene, twice a week, for 72 weeks.
Frei & Kingsley (1968) examined the promoting effect of toluene on skin tumour induction in Swiss mice following initiation with 7,12-dimethylbenz[a]anthracene (DMBA). Results showed that, in 11 out of 35 mice, DMBA plus toluene gave 6 permanent and 5 regressing skin papillomas. With toluene alone, one permanent and one regressing tumour were observed in 14 mice. It was concluded from this study that toluene had some weak promotor activity, but these results were not confirmed by Frei & Stephens (1968).

8.8   Special Studies

8.8.1   Central nervous system (CNS)

Earlier studies on the distribution of toluene demonstrated the affinity of the compound for organs with a high lipid content, so it is not surprising that CNS effects have been observed. A biphasic response to toluene exposure has been found with initial excitability followed by a depression in response, which is dose related. This response is typical of a narcotic drug. Toluene has also been shown to produce seizures in the limbic system, which identifies it as

a CNS stimulant according to the neuropharmacological scheme of Winters et al. (1972).

8.8.2   Effects on electrical activity in the brain

Studies that were carried out to study the influence of toluene on electroencephalogram (EEG) changes and sleep rhythms are summarized in Table 9. These studies were mainly carried out on rats and the route of administration was by inhalation or ip injection. In essence, high levels of exposure (above 3750 mg/m^3) produced initial excitability with subsequent depression of cortical activity resulting in coma (Contreras et al., 1979). Seizure activity was found with high exposure levels (Takeuchi & Suzuki, 1975; Takeuchi & Hisanaga, 1977; Contreras et al., 1979). Short-term exposure to 7500 mg/m^3 for 24 weeks caused interruption of the sleep cycle in rats (Takeuchi et al., 1977, 1979).

8.8.3   Effects on neurotransmitters

Studies on changes in the concentrations of various neurotransmitters in rat brain following inhalation exposure to high concentrations of toluene have been reported and details are summarized in Table 10. The significance of the changes found and their relationship to behavioural changes is not known.

Repeated exposure of male Sprague Dawley rats to high concentrations of toluene vapour (1875 - 3750 mg/m^3, 6 h/day, for 3 days) led to increased noradrenaline levels in the subependymal layer of the median eminence (SEL) and to an increase in noradrenaline turnover within the subependymal layer, and the paraventricular hypothalamic nucleus (PVI). Increased dopamine (DA) levels in the lateral palisade zone of the medial palisade zone (MPZ) were also produced. Measurement of the anterior pituitary hormone secretion showed a significant increase in follicle-stimulating hormone (FSH) and delayed increase in corticosterone secretion, following toluene exposure (Andersson et al., 1980). The toluene-induced increase in catecholamine turnover in the MPZ could, in part, reflect an increase in DA turnover in the MPZ (Fuxe et al., 1978; Andersson et al., 1980).

8.8.4   Behaviour

A number of behavioural studies were carried out on rats and mice. The exposure route was mainly inhalation. The dose levels that were studied were in the range of 3.75 - 86 250 mg/m^3 during periods ranging from a few hours to many weeks (Table 11).

Table 9. Central nervous system effects of toluene

Species	Route	Dose (mg/m³)	Duration	Effects	Reference
Cat	inhalation	25 500	10 min/day x 40 days	restlessness, tachypnoea, coughing, sneezing, salivation, mydriasis, lachrymation	Contreras et al. (1979)
		153 500	10 min/day x 40 days	ataxia, collapse; EEG changes in cerebellum, amygdala, and visual cortex; seizures with repeated high-level exposure; recovery occurred 12 min after exposure	
Rat	inhalation	3750; 7500	4 h/day	EEG changes (decreased cortical and hippocampal components)	Takeuchi & Hisanaga (1977)
		15 000	4 h/day	increased excitability followed by depression and inability to stand; changed sleep cycle myo-clonic seizures; increased pulse rate	
Rat	inhalation	7500	8h/day x 8 weeks	decreased threshold for Bemegride-induced convulsions	Takeuchi & Suzuki (1975)

Table 9 (contd).

Species	Route	Concentration	Exposure	Effect	Reference
Rat	inhalation	3750	6 h/day x 6 days/week x 4 weeks	increased spontaneous activity during light period after repeated exposure; single exposure did not influence circadian rhythm	Ikeda et al. (1981)
Rat	inhalation	7500	4 h/day x 24 weeks	interrupted sleep cycle; decreased duration of REM sleep	Takeuchi et al. (1979)
Rat	inhalation	26 250	15 min x 1, 7, or 14 days	hind-limb abduction, resting tremor, head weaving; ataxia; tachypnoea, salivation, diarrhoea, and convulsions; frequency unchanged after 2 weeks of exposure	Yamawaki et al. (1982)
Rat	inhalation	15 000	4 h/day x 4 weeks	changes in sleep cycle and EEGs continued 1 week after exposure	Hisanaga & Takeuchi (1983)
Rat	inhaltion	3750	24 h	increased REM sleep	Fodor et al. (1973)
Rat	ip	200, 400, or 600 mg/kg body weight	single dose	no effect on circadian sleep-waking rhythm; rhythm of paradoxical sleep and wakefulness were changed; at 600 mg/kg, EEG was abnormal; on second day, 200 mg/kg-exposed group showed increase in para- doxical sleep phase during dark period; sleep-waking rhythm returned to normal by third day	Nakagaki et al. (1983)

Table 10. Changes in neurotransmitters after toluene exposure

Species	Route	Dose (mg/m³)	Duration	Effects	References
Rat	inhalation	26 250	15 min/14 days	decrease in 5HT binding in whole brain, especially hippocampus, pons, and medulla	Yamawaki et al. (1982)
Rat	inhalation	375; 1125	8 h	increased DA levels	Rea et al. (1983)
Rat	inhalation	3750	8 h	increased DA levels in striatum; increase NA in medulla and midbrain; increased 5HT in cerebellum, medulla, and striatum	
Rat	inhalation	750, 1500, 3000	continuous exposure for 30 days	increased DA in striatum (dose-dependent); reduced 5HT in cortex and hippocampus, NA in hypothalamus, cortex, and hippocampus; reduced ACh in striatum and whole brain; cAMP in striatum; amino acids: GABA increased by mid- and highest doses while glycine was reduced by the 750 mg/m³ exposure	Honma et al. (1983)
Rat	inhalation	15 000	8 h	glutamine levels in midbrain increased significantly	Honma et al. (1982)

Table 10 (contd).

Species	Route	Dose (mg/m³)	Duration	Effects	References
Rat	inhalation	3750 - 30 000	8 h	AchE increased at low dose and reduced at high dose; AchEg elevated at both exposures; CHATh activity reduced; dose-dependent	Honma (1983)
Rat (Sprague Dawley)	inhalation	1875	6 h/day x 3 days; killed 16 - 18 h after exposure	increase in catecholamines (DAb + NAc) in lateral palisade zone of median eminence	Andersson et al. (1980)
		3750	6 h/day x 5 days; decapitated 4 h after exposure	increase in catecholamines (DAb + NAc) in sub-ependymal layer of median eminence; increase in FSHi in plasma and delayed increase in corticosterone secretion	
Rat	inhalation	300	6 h/day x 3 days	decreased DAb levels in marginal zone of nucleus, caudatus, and anterior nucleus accumbens; DAb turnover significantly reduced in all parts of of anterior caudate nucleus	Fuxe et al. (1982)
Rat	inhalation	1875	6 h/day x 3 days	reduction in DAb turnover in anterior nucleus accumbens	Fuxe et al. (1982)

Table 10 (contd).

Species	Route	Dose (mg/m³)	Duration	Effects	References
Rat (contd).	inhalation	5625	6 h/day x 3 days	effects on DA̱b in anterior nucleus accumbens disappeared, while a selective increase in DA̱b in the DA̱b-CCḴj immunoreactive nerve terminals	Fuxe et al. (1982)
		11 250	6 h/d x 3 d)	significantly-increased DA̱b turnover in tuberculum olfactorium; significant increases in amine levels in DA̱b-CCḴj immunoreactive-nerve terminals in the nucleus accumbens, especially in the tuberculum olfactorium	

5HT = 5-hydroxytryptaline.
DA = dopamine.
NA = noradrenaline.
ACh = acetylcholine.
cAMP = cyclic 3',5'-adenosine monophosphate.
GABA = γ-aminobutyric acid.
AChE = acetylcholinesterase.
ChAT = choline acetyltransferase.
FSH = follicle-stimulating hormone.
CCK = cholecystokinin.

[a]
[b]
[c]
[d]
[e]
[f]
[g]
[h]
[i]
[j]

Table 11. Behavioural effects of different doses of toluene

Species	Route	Dose (mg/m³)	Duration	Effects	Reference
Rat (Sprague Dawley)	inhalation	563	0.5, 1, 2, or 4 h	initial stimulation followed by depression in multiple FR-FI response schedule performance	Geller et al. (1979)
Rat	inhalation	375, 668, 2100		no-observed-adverse-effect level	Wood et al. (1983)
		3750, 6675, 11 250	4 h	deficit in conditioned reflex; less when external signal cued response	
Rat (male)	inhalation	2063 - 3000	4 h/day x 3 weeks	no effect on avoidance response	Battig & Grandjean (1964)
Rat (male)	inhalation	7500	8 h/day x 52 days	process of extinction in conditioned behaviour worsened	Maeda (1970)
Rat (male)	inhalation	11 250	4 h	deficit in conditioned avoidance response	Shigeta et al. (1978)
		3750	4 h	no effect	
Rat (male)	inhalation	12 000 and 24 000	4 h	deficit in conditioned avoidance response	Krivanek & Mullin (1978); Mullin & Krivanek (1982)

Table 11 (contd).

Species	Route	Dose (mg/m³)	Duration	Effects	Reference
Rat (male)	inhalation	3000 and 6000	4 h	no effect	Krivanek & Mullin (1978); Mullin & Krivanek (1982)
Rat (male)	inhalation	3000	4 h	deficit in unconditioned reflexes and simple behaviour	Krivanek & Mullin (1978); Mullin & Krivanek (1982)
Rat	inhalation	15 000	2 h/day x 60 days	multiple response schedule; no effect on CRF or FR30; deficit in DRL in 12-second schedule	Ikeda & Miyake (1978)
Rat (Sprague Dawley)	inhalation	86 250	30 min/day x 7.6 days	induced forced turning	Ishikawa & Schmidt (1973)
Mice (male)	inhalation	3.75, 37.5, 375, 3750	6 h/day x 10 days	deficit in wheel-turning	Horiguchi & Inoue, (1977)
Mice	inhalation	15 000 40 000	3 h 10 min	deficit in visual placing, grip strength, wire maneuvre tail pinch, righting reflex	Peterson & Bruckner (1978)
Mice	inhalation	45 000	3 h/day, 5 days/week for 8 weeks	deficit in performance tests	Bruckner & Peterson (1976)

The results of some studies suggest that low levels (3.75 mg toluene/m^3) of exposure may have behavioural effects (decreased wheel-turning activity) in mice (e.g., Horiguchi & Inoue, 1977), but most have only shown effects with higher concentrations (Table 11).

Repeated exposure of a male mouse to a high concentration of toluene (22 500 mg/m^3) for 30 min/day, 7 days/week, for 7 weeks, did not result in the development of tolerance to the acute behavioural effects of toluene. However, by 3 days after cessation of exposure, responses had returned to baseline levels indicating that there were no residual effects of toluene (Moser & Balster, 1981).

8.8.5 Liver

In a long-term study on rats exposed to 112, 375, or 1125 mg/m^3, for 6 h/day, 5 days/week, for 24 months, no histopathological evidence of liver damage was observed (Gibson & Hardisty, 1983). Jenkins et al. (1970) reported that there were no histopathological liver changes in a variety of species exposed to 4069 mg toluene/m^3 during a 6-week inhalation period. Short-term studies, generally using biochemical and morphological methods to study the effects of toluene on the liver, have been carried out on different animal species (rats, mice, guinea-pigs, rabbits, dogs, and monkeys) using different routes of application, i.e., inhalation (Gut, 1971, 1983; Reynolds, 1972; Tähti et al., 1977; Ungváry et al., 1980, 1982; Töftgard et al., 1982), oral (Wolf et al., 1956; Reynolds, 1972; Mungikar & Pawar, 1976a; Pyykkö, 1980, 1983; Ungváry et al., 1980, 1982), dermal, sc, and ip (DiVincenzo & Krasavage, 1974; Hudák et al., 1975; Ungváry et al., 1976, 1981; Wahlberg, 1976; Chand & Clausen, 1982).

Alterations observed in the short-term studies of Ungváry et al. (1980, 1982) are more or less representative of those often observed in rats and mice exposed to toluene. Though Ungváry and coworkers did not find any specific histological changes, two general types of alteration were identified. These included: (a) biochemical responses such as proliferation of smooth endoplasmic reticulum; increased enzymatic activity, e.g., succinate dehydrogenase (EC 1.3.99.1), aniline hydroxylase (EC 1.14.1.1), and aminopyrine N-demethylase activities; increased cytochrome P-450 (EC 1.14.14.1) and cytochrome b$_5$ (EC 1.6.2.2) concentrations; and alterations in liver weight (increased), liver glycogen (decreased), and BSP retention (decreased); and (b) morphological changes such as non-specific subcellular changes (in 10 - 15% of hepatocytes); dilatation of rough endoplasmic reticulum (RER), separation of ribosomes, variability in shape

of mitochondria, and increase in number of mitochondria and autophagous bodies.

Ungváry et al. (1980, 1982) observed these changes in both sexes and found such alterations to be dose-related and reversible. Alterations in various liver cell enzyme activities have been reported. No relationship to exposure time was observed. No changes were noted in the activities of alanine aminotransferase (SGPT) (EC 2.6.1.2) or aspartate aminotransferase (SGOT) (EC 2.6.1.1).

A dose-dependent induction of the total liver microsomal concentration of cytochrome P-450 was observed after exposure to 1875, 5625, and 11 250 mg toluene/m³ for 3 days for 6 h/day (Töftgard et al, 1982). The increase was significant at the 2 highest exposure levels. The authors also reported that the liver weights and liver to body weight ratio were significantly increased.

In oral, ip, and sc studies, adaptive responses comparable to those observed in inhalation studies were seen. Toluene induction of liver enzymes appeared to be less in adult females than in males (Pyykkö, 1983). Induced enzyme levels in young rats (13 days old) of both sexes were comparable to those in adults. Reversible morphological changes were noted, when toluene was injected sc and ip in rats (Ungváry et al., 1976) and when toluene was given orally to guinea-pigs (DiVincenzo & Krasavage, 1974).

8.9 Factors Modifying Toxicity; Toxicity of Metabolites

8.9.1 Effects of combined exposure to toluene and other chemicals

Occupational groups and, to a minor extent, the general population are mostly exposed to mixtures of chemicals rather than to pure toluene. The main exposure route is inhalation. Oral exposure occurs to a much less extent, and is generally to very low levels of toluene in the form of contaminants in food and drinking-water.

This criteria document will not include details of the studies carried out with mixtures, but they will be mentioned in a general sense and the available literature referred to for those who would like to know more.

8.9.1.1 Benzene and toluene

It is clear that, in general, the older studies were mainly carried out using toluene containing variable quantities of benzene. Simultaneous administration of benzene and toluene will result in interference in the metabolism of each chemical in the liver. The conversion of benzene to its

metabolites (such as phenol) is suppressed by toluene in rats and mice, and the disappearance of benzene from the blood is delayed. The hippuric acid excretion metabolites of toluene are reduced by benzene.

Simultaneous sc administration of toluene and benzene in mice and rats had an ameliorating effect on benzene toxicity. Toluene decreased the toxic effect of benzene on bone marrow. Furthermore, toluene diminished the clastogenic effect of benzene but produced an additive effect on chromosome damage (Ikeda & Ohtsuji, 1971; Dobrokhotov, 1972; Ikeda et al., 1972; Dobrokhotov & Enikeev, 1976; Mungikar & Pawar, 1976b; Pawar et al., 1976; Andrews et al., 1977; Sato & Nakajima, 1979b; Tätrai et al., 1980; Gut et al., 1981; Tunek et al., 1982; Gut, 1983; Gad-El-Karim et al., 1984).

8.9.1.2 Xylene and toluene

From the study of Ogata & Fujii (1979), it appears that these solvents do not significantly interfere with each other.

Riihimaki (1979) studied the possible kinetic interactions between toluene and xylene and their metabolites and found that full conjugation capacity with benzoic acid and methylbenzoic acid was reduced during inhalation of toluene and/or xylene. This suggests that the body has a relatively large capacity for the conjugation reaction of toluene and xylene metabolism. However, the consumption of a large amount of easily-metabolized glycine may impair the conjugation and hence the excretion of poorer substrates.

8.9.1.3 n-Hexane and toluene

It seems from a number of animal studies that toluene decreases the neurotoxicity of n-hexane. Toluene interfered in the metabolism of n-hexane in rats with a resulting decrease in the urinary excretion of n-hexane metabolites. The biotransformation of toluene to o-cresol and hippuric acid was not affected by n-hexane, as assessed by the urinary concentrations of these toluene metabolites (Takeuchi et al., 1981a; Honma, 1983; Perbellini et al., 1982).

8.9.1.4 Toluene and other chemicals

The ability of toluene to interfere with the biotransformation of several solvents has been reported by numerous authors. It interferes with the metabolism of styrene (Ikeda & Ohtsuji, 1969), acrylonitrile (Gut et al., 1981), trichloroethylene (Ikeda, 1974; Withey & Hall, 1975), and methylethylketone (Iwata et al., 1983).

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Further studies have been carried out with toluene and carbon tetrachloride (Tatrai et al., 1979), ethanol (Morvai & Ungváry, 1979; Sato et al., 1981; Waldron et al., 1983), acetylsalicylic acid (Ungváry, 1984), and a mixture of paraffins, naphthenes, and aromatic compounds (Carpenter et al., 1944, 1976a,b; Carpenter & Smyth, 1946; Wolf et al., 1956; Taylor & Harris, 1970).

9. EFFECTS ON MAN

9.1 Acute Toxicity

The acute effects of single doses of toluene in man are summarized in Table 12. The lowest dose level of 9.4 mg/m^3 seems to be the odour threshold, while dose levels of 37 500 and higher are associated with narcosis.

9.2 Effects of Short- and Long-Term Exposure Including Controlled Human Studies

Many studies are available on the effects of short- and long-term exposure to toluene including toluene abuse.

It is important to recognize that studies of intentional abuse and occupational studies have generally involved exposures to complex mixtures with toluene as the principal constituent. Prior to 1950-60, benzene was a common contaminant of commercial toluene. Thus, when evaluating the effects of toluene on human beings, the purity of the compound must be considered. In instances involving exposure to complex mixtures, no unequivocal cause-effect relationship with regard to toluene can be established.

9.2.1 Controlled human studies

Odour thresholds and sensory responses to inhaled vapours of toluene concentrate were investigated by May (1966) and Carpenter et al. (1976b). The most probable concentration for odour threshold, determined in 2 trials on 6 volunteers, was 9.4 mg/m^3 (Carpenter et al., 1976b). Mild eye and throat irritation was noted after an 8-h exposure to 750 mg/m^3 and lachrymation at 1500 mg/m^3. Based on sensory thresholds for irritation (eye, nose, throat), dizziness, taste, and olfactory fatigue, 6 out of 6 volunteers indicated their willingness to work for 8 h in a concentration of 825 mg toluene/m^3.

Ogata et al. (1970) reported that 23 Japanese volunteers exposed to 750 mg/m^3 toluene for 3 h or 3 h and 1 h break followed by an additional 4-h exposure showed a prolonged eye-to-hand reaction time, but no effect on critical flicker fusion frequency. No changes in either reaction time or flicker value were observed after exposure to toluene at 375 mg/m^3. Gamberale & Hultengren (1972) studied the effects of toluene on psychophysiological functions in 12 healthy male volunteers. There was significant impairment of reaction time

Table 12. Dose-response relationships for the acute effects
in human beings of single short-term exposures to toluene vapour

Dose	Effect
9.4 mg/m^3 (2.5 ppm)	odour threshold
138.8 mg/m^3 (37 ppm)	probably perceptible to most human beings
188 - 375 mg/m^3 (50 - 100 ppm)	subjective complaints (fatigue, drowsiness, or very mild headache) but probably no observable impairment of reaction time or coordination
750 mg/m^3 (200 ppm)	mild throat and eye irritation; prolonged eye-to-hand reaction time; some impaired cognitive function; slight headache, dizziness, sensation of intoxication; after effects: fatigue, general confusion, moderate insomnia
1125 mg/m^3 (300 ppm)	detectable signs of incoordination may be expected during exposure periods up to 8 h
1500 mg/m^3 (400 ppm)	irritation of the eyes and throat and lachrymation; skin paraesthesia, gross signs of incoordination, and mental confusion expected during exposure periods up to 8 h
1875 - 2250 mg/m^3 (500 - 600 ppm)	anorexia, staggering gait, nausea, nervousness (persist to next day), momentary loss of memory, significant reduction in reaction time
3000 mg/m^3 (800 ppm)	pronounced nausea (after 3-h exposure); confusion, lack of self-control; extreme nervousness, muscular fatigue, and insomnia lasting for several days
5625 mg/m^3 (1500 ppm)	probably not lethal for exposure periods of up to 8 h; incoordination likely; extreme weakness
15 000 mg/m^3 (4000 ppm)	would probably cause rapid impairment of reaction time, and coordination exposures of 1 h or longer might lead to narcosis and possibly death
37 500 - 112 500 mg/m^3 (10 000 - 30 000 ppm)	onset of narcosis within a few min; longer exposures may be lethal

at 1125 mg/m^3, which was further impaired at 1875 and 2625 mg/m^3. No impairment was observed at 375 mg/m^3. Perceptual speed was unaffected at exposure levels below 2625 mg/m^3.

Winneke (1982) noted that exposure to 375 mg toluene/m^3 for 3.5 h did not affect psychophysiological performance in 18 volunteers. Simple reaction time began to increase at 1125 mg/m^3. Complex reaction time did not change until vapour concentrations had reached 1875 mg/m^3. The parameters evaluated in this study included performance in a bisensory (auditory and visual) vigilance task, psychomotor performance, critical flicker fusion frequency, and auditory-evoked potentials.

Three human volunteers were exposed repeatedly to toluene (benzene $\leq$ 0.01%) for 8-h periods at concentrations ranging from 188 to 3000 mg/m^3, in an exposure chamber. A maximum of 2 exposures a week was maintained to allow sufficient time for recovery between exposures; a total of 22 exposures was performed over an 8-week period. The design of the study is complex and not clear. For instance, the number of h per day is different for the several groups. Seven of the 22 exposures were controls (exposed to air only) and exposures to particular levels of toluene were replicated only 1 - 4 times. The effects that were observed at each toluene concentration are summarized in Table 13. Subjective complaints of fatigue, muscular weakness, confusion, impaired coordination, enlarged pupils, and accommodation disturbances were reported at 750 mg/m^3. These effects increased in severity with increases in toluene concentration until, at 3000 mg/m^3, the subjects experienced severe fatigue, pronounced nausea, mental confusion, considerable incoordination and staggering gait, strongly impaired pupillary light reflex, and after-effects (muscular fatigue, nervousness, and insomnia), which lasted for several days (von Oettingen, 1942a,b).

Sixteen healthy volunteers were exposed to increasing concentrations of toluene ranging from 37.5, 150, to 375 mg/m^3, by inhalation, for 6 h/day, for 4 days. At the 375 mg/m^3 exposure, the multipication errors, Landolt's rings, and screw plate tests were significantly affected in addition to the occurrence of headache, dizziness, and a reported sensation of intoxication. The two lower levels did not result in any adverse effects (Andersen et al., 1983).

Suzuki. (1973) found an effect on heart rate, a mean decrease of 7 beats/min in 5 male volunteers exposed to 750 mg toluene/m^3 for 6 h compared with controls. Other studies have shown that exposure to toluene at levels of 375 - 750 mg/m^3 for up to 30 min (Astrand et al., 1972; Gamberale & Hultengren, 1972) or 188 - 3000 mg/m^3 for 8h (von Oettingen

Table 13. Effects of controlled 8-h exposures to pure toluene on 3 human subjects[a],[b]

Concentration	Number of exposures	Effects
0 mg/m³	7	no complaints or objective symptoms, except occasional moderate tiredness toward the end of each exposure, which was attributed to lack of physical exercise, unfavorable illumination, and monotonous noise from fans
188 mg/m³	2	drowsiness with a very mild headache in 1 subject; no after effects
375 mg/m³	4	moderate fatigue and sleepiness (3), and a slight headache on one occasion (1)
750 mg/m³	3	fatigue (3), muscular weakness (2), confusion (2), impaired coordination (2), paraesthesia of the skin (2), repeated headache (1), and nausea (1) at the end of the exposure; in several instances, the pupils were dilated, pupillary light reflex was impaired, and the fundus of the eye was engorged; after-effects included fatigue, general confusion, moderate insomnia, and restless sleep in all 3 subjects
1125 mg/m³	2	severe fatigue (3), headache (2), muscular weakness and incoordination (1), and slight pallor of the eyeground (2); after-effects included fatigue (3) and insomnia (1)
1500 mg/m³	2	fatigue and mental confusion (3), headache, paraesthesia of the skin, muscular weakness, dilated pupils, and pale eyeground (2); after effects were fatigue (3), skin paraesthesia (1), headache (1), and insomnia (2)
2250 mg/m³	1	extreme fatigue, mental confusion, exhilaration, nausea, headache, and dizziness (3), and severe headache (2) after 3 h of exposure; after 8 h exposure, the effects included considerable incoordination and staggering gait (3), and several instances of dilated pupils, impaired pupillary light reflex, and pale optic discs; after-effects included fatigue and weakness, nausea, nervousness, and some confusion (3), severe headache (2), and insomnia (2); fatigue and nervousness persisted on the following day

Table 13 (contd).

Concentration	Number of exposures	Effects
3000 mg/m³	1	rapid onset of severe fatigue and, after 3 h, pronounced nausea, confusion, lack of self-control, and considerable incoordination and staggering gait in all 3 subjects; also, pupillary light reflex was strongly impaired (1), and optic discs were pale (2); all 3 subjects showed considerable after-effects, lasting at least several days, which included severe nervousness, muscular fatigue, and insomnia

[a] From: von Oettingen et al. (1942a,b).
[b] Exposures were twice weekly for 8 weeks. The number of subjects affected is noted in parentheses.

et al., 1942a,b) did not cause any definite effects on heart rate or blood pressure.

Tähti et al. (1981) studied 46 workers exposed to various concentrations of toluene in air ranging from 75 to 750 mg/m³, for 10 – 20 years and found no correlation between the occurrence of chronic diseases and toluene exposure.

No studies have demonstrated a cause-effect relationship between toluene exposure and teratogenic effects in human beings. There are, however, a few publications, such as those of Euler (1967) and Holmberg (1979), in which cases of children with malformations and central nervous system defects have been reported, but the studies were all concerned with exposures to mixtures of solvents. In a study in which 132 women exposed to mixtures containing toluene were compared with 201 female controls, the exposed women recorded high percentages of menstrual disorders, effects on the duration of labour, perinatal mortality, or adverse effects on the newborn infant (Syrovadko, 1977).

9.2.2   Short- and long-term abuse in the general population

It is important to recognize that studies of intentional abuse are generally concerned with exposures to complex mixtures in which toluene is usually the principal

constituent. Benzene is one of the most important
contaminants in commercial toluene.

Solvent abuse is a major problem throughout the world. As
an example, in Scotland alone, 1300 new cases of solvent abuse
had been reported to the police between 1977 and 1980 in a
secondary school population of almost half a million (King,
1982). In the same period, 6 deaths following glue sniffing
were recorded in Scotland (King et al., 1981). King (1982)
and King et al. (1981) diagnosed a series of 20 cases of acute
encephalopathy in children aged 8 - 14 years following toluene
abuse; 5 presenting in coma, 5 with ataxia and dysarthria, 3
with convulsions, and 2 with diplopia and behaviour
disturbance. In 6 of these subjects, the diagnosis of
solvent-induced encephalopathy was made solely by a
blood-toluene assay (0.8 - 8.0 mg/litre). Six of these
children left hospital with neurological impairment and one,
seen 1 year later, had persistent cerebellar signs. Thirteen
children recovered completely. The authors emphasized the
importance of diagnosis, if further damage due to continued
abuse is to be prevented.

The extent of "sniffing" solvents containing toluene has
been extensively reviewed (Massengale, et al, 1963; Barman et
al., 1964; Press & Done, 1967a,b; Gellman, 1968; Wyse, 1973;
Linder et al., 1975; Faillace & Guynn, 1976; Oliver & Watson,
1977; Walter et al., 1977; Watson, 1979). The concentrations
of toluene inhaled under these conditions can approach 112 500
mg/m^3, i.e., saturation concentration at 20 $^\circ$C. Such severe
exposures can result in gross disorientation and
unconsciousness (Hayden et al., 1977).

Episodes of toluene abuse are characterized by the
progressive development of CNS symptoms of dysfunction.
Toluene sniffers experience an initial excitatory stage that
is typically characterized by drunkenness, dizziness,
euphoria, delusions, nausea, and vomiting, and, less commonly,
visual and auditory hallucinations (Press & Done, 1967a,b;
Wyse, 1973; Lewis & Patterson, 1974; Hayden et al., 1977;
Oliver & Watson, 1977; Tarsh, 1979; Streicher et al., 1981).
As the duration of exposure increases, symptoms indicative of
CNS depression become evident including confusion and
disorientation, headache, blurred vision and reduced speech,
drowsiness, muscular incoordination, ataxia, depressed
reflexes, and nystagmus. In extreme cases, there is loss of
consciousness possibly associated with convulsions (Helliwell
& Murphy, 1979). The duration and severity of these effects
vary greatly, depending on the intensity of exposure; the
duration may range from 15 min to a few hours (Press & Done,
1967b). There are reports of seizures including status
epilepticus occurring as the primary presentation of acute

intoxication in toluene sniffers (Helliwell & Murphy, 1979; King et al, 1981).

A case of permanent encephalopathy from repeated, prolonged exposure (14 years) to pure toluene vapour was reported. A 33-year-old man purchased approximately 4 litres of toluene from a paint store every 4 - 6 weeks for 14 years to satisfy his addiction to toluene vapour. The result of this addiction was permanent cerebral atrophy. The clinical signs were ataxia, tremulousness, unsteadiness, emotional lability, marked snout reflex (distorted nostrils on subjection to sniff test), and positive Babinski sign on the right side. The brain (cerebral hemispheres) damage was confirmed by EEG and pneumoencephalography. This same individual was the subject of a report published by Grabski (1961) who reported cerebellar degeneration, hepatomegaly, and impaired liver function after 6 years of toluene vapour inhalation (Knox & Nelson, 1966).

O'Brien et al. (1971) reported reversible hepatorenal damage, confirmed by biochemical tests, in a 19-year-old male who sniffed glue while employed as a sign painter. The blood-toluene level was 0.61 mg/litre.

These findings lead to the conclusion that should adverse effects result from the abuse of toluene-based products, the effects are likely to be transient and to follow closely on intensive solvent exposure.

Schikler et al. (1982) reported the findings on 11 out of 42 cases of toluene abuse, who were examined by computed tomography (CT) scan because of neurological abnormalities; 6 out of the 11 were found to have cerebellar cortical atrophy; 2 of the 6 had cerebellar atrophy. The mean age of the patients was 22 years (range 14 - 31 years) with a mean exposure of 10 years (range 4 - 16 years).

Fornazzari et al. (1983) noted a marked impairment of neurological and neuropsychological test performance in 65% of 24 solvent abusers. Cerebellar symptoms were particularly prominent. The impairment was significantly correlated with CT scan measurements of cerebral and cerebellar atrophy.

Chronic neurological damage from solvent abuse (Table 14) has been sporadically reported in patients who have abused toluene for from 1.5 to 14 years and takes the form of dementia with cerebellar ataxia (Satran & Dodson, 1963; Kelly, 1975; Hänninen et al., 1976; Boor & Hurtig, 1977; Sasa et al., 1978; Malm & Lying-Tunell, 1980; Lewis et al., 1981; Metrick & Brenner, 1982; Fornazzari et al., 1983; Lazar et al., 1983).

Pathologically, in a post-mortem analysis of a 27-year-old man addicted to a thinner containing approximately 40% toluene for 12 years, the most striking feature was diffuse cerebral

Table 14. Summary of chronic toluene-abuse cases

Subject (age)	Inhalation period (years)	cerebellar dysfunction	mental retardation	abnormal EEG	brain atrophy	visual impairment	liver impairment	others	Reference
Pure toluene									
Male (25)	6	+	+						Grabski (1961)
Male (33)	14	+	+	+	+	-	+		Knox & Nelson (1966)
Female (18)	6	+	+	+	-	-	+		Takeuchi et al (1981b)
Male (21)	12		+		+	+	+¡		Lazar et al. (1983)
99% Toluene									
Male (25)	10	+	+	-	+		-		Boor & Hurtig (1977)
Male (59)	long	+	+	-	-		-		Boor & Hurtig (1977)
Toluene									
Male (30)	10	+	+	+	-		-		Satran & Dodson (1963)
Male (25)	0.3		+	-	¡				Escobar & Aruffo (1980)
Male (11)	< 1	+	+	+	¡				King (1982)
Male (25)	5	+	-		+	+	-	hearing loss	Lazar et al. (1983)
Male (18)	3		-		¡	+	-	poly-neuro-pathy	Ehyai & Freemon (1983)
Male (23)	7		+		-	-			Ehyai & Freemon (1983)
68-30% Toluene									
Male (19)	0.8	+	+	+	-	+	+	hallucin-ation, aspermia	Suzuki et al. (1983)

Table 1: (contd).

Male (23)	12	+	+	+	+	+	-	haematuria brainstem disorder	Metrick & Brenner (1982)
Aromatic hydrocarbon									
Female (30)	5	+	+	+	+	+	-		Prockop (1977)
Thinner									
Male (2)	?	+	+	+	+	-	-	hearing loss	Weisenberger (1977)
Male (28)	10	+	+	+	+	-	-		Lazar et al. (1983)
Paints									
Female (19)	1.5	+	-	-	+	+	-		Kelly (1975)
Male (20)	3	+	+	-	+	-	-		Keane (1978)
Male (28)	16	+	+	+	+	+	+/-	haematuria brainstem disorder	Metrick & Brenner (1982)
Glue or thinner									
Male (27)	10	+	+	+	-	+	-	grand mal seizure	Sasa et al. (1978)
Male (29)	12	+	+	+	+	+	-		Allister et al. (1981)
Glue									
Male (15)	?		+	+	+/-		-	microscopic haematuria hearing loss	Lazar et al. (1983)
Male (16)	0.25		+	+	-	-		hearing loss	Lazar et al. (1983)
Male (27)	5	+	-	-	+	+	+		Ehyai & Freemon (1983)

cerebellar cortex atrophy. There was a 70% loss of cerebellar
Purkinje cells and giant axonal degeneration in the posterior
and lateral columns of the spinal cord (Escobar & Aruffo,
1980).

Other effects attributed to chronic glue sniffing
(different types of mixtures) besides cerebellar dysfunction
include optic atrophy with blindness (Keane, 1978; Ehyai &
Freemon, 1983), sensori-neural hearing loss (Ehyai & Freemon,
1983), and convulsions (Helliwell & Murphy, 1979; Allister et
al., 1981). Evidence of chronic neurological damage after a
much shorter duration of glue sniffing has appeared recently.
Channer & Stanley (1983) reported the case of a 16-year-old
boy presenting with persistent visual hallucinations after
cessation of glue sniffing for several months, who had
evidence of a diffuse encephalopathy characterized by an
abnormal EEG and delayed visual evoked responses (VERs) to
checkerboard pattern reversal. In another study (Cooper et
al., 1985), VERs were studied in 12 young asymptomatic glue
sniffers who had abused glue for several months, but not on
the day of the recordings. The mean latencies of the VERs in
the sniffers were significantly prolonged in all compared with
27 controls and outside the normal range in nine. In 2
subjects, the recordings were repeated after abstinence for 6
months and remained abnormal. The recovery process after
damage has occurred seems to be slow if the sniffing is
stopped. The time scale is at least 6 months and it may be
that the damage is permanent.

Haematological abnormalities have been occasionally
reported in sniffers of toluene-based glues. In a clinical
survey of 89 glue sniffers (aged 8 - 18 years), abnormalities
of the blood were found in 68 of the cases (Sokol & Robinson,
1963). An effect on the white blood cells was indicated by
findings of eosinophilia (25 subjects), leukocytosis (12
cases), and lymphopenia (4 subjects). They also reported low
haemoglobin values in 20 subjects and basophilic stippling of
erythrocytes in 42 of the patients, and noted the frequent
occurrence of poikilocytosis (25 cases), anisocytosis (20
cases), hypochromia (14 cases), and polychromasia (10 cases).

Examination of peripheral blood samples from 24 solvent
abusers, admitted to hospital, showed that 5 had lymphopenia,
3 lymphocytosis, and 3 normochromic normocytic anaemia
(including 2 females) (Fornazzari et al., 1983).

In a total of 90 cases surveyed by 4 groups of
investigators, there were no instances of anaemia or
lymphopenia, a single report of neutropenia, and 6 cases
characterized by an eosinophilia greater than 5% were
described (Christiansson & Karlsson, 1957; Massengale et al.,
1963; Barman et al., 1964; Press & Done, 1967b). Powars

(1965) diagnosed 1 fatal case of acute aplastic anaemia associated with pancytopenia and 5 patients with homozygous sickle cell anaemia that showed a reversible erythrocytic aplastic crisis associated with glue sniffing.

Despite occasional reports to the contrary, Assennato et al. (1977) and Trevisan & Chiesura (1978) came to the conclusion that there appears to be a low incidence of hepatorenal injury in persons who abuse toluene-based products. Litt et al. (1972) found modest elevations in serum glutamic pyruvic transaminase (SGPT) (EC 2.6.1.2) levels in only 2% and increased alkaline phosphatase (EC 3.1.3.1) levels in 5% of a group of 982 glue sniffers. Press & Done (1967b) observed slight but transient abnormalities in the urinalysis of a small percentage of the glue sniffers they examined. Liver function tests were normal. Weisenberger (1977) observed some disturbances of aspartate aminotransferase (EC 2.6.1.1) and LDH in a toluene addict who was hospitalized in a catatonic state. These abnormalities disappeared early in the patient's hospital stay. Fornazzari et al. (1983) found transient elevations of serum alkaline phosphatase in 13, and SGOT in 7, solvent abusers. These changes returned to normal after 2 weeks' abstinence.

Russ et al. (1981) reported irreversible renal failure in a 20-year-old male who had sniffed glue containing 16.5% toluene twice a week for 9 months. Repeated renal biopsies showed progressive tubular damage.

It appears that deliberate inhalation of glues and paint is associated with renal tubular defects documented by the presence of metabolic acidosis (Taher et al., 1974; Fischman & Oster, 1979; Bennett & Forman, 1980; Kroeger et al., 1980; Moss et al., 1980; Voigts & Kaufman, 1983). The cases of acidosis described by these investigators are characterized by serious electrolyte abnormalities (hypokalemia, hypophosphatemia, hyperchloremia), and may be related to impaired hydrogen ion secretion in the distal renal tubule (distal renal tubular acidosis). Other metabolic abnormalities include pyuria, haematuria, and proteinuria (Voigts & Kaufman, 1983). The role of toluene in the causation of renal damage in these cases is unclear, since solvent mixtures were abused.

Toutant & Lippman (1979) reported the outcome of pregnancy in a woman addicted to solvents containing toluene for 14 years. In addition to her heavy solvent abuse, she had a 3-year history of alcohol intake (6 packs of beer/week). The male child born at term was at the 10th percentile for weight and the 5th percentile for head size. It had similar features to fetal alcohol syndrome (microcephaly, flat nasal bridge, hypoplastic mandible, etc.). The authors suggested that there might be an analogous "fetal solvents syndrome" or that excessive solvent intake might enhance the toxicity of

alcohol. Recently, Streicher et al. (1981) reported that of 3
women who continued to sniff paint throughout pregnancy, one
had a child with cerebellar dysfunction.

Reisin et al. (1975) published a report regarding the
development of severe myoglobinuria and non-oliguric acute
renal failure in a paint factory worker who was exposed to
pure toluene by skin contact and aspiration when a hose
burst. The patient had inhaled sufficient amounts of toluene
to cause loss of consciousness for 18 h and subsequent
development of chemical pneumonitis. He also sustained
superficial burns on approximately 10% of his body surface
area. Acute renal failure apparently developed from the lack
of fluid intake accompanied by heavy myoglobinuria rather than
from a direct effect of toluene. The early administration of
intravenous fluids and diuretics, and the use of haemo-
dialysis, led to complete recovery.

Askergren (1981) and Askergren et al. (1981a,b) observed
that exposure of rotogravure workers to toluene was associated
with an elevated excretion of erythrocytes and leukocytes in
the urine. Exposure levels in the work-place were reported to
be below 300 mg/m^3, though some subjects were exposed for
short periods to levels 2 - 3 times as high. Franchini et al.
(1983) reported that renal function impairment indicators such
as total proteinuria, albuminuria and urinary excretion of
muramidase (EC 3.2.1.17) and beta-glucuronidase (EC 3.2.1.31)
provided some evidence of renal damage due to occupational
exposure to organic solvents and suggested that the kidney
lesions are tubular rather than glomerular and mild.

9.2.3   Epidemiological studies

No epidemiological studies on populations exposed to
toluene are available.

9.3   Occupational Exposure

Using data obtained from a survey conducted in the USA by
the US Bureau of Occupational Safety and Health in 1977, US
NIOSH estimated that 1.6 million persons in the work force
could have potential exposure to toluene.

9.3.1   Skin and mucous membranes

Repeated or prolonged skin contact with liquid toluene
will remove natural lipids from skin, causing dryness,
fissures, and contact dermatitis (Gerarde, 1960; Browning,
1965) or an injury to the epidermal stratum corneum (Malten et
al., 1968).

Parmeggiani & Sassi (1954) reported irritation of the upper respiratory tract and conjunctiva in male subjects who were exposed to 750 - 3000 mg toluene/m^3 for "many" years.

Transient epithelial injury to the eyes, which consisted of moderate conjunctival irritation and corneal damage, with no loss of vision, was observed in workers who were accidentally splashed with toluene (McLaughlin, 1946; Grant, 1962). Complete recovery generally occurred within 48 h. The results of opthalmological examinations of 106 spray painters who were exposed to toluene in mixtures at levels of 375 - 4125 mg/m^3 for periods ranging from 2 weeks to more than 5 years were reported to be without clear symptoms (Greenburg et al., 1942). Loss of visual acuity, optical neuropathy, and nystagmus in toluene or solvents- and thinner-sniffers have been reported by Prockop (1977), Keane (1978), Malm & Lying-Tunell (1980), Takeuchi et al. (1981b), and Kimura et al. (1982).

9.3.2   Central nervous system

Wilson (1943) described the effects of exposure to "commercial" toluene vapour on 100 workers (out of a total of 1000 workers) who showed symptoms severe enough to seek examination at a hospital. The workers were exposed daily to toluene concentrations ranging from 188 to 5625 mg/m^3 for periods of 1 - 3 weeks. The concentration of toluene was determined shortly after each exposed person appeared at the hospital with symptoms, and the patients were classified into groups according to extent of exposure. The following effects were reported:

at 188 - 750 mg/m^3 (approximately 60% of the patients): headache, lassitude, and loss of appetite; these symptoms were so mild that they were considered to be due primarily to psychogenic and other factors rather than to toluene fumes;

at 750 - 1875 mg/m^3 (approximately 30% of the patients): headache, nausea, bad taste in the mouth, anorexia, lassitude, slight but definite impairment of coordination and reaction time, and momentary loss of memory; and

at 1875 - 5625 mg/m^3 (approximately 10% of the patients): nausea, headache, dizziness, anorexia, palpitation, and extreme weakness; loss of coordination was pronounced and reaction time was definitely impaired.

No clear distinction has been made between the effects attributable to the direct depressant action on the nervous

system of toluene present in the organism, and those that may be persisting functional (or even morphological) sequelae of past exposure. Psychological examinations, carried out 16 h after the working shift, revealed some impairment in psychological performance, which suggests the possibility that the functional changes may persist for some time after the direct narcotic effect (Hänninen et al., 1976). The impaired mental functions included visual intelligence, sensory and vestibular function, memory functions, and verbal intelligence (Lindstrom, 1973, 1982; de Rosa et al., 1974; Rouskova, 1975; Hänninen et al., 1976; Seppäläinen et al., 1978; Elofsson et al., 1980; Husman & Karli, 1980; Biscaldi et al., 1981; Iregren, 1982; Seppäläinen, 1982; Coscia et al., 1983).

Narcosis is the likely result of acute toluene exposure at high concentrations. A number of accounts of workers who were rendered unconscious by toluene vapour have been published (Lurie, 1949; Browning, 1965; Longley et al., 1967; Reisin et al., 1975). Most of these cases involved the exposure of workmen to high levels of toluene during maintenance operations in confined areas with poor ventilation.

9.3.3 Peripheral nervous system

There have been no reports of peripheral neuropathy occurring in association with exposure to toluene alone. Most of the reported cases have involved exposures to mixtures containing either n-hexane or methyl ethylketone, which are known to cause damage to peripheral nerves (Herskowitz et al., 1971; Goto et al., 1974; Shirabe et al., 1974; Korobkin et al., 1975; Towfighi et al., 1976; Alkenkirch et al., 1977; Boor & Hurtig, 1977).

Peripheral biopsy of radial cutaneous nerves showed distention of axons, thinning of the myelin sheath, and widening of the nodes of Ranvier (Korobkin et al., 1975); and axonal degeneration of large diameter fibres in sural nerve (Shirabe et al., 1974; Towfighi et al., 1976). Neurological examination revealed autonomic vascular dysfunction in 28% (15% in control) and spinal root syndrome in 9% (0.05% in control) (Syrovadko, 1977). The author attributed the spinal root syndrome and also uterine prolapse to the working posture; other changes (neurological, haematological, and gynaecological) were considered to be due to the action of toluene.

9.3.4 Blood and haematopoietic system

Early reports of occupational exposures (generally prior to the 1950s) ascribed myelotoxic effects to toluene exposure (Ferguson et al., 1933; Greenburg et al., 1942; Wilson,

1943). However, most of the recent evidence indicates that
the chemical is not toxic to the blood or bone marrow
(Parmeggiani & Sassi, 1954; Capellini & Alessio, 1971;
Matsushita et al., 1975; Tähti et al., 1981). The myelotoxic
effects previously attributed to toluene are now generally
regarded to be the result of concurrent exposure to benzene,
present as a contaminant.

Banfer (1961) examined 112 rotogravure printers and
helpers who were exposed to the vapours of toluene-containing
printing inks for at least 3 years. Controls included 478
unexposed persons from 2 groups. The available commercial
toluene used in these inks reportedly contained only traces of
benzene ($\leq$ 0.3%). Analysis of the room air for toluene by
infrared spectroscopy was limited to samples taken on a single
day from 5 different locations in the machine room (750 - 1500
mg/m³). Haematological examinations of the workers and
controls did not reveal any significant changes in the total
number of leukocytes, lymphocytes, granulocytes, or
erythrocytes, or in haemoglobin levels. Matsushita (1966)
investigated 97 painters exposed to toluene (up to 6750
mg/m³) and xylene for an average of 6.2 years and 49 control
workers. No significant differences were found in the
specific gravity of whole blood, erythrocyte counts,
haemoglobin concentration, and leukocyte counts between the
exposed workers and the controls, except for a significant
increase in Mommsen's toxic granules in the exposed workers.

9.3.5   Liver and kidney

Liver enlargement (palpation) was reported in 61 aeroplane
painters exposed to 375 - 4125 mg toluene/m³ for up to 5
years. Urinalysis and bilirubin in serum did not show any
abnormalities (Greenberg et al., 1942).

Waldron et al. (1982) examined liver function in 59 males,
who had been exposed to toluene for various periods, in
comparison with 59 controls. At the time of the study, levels
of exposure were about 375 mg/m³; however, in previous
years, the levels had been considerably higher (up to 1875
mg/m³). Exposed males had significantly lower levels of
alanine aminotransferase (EC 2.6.1.2). There was no evidence
of a trend towards higher levels with increasing duration of
exposure. None of the men had any symptoms of liver
dysfunction on clinical examination.

Szilard et al. (1978) reported the results of periodic
observation of 170 persons working in toluene-containing
atmospheres (duration of exposure 2 - 14 years at
concentrations of 200 - 300 mg/m³ rising at times to 3000
mg/m³). They found hepatomegaly and increased SGOT activity
in 20 - 50% of workers. Twenty-two of the 170 workers had

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liver biopsies. Routine histology revealed no pathological
changes. Electron microscopy revealed changes in the shape of
mitochondria and degranulation of the RER.

Abnormalities in the glycoprotein, serum mucoid, and
haptoglobin patterns were reported among 53 women with
histories of occupational exposure to toluene (Kowal-Gierczak
et al., 1969), and 51 showed changes in the serum levels of
iron and copper, and urinary excretion of porphyrin
(Cieslinska et al., 1969), while exposed to toluene at about
250 mg/m^3 for 2 - 17 years.

In an examination of 94 rotogravure printers with a
history of exposure to 68 - 1875 mg toluene/m^3 and of a
reference group of 30 municipal clerks, Szadkowski et al.
(1976) found a significant reduction in bilirubin and alkaline
phosphatase levels in the exposed group, but no difference
from controls in SGOT, SGPT, leucine aminopeptidase (EC
2.6.1.6), or cholinesterase (EC 3.1.1.8) levels.

9.3.6   Menstruation

Michon (1965), Matsushita et al. (1975), and Syrovadko
(1977) described studies concerning the complaints of women
exposed to toluene, mainly in combination with other aromatic
hydrocarbons. These complaints included menstrual disturb-
ances such as prolonged and intensive menstrual bleeding.
From the available data, it was emphasized that a specific
effect of toluene could not be determined.

9.3.7   Chromosome damage

General

There are discrepancies in findings related to chromosome
damage in peripheral lymphocytes among workers exposed to
toluene. An unequivocal evaluation of the genetic effects of
occupational toluene exposure, based on available studies,
cannot be made because of the relatively small number of
subjects analysed, variation in the extent of exposure between
these studies, and insufficient information on possible
exposure to other chromosome-damaging agents (benzene, tobacco
smoke, etc.).

Conventional chromosome aberration analyses from 24
rotogravure workers (exposed only to toluene after 1953)
(Forni et al., 1971) and SCEs and chromosome aberration
analyses from 32 rotogravure workers (average length of
exposure = 14 years) (Mäki-Paakkanen et al., 1980) revealed no
increase in the rate of chromosome damage in cultured blood
lymphocytes compared with controls. In the former study, the
concentration of toluene, containing traces of xylene, was

generally below, but occasionally above, 750 mg/m^3, in the working zone. However, between the working machines, it was well over 750 mg/m^3. In the second study, individual exposures varied from 26 - 420 mg toluene containing < 0.05% benzene/m^3.

Haglund et al. (1980) reported negative findings from 17 workers in the paint industry exposed to a mixture of organic solvents, mainly containing xylene and toluene. In the chromosome aberration analyses, no differences were found between 5 workers (employed from 0.8 to 44 years with the highest exposure to toluene concentration > 100 mg/m^3), and their matched controls.

Funes-Cravioto et al. (1977) presented data on 14 workers who were exposed to toluene (possibly containing a low percentage of benzene) in a rotogravure factory. Length of exposure ranged from 1.5 to 26 years and air measurements of toluene showed time-weighted average values of 375 - 750 mg/m^3 with occasional rises to 1875 and 2655 mg/m^3. In most cases, the exposures were sufficient to cause frequent headaches and fatigue, and occasional vertigo, nausea, and feelings of drunkenness. Analyses of cultured blood lymphocytes showed an excess of chromosome aberrations in the 14 toluene-exposed workers compared with a control group of 49 adults.

Bauchinger et al. (1982) reported a statistically-significant increase in the mean number of SCEs and structural chromosomal aberrations in cultured blood lymphocytes from a group of 20 male rotogravure workers exposed to 750 - 1125 mg toluene/m^3 (benzene content < 0.3%) for more than 16 years, in comparison with 24 unexposed persons. Their results were similar to the observations of Funes-Cravioto et al. (1977). For the statistical evaluation of SCE data, the subjects of both groups were subdivided into smokers and non-smokers. Such an analysis revealed significantly higher SCE values for non-smoking rotogravure workers than for non-smoking controls. This was also true for smoking rotogravure workers compared with smoking controls. In both groups, smokers had significantly higher SCE values than non-smokers. Later, Schmid & Bauchinger (1984) repeated the chromosome aberration and SCEs analyses from 27 workers of the same plant with earlier exposure to toluene. The workers had not been exposed for between 4 months and 5 years. In a subgroup of 13 workers without toluene exposure for up to two years, a significantly higher number of cells with aberrations was found (mainly chromatid types) compared with controls, whereas the frequency of gaps was not elevated. A subgroup of 14 workers without toluene exposure for between 2.5 and 5 years did not show any increase in the number of cells with structural chromosome aberrations. In both subgroups, the SCE

values for smoking and non-smoking workers were unchanged compared with the corresponding controls. The authors concluded that structural chromosome changes induced by toluene exposure could persist for up to 2 years after exposure, but that after this time, the number of gaps and SCEs dropped to the control level.

According to Bauchinger et al. (1982), a weak clastogenic effect of toluene can only be detected if there is a sufficiently large number of subjects exposed to high toluene concentrations (> 750 mg/m^3) and a large number of cells are scored. The authors state that in the previously published studies too few metaphases (100 cells per individual) were analysed and that the negative result of Forni et al. (1971) and Mäki-Paakkanen et al. (1980) may be explained by the lower toluene exposure of the workers.

The work of Vijayalaxmi & Evans (1982) and that of Obe et al. (1982) quite clearly showed that the frequency of chromosome aberrations (and also of SCEs) is increased in cultured blood lymphocytes of smokers as compared with non-smokers. Moreover, Mäki-Paakkanen et al. (1984) have found that smoking causes the same type of damage (chromatid-type) observed by Bauchinger et al. (1982) and Schmid & Bauchinger (1984).

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of Human Health Risks

The major route of human exposure is through inhalation. Toluene is readily absorbed from the respiratory tract with an uptake of approximately 40 - 60% in human beings. Smaller amounts are rapidly absorbed via the skin and complete absorption occurs in the gastrointestinal tract, but at a slower rate. However, the presence of small amounts of toluene in drinking-water and food adds only minor quantities to man's total daily uptake. Once absorbed, toluene is rapidly metabolized to benzoic acid and excreted in the urine as hippuric acid and its conjugates. In the case of daily exposure to high concentrations, for instance, under occupational conditions, significant uptake of toluene into lipid-rich tissues, such as adipose tissue and the central nervous system, occurs.

10.2 Acute and Short-Term Effects on Man

Based on the available studies, the odour threshold for toluene in human beings is estimated to be 9.4 mg/m^3 (2.5 ppm). The acute and short-term effects of toluene can be summarized as follows:

- levels up to 375 mg/m^3 for a few hours showed subjective complaints of fatigue and drowsiness, but no observable impairment of reaction time or coordination;

- up to 750 mg/m^3 for 8 h resulted in mild throat and eye irritation, some impairment of cognitive function, headache, dizziness, and sensation of intoxication;

- up to 1500 mg/m^3 for 8 h, besides the symptoms already mentioned, caused lachrymation, skin paraesthesia, gross signs of incoordination, and mental confusion.

These effects are reversible on cessation of exposure, but become increasingly severe and persistent with increasing concentration and/or duration of exposure. No toxicity was observed in human beings repeatedly exposed to toluene levels of less than 188 mg/m^3 for short periods of time or exposed once to a level of 375 mg/m^3 for a few hours.

The critical target organs for toluene are the central nervous system, probably because of the accumulation of toluene in the lipid-rich tissues, from which it is slowly released (toluene concentrations are higher in brain and adipose tissues than in the blood).

Effects on the central nervous system begin to appear with an inhalation exposure of 375 mg/m^3, for 6 h/day, over 4 days. Gross signs of incoordination, depression of the central nervous system, and mental confusion are produced with exposure to a toluene concentration of approximately 1500 mg/m^3 for more than 8 h. Convulsions, nausea, and coma have been noted in human beings at concentrations of 2250 mg/m^3 and higher. Exposure to very high concentrations (above 15 000 mg/m^3) leads to narcosis and death.

The toxic effects of toluene in human beings after long-term exposure are, in principal, the same. The CNS effects may be depressant or excitatory, with euphoria preceeding disorientation, tremulousness, hallucinations, ataxia, and coma. Human beings are more sensitive than certain animal species. Effects induced in human beings at 750 mg/m^3 were seen in rats only after exposure to 1875 mg/m^3. Animal studies showed that sensitivity to toluene varies with species. Differences were also found according to the sex and age of the animals. The acute LC_{50} for mice and rats has been reported to be higher than 20 000 mg/m^3.

A proper multiple generation reproduction study is not available. From the teratogenicity studies on mice, rats, and rabbits, toluene can be considered negative after inhalation exposure. In rats, given high doses of 1000 - 1500 mg/m^3, for 8 h/day, during the period of organogenesis, no maternal toxicity was noted, but an influence on fetal weight and delayed ossification was observed. An embryotoxic effect cannot be excluded. No adverse effects were noted in mice at 375 mg/m^3. Toluene caused spontaneous abortions in rabbits at 1000 mg/m^3 and embryolethality and fetotoxicity in rats administered a dose level of 6000 mg/m^3 for 24 h/day, on days 4 - 21 of gestation.

A significantly increased incidence of cleft palate was induced in mice after oral administration of 870 mg toluene/kg body weight on days 6 - 15 of gestation, but not with a dose level of 430 mg/kg body weight.

The effects of toluene on human male reproduction have not been examined; however, degeneration of germinal cells in the rat testes has been observed in one study after exposure to 750 mg/m^3 for 8 h/day, 6 days/week, for one year. This finding was not confirmed in other studies at much higher dose levels.

Numerous studies on experimental animals and studies of groups of workers exposed to different concentrations of

toluene, sometimes for more than 10 years failed to demonstrate effects on the haematopoietic system. At exposure levels exceeding 4000 mg/m^3, cardiac arrhythmia was seen in rats and, at a dose level of 7500 mg/m^3, kidney damage was found in dogs. Renal function impairment was also seen in workers exposed to levels exceeding 300 mg toluene (mixtures)/m^3 air. Indicators studied were proteinuria, albuminuria, and excretion of muramides and beta-glucuronidase. Effects on the liver were seen only at very high levels.

In long-term carcinogenicity studies on rats, inhalation of concentrations of 112.5, 375, and 1125 mg/m^3 did not show clear effects, with the exception of a reduction in haematocrite and increase in mean corpuscular haemoglobin concentration at the highest dose level. No increase in tumour incidence was observed. Two long-term studies concerning the oral administration of toluene to rats and mice are in progress.

Pure toluene does not seem to have any, or only negligible, mutagenic effects in different test systems. However, the potential mutagenic effects of mixtures cannot be assessed at this time.

No epidemiological studies have been carried out following exposure to toluene.

Assessment of the toxicity of toluene in the work-place is frequently complicated by the impurity of the technical toluene used and/or the presence of other solvents that may themselves be toxic. A similar situation exists in relation to solvent abuse. Other solvents that complicate the evaluation are benzene and n-hexane.

Although data are fairly conclusive for the evaluation of human health risks from pure toluene, no evaluation can be made for exposure to solvent mixtures containing toluene. Data on persons exposed to high levels of mixtures are available and indicate a difference in target organs; an increased risk of liver damage or toxic effects on the haemopoietic tissue, the immune system and endocrine system. However, no quantitative risk evaluation can be made at present.

Persons involved in long-term abuse routinely exceed concentrations of 3750 mg/m^3, which causes a significant incidence of solvent-induced morbidity or permanent neurological deficit. Irreversible neurological sequelae may present as encephalopathy, optic atrophy, equilibrium disorders, diencephalic syndrome, and cerebellar ataxia. These have been described in adults, as well as in children of 8 - 14 years of age.

10.3 Evaluation of Environmental Hazards of Toluene

In areas without wind, toluene vapour can concentrate in depressions. A potentially serious safety hazard can result where the explosive limits (1.17 - 7.10% volume in air) are exceeded.

Present evidence indicates that toluene concentrations in natural waters seldom exceed 0.1 mg/litre, though higher concentrations may be found near spills. Toluene is non-persistent and is rapidly volatilized or biodegraded. It is unlikely that toluene is bioaccumulated in fish and the food chain.

Toluene is of moderate to low toxicity for water organisms. The LC_{50} ranges from 3.7 to 1180 mg/litre. The LC_{50}s for most of the fish and invertebrates studied have been of the order of 15 - 30 mg/litre. Photosynthesis and respiration by marine plankton communities are inhibited at concentrations of 30 mg/litre. The first effects on aquatic communities including inhibition of reproduction and growth may be experienced at concentrations of toluene in water of 2 mg/litre.

Toluene probably exists in soils in the adsorbed state and may participate in chemical reactions and biological degradation and transformation. Volatilization takes place and is dependent on the nature of the soil. Transfer of toluene from soil to groundwater takes place and this will result in contamination of sources of drinking-water.

Toluene is easily degraded by activated sludge in sewage and biodegraded by a variety of soil microorganisms.

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The average daily maximum allowable concentration (MAC_{ad}) and the highest momentary (single-occasion MAC_{hm}) for toluene in the ambient air of residential areas in the USSR is 0.6 mg/m^3, and the maximum acceptable limits of toluene in bodies of water for sanitary-domestic uses is 0.5 mg/litre (IRPTC, 1982).

Examples of occupational exposure limits as time-weighted averages (TWA) for an 8-h day and a 40-h week include: 200 mg/m^3 in Czechoslovakia and the German Democratic Republic; 375 mg/m^3 in Ireland, Japan, and the USA (NIOSH); 750 mg/m^3 in the Federal Republic of Germany and the USA (OSHA); and 300 mg/m^3 in Sweden. Other limits include: 100 mg/m^3 as a ceiling concentration in Hungary; and 50 mg/m^3 as the maximum allowable concentration in the USSR.

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