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Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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HEALTH EFFECTS ASSESSMENT FOR TOLUENE

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with toluene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1982a. Health and Environmental Effects Profile for Toluene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1982b. Health Effects Assessment Document for Toluene. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

U.S. EPA. 1983b. Reportable Quantity for Toluene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Drinking Water Criteria Document for Toluene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. External Review Draft.

U.S. EPA. 1985. Drinking Water Criteria Document for Toluene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final Draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Considerable data are available concerning the inhalation exposure effects of toluene. U.S. EPA (1985) has explored a number of risk assessment strategies and has chosen to use the CIIT (1980) rat inhalation study as a basis for their drinking water AADI since it provides the most protective estimate. The inhalation AIS and AIC, both 104.9 mg/day, are based on the same rat inhalation study (CIIT, 1980). It is reasonable that the AIS and AIC should be closely aligned since, as U.S. EPA (1985) points out, cumulative effects following low level exposures to toluene are not anticipated. A CS of 7 based on CNS dysfunction in humans occupationally exposed to 300 ppm has been calculated.

Data concerning the toxicological consequences of oral toluene exposure are extremely limited. One study was located in which rats were administered 118, 354 or 590 mg/kg toluene by gavage, 5 days/week for 27-28 weeks (Wolf et al., 1956). All of these doses were reported to be NOELs. NOELs are generally not used for risk assessment purposes in the absence of a LOEL; however, in this instance the estimate agrees with estimates developed for inhalation exposure where data are more complete. Therefore, an oral AIS of 30 mg/day (590 mg/kg x 5/7 x 70 kg ÷ an uncertainty factor of 100) is suggested as an interim estimate. The U.S. EPA (1985) derived an oral AADI of 20.3 mg/day from the rat inhalation study by CIIT (1980). For the purposes of this document, the ADI of 20.3 mg/day is proposed for the oral AIC until more appropriate data are available. This estimate should be reviewed when more complete data are available.

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
FEL	Frank-effect level
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of toluene (CAS No. 108-88-3) are given below.

Chemical class:	monocyclic aromatic hydrocarbon (purgeable aromatic)
Molecular weight:	92.1
Vapor pressure:	28.1 mm Hg at 25°C (Mackay et al., 1982)
Water solubility:	534.8 mg/ℓ at 25°C (U.S. EPA, 1982b)
Octanol/water partition coefficient:	537 (Hansch and Leo, 1981)
Soil mobility: (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	1.8 (Wilson et al., 1981)
BCF:	13.2 (in eel, Anguilla japonica) (Ogata and Miyake, 1978)
	20 (in bluegill, Lepomis macrochirus) (Berry, 1980)
	24.5 (in crayfish, Orconectes rusticus) (Berry, 1980)
Half-life in air:	1.3 days (Singh et al., 1981)
Half-life in water:	4.1 hours (Mackay and Yeun, 1983)

The half-life of toluene (1.3 days) in air is based on its reaction with OH• radicals. In the presence of smog, however, the half-life of toluene may be shorter because of its reaction with NO_x (Van Aalst et al., 1980).

The values for the half-life of toluene in soil could not be located in the available literature. However, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation is expected to be longer than its evaporation half-life from water. In subsurface soil, toluene may undergo variable degrees of biodegradation depending on the nature of the soil (Wilson et al., 1981, 1983; McNabb et al., 1981), but a certain portion of the undegraded toluene may percolate through soil into groundwater (Wilson et al., 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Urinary excretion accounted for 74-80% and pulmonary exhalation accounted for an additional 18-19% of the toluene administered orally to rabbits (El Masry et al., 1956; Smith et al., 1954), indicating that toluene is almost completely absorbed from the gastrointestinal tract in rabbits. Maximum absorption of toluene from the gastrointestinal tract of rats occurs within 2 hours of intubation, as evidenced by blood-toluene levels (Pyykko et al., 1977).

2.2. INHALATION

Dogs absorbed 85-94% of the toluene that entered their lungs (Egle and Gochberg, 1976). Mice retained ~60% of the inspired toluene after a 10-minute exposure (Bergman, 1979).

In humans, the arterial concentration of toluene was increased quickly as compared with both the concentration of toluene in the alveolar air and its concentration in the inspired air (Astrand et al., 1972; Astrand, 1975). Although the human absorption rate during the first hour of toluene inhalation was 57%, its absorption rate leveled off at 37% of the inspired dose 2-4 hours after the start of exposure (Nomiyama and Nomiyama, 1974). Exercise affects the absorption rate of toluene in humans (Astrand et al., 1972; Carlsson, 1982).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In the only animal study on subchronic oral exposure to toluene, 30 female Wistar rats received 118, 354 or 590 mg/kg/day of toluene in olive oil, 5 days/week for 27-28 weeks (Wolf et al., 1956). There were 20 control rats. After clinical and gross inspection as well as histological evaluation of the kidneys and liver, no effects were reported for any dose level (Table 3-1).

3.1.2. Inhalation. Subchronic inhalation studies in animals indicate that female rats are more sensitive to toluene than male rats (Ungvary et al., 1980) and that changes in the liver, blood and body weight are the first effects seen after subchronic inhalation of toluene (see Table 3-1) (Ungvary et al., 1980; American Petroleum Institute, 1980; Pryor et al., 1983a,b). Male and female CFY rats were exposed to 1000 mg/m^3 (265 ppm) toluene for 6 hours/day, 5 days/week for 6 months (Ungvary et al., 1980). No effect was seen in the males. However, the females had an increased level of cytochrome P-450, decreased body weight and an increased ratio of liver weight to total body weight. At the next exposure level, 3500 mg/m^3 (928 ppm), male rats were exposed for 8 hours/day, 5 days/week for 6 months. Effects were similar to those seen in the females at the lower dose. No females were tested at the higher dose level.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic oral exposure to toluene could not be located in the available literature.

3.2.2. Inhalation. Male and female Fischer rats were exposed to 30, 100 and 300 ppm of toluene for 6 hours/day, 5 days/week for 24 months (CIIT, 1980). At a dose of 30 ppm, there was no difference in hematology,

TABLE 3-1

Subchronic Toxicity of Toluene

Route	Dose/Exposure	Duration of Exposure	Species/Sex	Number	Effect	Reference
Oral*	controls 118 mg/kg/day 354 mg/kg/day 590 mg/kg/day	5 days/week for 27.6 weeks (138 doses)	Wistar rats/F	20 10 10 10	No effect after gross and clinical inspection and histological evaluation of kidneys and liver at any dose level tested.	Wolf et al., 1956
Inhalation	265 ppm	6 hours/day, 5 days/week, 3 months	CFY rats/M&F	NR	Cytochrome P-450 increased; decreased body weight and increased liver weight in females.	Ungvary et al., 1980
		6 hours/day, 5 days/week, 6 months			Cytochrome P-450 increased; increased liver to body weight ratio; decreased body weight in females.	
Inhalation	928 ppm	8 hours/day, 5 days/week, 6 months	CFY rats/M	NR	Increased cytochrome P-450; increased dilation of rough endoplasmic reticulum and autophagous bodies in hepatocytes; decreased glycogen and total body weight; increased relative liver weight.	Ungvary et al., 1980
Inhalation	0 ppm 100 ppm 1500 ppm	6 hours/day, 5 days/week, 26 weeks	Sprague-Dawley rats/M&F	15/sex/exposure level	None	American Petroleum Institute, 1980
Inhalation	controls 900 ppm 1400 ppm	14 hours/day, 7 days/week, 14 weeks	F-344 rats/M	11-12	900 ppm: Initial decreased body weight; reduction in motor neuron activity 2-8 weeks. 1400 ppm: Sustained decreased body weight; reduction in motor neuron activity 2-8 weeks; loss of tone-intensity discrimination hearing ability; decreased learning behavior.	Pryor et al., 1983a,b
Inhalation	107 ppm	continuous for 90 days	rats/NR guinea pigs/NR dogs/NR monkeys/NR	NR NR NR NR	Two rats died, but other effects not observed. The parameters evaluated were hematology, body weight and histology of lung, liver, kidney, heart and spleen.	Jenkins et al., 1970

*Administered by gavage in olive oil

NR = Not reported

urinalysis or clinical chemistry between the treated and control groups. At the 100 and 300 ppm dose levels, the only reported effect was a decrease in the hematocrit of female rats.

Because of its widespread use in the workplace and because of toluene abuse (glue sniffing), the effects of chronic exposure to toluene have been studied extensively in humans. Some of the occupational exposure studies are summarized in Table 3-2. One of the more striking features of the data on the subchronic and chronic effects of toluene exposure on humans is the failure of increased periods of intermittent exposures to cause clearly increasing severe effects. Although the utility of the available studies for estimating firm dose-response relationships is somewhat limited by the failure to define precise levels and duration of exposure, problems of sample size, the potential role of other toxic agents in eliciting the reported effects, and some apparent inconsistencies among the available studies, the weight of evidence suggests that the types of effects seen and the levels at which effects are seen are relatively independent of the duration of exposure. For mean exposure levels >200 ppm, all of the available studies except that of Suhr (1975) report some evidence of neurologic effects (see Table 3-2); interpretation of the significance of the large scale, Suhr (1975) study is confounded by the factors outlined in the footnote to Table 3-2.

For exposures of ≥200 ppm, the reports of headache, nausea and concentration-related impairment of coordination (Wilson, 1943) are consistent with the relatively well-documented CNS effects of single exposures to toluene. This is not unexpected since blood levels of toluene decline rapidly following cessation of inhalation exposure (toluene is rapidly absorbed and eliminated) (SRC, 1981). For single experimental exposures

TABLE 3-2

Effects of Intermittent Subchronic/Chronic Vapor Exposures to Toluene on Humans

Exposure	Effects	Reference
Daily exposure to commercial toluene for 1-3 weeks:	100 of a total of 1000 workers showed symptoms severe enough to cause them to present themselves for hospital examination	Wilson, 1943
500-1500 ppm (~10% of the patients)	Nausea, headache, dizziness, anorexia, palpitation, extreme weakness; pronounced loss of coordination and impaired reaction	Wilson, 1943
200-500 ppm (~30% of the patients)	Headache, nausea, bad taste in mouth, anorexia, lassitude, slight impairment of coordination and reaction time, transient memory loss	Wilson, 1943
50-200 ppm (~60% of the patients)	Headache, lassitude and loss of appetite; mild symptoms that were attributed to psychogenic and other factors rather than exposure	Wilson, 1943
200-800 ppm for "many" years	Signs of "nervous hyperexcitability" in 6/11 paint and pharmaceutical industry workers	Parmeggiani and Sassi, 1954
250 ppm for "diverse" years	Stupor, nervousness and insomnia in one V-belt manufacturing worker	Capellini and Alessio, 1971
125 ppm	No CNS effects in 17 V-belt manufacturing workers	Capellini and Alessio, 1971
200-400 ppm pure toluene (<0.3%)	No evidence of adverse neurological effects (subjective complaints indicative of CNS depression, abnormal reflex reactions, impaired muscular coordination) in 100 rotogravure workers*; responses compared with an unexpected control group of equal size.	Suhr, 1975

TABLE 3-2 (cont.)

Exposure	Effects	Reference
300 ppm for 18 years 430 ppm for 12 years	Subjective memory, thinking and activity disturbances in 21% of the 300 ppm group (printers) and 40% of the 430 ppm group (printers' helpers); 110 workers tested (no control subjects); Rorschach test results consistent with the findings in 83% of the cases	Munchinger, 1963
30 ppm toluene and 2-7 ppm other organic solvents for 1-40 years	Impaired behavioral responses in 100 car painters relative to 101 age-matched nonexposed controls; a battery of behavioral tests indicated that impairments in visual and verbal intelligence and in memory as well as a reduction in emotional reactivity (Rorschach test) were the predominant effects of exposure	Hanninen et al., 1976
60-100 ppm toluene with 20-50 ppm gasoline in a "few" working places	Evidence of peripheral neuropathy (e.g., abnormal tendon reflexes and grasping power) in up to 14/38 female shoemakers; responses compared with 16 unexposed controls; 19/38 exposed women (3 of 16 controls) complained of dysmenorrhea	Matsushita et al., 1975
>250 ppm and trichloroethylene (concentration not stated)	Changes in EEG response to photic stimulation	Rouskova, 1975

*This conclusion is considered equivocal (SRC, 1981) because the control group was undefined, because blood toluene levels may have significantly declined at the time of reflex reaction and muscular coordination testing, and because muscular coordination was evaluated with an apparently unvalidated device (sphallograph).

that approximated a normal working day (7-8 hours) and involved a combined total of five subjects on multiple exposure/recovery schedules, it was found that subjective complaints such as fatigue, muscular weakness, confusion, impaired coordination, slight exhilaration, enlarged pupils and accommodation disturbances were first observed at levels of 200 ppm (von Oettingen et al., 1942a,b; Carpenter et al., 1944). These effects increased in severity with increases in toluene concentrations until at 800 ppm the subjects experienced changes such as severe fatigue, pronounced nausea, mental confusion, headaches, considerable incoordination and staggering gait, strongly impaired accommodation to light and scotomata (areas of depressed vision). Carpenter et al. (1944) also reported that toluene causes mild throat and eye irritation at 200 ppm and lacrimation at 400 ppm. Short-term experimental exposures to toluene at concentrations >100 ppm have also elicited increases in reaction time (200 ppm x 3 hours) (Ogata et al., 1979) and reduction in perceptual speed (300 ppm x 20 minutes) (Gamberale and Hultengren, 1972).

Toluene abuse, in several cases for as long as 10-14 years, caused severe effects including ataxia, tremors, incoordination, emotional instability, nystagmus, a positive Babinski response, psychoses and decreased cerebellar functioning (Knox and Nelson, 1966; Satran and Dodson, 1963; Kelly, 1975; Boor and Hurtig, 1977; Weisenberger, 1977; Sasa et al., 1978; Keane, 1978; Tarsh, 1979; Malm and Lying-Tunell, 1980).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. In an abstract, Nawrot and Staples (1979) reported that there was a significant increase in fetal mortality when pregnant CD-1 mice were treated by gavage with 0.3, 0.5 and 1.0 mℓ/kg/day (0.26, 0.43 and 0.87 g/kg/day) of toluene in cottonseed oil on days 6-15 of gestation.

Increased (statistically significant) fetal mortality was observed at all dose levels and fetal weights were decreased when the pregnant mice were exposed to 0.43 and 0.87 g/kg/day toluene on days 6-15 of gestation. Only the highest dose level (0.87 g/kg/day) caused an increased incidence of cleft palate in the offspring. Maternal toxicity was not seen under any of the conditions described above. Because these results appeared only in an abstract without statistical analysis they must be considered preliminary.

3.3.2. **Inhalation.** Pregnant ICR mice were exposed to toluene vapor at a level of 100 ppm (377 mg/m^3) and 1000 ppm (3770 mg/m^3) for 6 hours/day on days 1-17 of gestation (Shigeta et al., 1982). There were 18 mice exposed to the low dose, 14 mice exposed to the high dose and 15 controls. Approximately two-thirds of each group of animals were sacrificed on day 18 of gestation. The fetuses were examined for extra ribs, fused ribs, cleft vertebrae, cleft sternum, cranioschisis and polydactyly, and in the absence of observed effects, the authors concluded that toluene was not fetotoxic or teratogenic. Although there were more resorbed fetuses in treated mice, the increased resorption was neither statistically significant nor dose-related. No abnormalities were detected up to 14 weeks after birth in the offspring of toluene-exposed mothers (Shigeta et al., 1982). CFLP mice (Hudak and Ungvary, 1978) were exposed to toluene vapor at a level of 500 and 1500 mg/m^3 continuously on days 6-13 of gestation. All of the mice exposed to 1500 mg/m^3 died within 24 hours of exposure. Decreased fetal weight, indicating fetotoxicity, occurred in the offspring of mice treated at 500 mg/m^3.

The offspring of Charles River rats exposed to toluene vapor at concentrations of 100 and 400 ppm (377 and 1500 mg/m^3), respectively, for 6 hours/day on days 6-15 of gestation (Litton Bionetics, Inc., 1978a) did not

have an increased incidence of visceral or skeletal abnormalities as compared with a control group. No maternal or fetal toxicity was reported (Litton Bionetics, Inc., 1978a). A group of 20 CFY pregnant rats were exposed to toluene vapor at a concentration of 1000 mg/m³ (ppm) for 24 hours/day on days 7-14 of gestation (Tatrai et al., 1980). A group of 22 pregnant CFY rats constituted the control group. Although toluene exposure at this level did not significantly alter maternal or fetal mortality or body weights, retarded skeletal growth as judged by inspection of alizarine stained fetuses occurred at a statistically significant level in the toluene exposure group. In another experiment, one group of 10 CFY rats was exposed to toluene vapors at a concentration of 1000 mg/m³ for 8 hours/day on days 1-21 of gestation; another group of 9 rats was exposed to 1500 mg/m³ continuously on days 1-8 of gestation; and a third group of 26 rats was exposed to 1500 mg/m³ continuously on days 9-14 of gestation. Although there were no visceral or external malformations because of toluene exposure at the levels tested, retarded skeletal development (poorly ossified sternebrae, split vertebral centra and shortened free ribs) or skeletal anomalies (extra ribs and fused sternebrae) occurred at all three levels tested (Hudak and Ungvary, 1978).

3.4. TOXICANT INTERACTIONS

The interactions of toluene with benzene, xylene, hexane, ethanol, acetylsalicylic acid, trichloroethylene and perchloroethylene are summarized in Table 3-3.

TABLE 3-3

Interaction of Toluene with Other Chemicals During Simultaneous Exposure

Route of Toluene Exposure	Dose of Toluene Exposure	Other Chemical	Route of Exposure	Dose of Other Chemical	Species	Effect	Reference
NR	NR	benzene	NR	24.2-97.7 mg/kg 390.6 mg/kg	rats	Dose-dependent inhibition of benzene metabolism by toluene at higher dose levels	Sato and Nakajima, 1979
Inhalation	100 ppm, 2 hours	benzene	inhalation	25 ppm, 2 hours	humans	No effect on metabolism of toluene or benzene	Sato and Nakajima, 1979
Inhalation	1060 ppm, 6 hours/day, 5 days/week, 4 weeks	ethanol	oral	NR	rats	Additive effect on myocardial increased vascular resistance	Morval and Ungvary, 1979
Inhalation	80 ppm, 3 hours	ethanol	oral	1.5 mL/kg	humans	Inhibited toluene metabolism (however, regular alcohol consumption lowered blood toluene levels in workers occupationally exposed to toluene)	Waldron et al., 1983
Inhalation	1000, 2000 and 3600 mg/m³, continuously on days 10-13 of pregnancy	acetylsalicylic acid (aspirin)	oral	250 mg (on day 12)	CFY rats	Toluene potentiated the effect of aspirin on mothers (decreased weight gain and increased liver weight) and on fetuses (increased skeletal and renal anomalies and increased incidence of clubfoot, cleft palate and polydactyly).	Ungvary et al., 1983
Intraperitoneal	430 mg/kg	trichloroethylene	intraperitoneal	730 mg/kg	NR	Competitive inhibition	Ikeda, 1974
Oral	NR	perchloroethylene	oral	NR	rats	Toluene toxicity potentiated.	Smyth et al., 1969
Intraperitoneal	0.1 mg/kg 0.2 mg/kg	m-xylene	intraperitoneal	0.1 mg/kg 0.2 mg/kg	male rats	No effect on total urinary excretion, but the rate was slightly depressed.	Ogata and Fujii, 1979

NR = Not reported

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the human carcinogenicity of toluene following oral exposure could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the human carcinogenicity of toluene following inhalation exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenicity of toluene to experimental animals following oral exposure could not be located in the available literature.

4.2.2. Inhalation. The chronic bioassay (2 years) of toluene in Fischer 344 rats of both sexes showed no carcinogenic effects (CIIT, 1980). Approximately 90 rats/sex/dose were exposed to 30, 100 or 350 ppm (113, 377 or 1130 mg/m^3, respectively) toluene for 6 hours/day, 5 days/week. Although females exposed to 100 and 300 ppm (370 or 1130 mg/m^3) had significantly reduced hematocrit levels, no dose-response effect was present. After hematological and histopathological evaluation, no other difference between treated and control groups was observed. However, there was a high spontaneous incidence (16%) of mononuclear cell leukemia in the control group.

4.3. OTHER RELEVANT DATA

Toluene has been shown not to be mutagenic in the presence or absence of rat liver homogenate in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 (Litton Bionetics, Inc., 1978b; Mortelmans and Riccio, 1980; Nestmann et al., 1980; Snow et al., 1981; Bos et al., 1981), in Escherichia coli strain WP2 (Mortelmans and Riccio, 1980) and in Saccharomyces

cerevisiae strains D4 and D7 (Mortelmans and Riccio, 1980). Toluene did not damage DNA in DNA repair deficient strains of E. coli (Fluck et al., 1976) and S. typhimurium (Mortelmans and Riccio, 1980).

Preliminary data indicate that toluene may decrease fetal weight gain and increase fetal mortality and the incidence of cleft palate in the fetus when CD-1 mice are exposed orally on days 6-15 of gestation at doses of 260, 430 and 870 mg/kg/day (Nawrot and Staples, 1979). Maternal inhalation of toluene in mice and rats during pregnancy did not cause a statistically significant effect, although skeletal anomalies and resorption were increased in some experiments (Tatrai et al., 1980; Litton Bionetics, Inc., 1978a; Shigeta et al., 1982).

4.4. WEIGHT OF EVIDENCE

The rate and incidence of tumor formation in rats exposed to toluene for 2 years were not significantly different from the rate and incidence of tumor formation in control rats (CIIT, 1980). Because human exposure to toluene in the workplace occurs often and because toluene is an abused substance, there are many reports of human exposure in the literature. None of the reports associates toluene exposure with increased rate or incidence of cancer. IARC has not evaluated the risk to humans associated with oral or inhalation exposure to toluene. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), toluene is most appropriately designated a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) currently recommends a TWA-TLV of 100 ppm and a STEL of 150 ppm. NIOSH (1973) recommends a TWA of 100 ppm, with a ceiling of 200 ppm. OSHA currently limits occupational exposure to toluene to a TWA concentration of 200 ppm, with a ceiling of 300 ppm (Code of Federal Regulations, 1981).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. In the only study available on oral subchronic exposure to toluene (Wolf et al., 1956), all the dose levels including the highest dose level of 590 mg/kg/day, 5 days/week for 27.6 weeks were NOELs. In an abstract, Nawrot and Staples (1979) reported increased embryo death in all treatment groups when pregnant mice received 260, 430 and 870 mg/kg/day of toluene by gavage on days 6-15 of gestation. Although the experimental design and results were sparsely reported in this abstract, the data cannot be discounted.

An AIS for oral exposure can be calculated using the highest freestanding NOEL (590 mg/kg) from the Wolf et al. (1956) study. Multiplying by 5/7 to estimate continuous exposure, by 70 (the assumed human body weight) and dividing by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for intraspecies differences in sensitivity and 10 because of concern for potential fetotoxic effects) results in an estimated AIS of 30 mg/day.

6.1.2. Inhalation. Animal studies indicate that toluene is fetotoxic in mice and rats (Hudak and Ungvary, 1978; Tatrai et al., 1980; Litton Bionetics, Inc., 1978b; Shigeta et al., 1982). However, the NOAEL for fetotoxicity in mice is 833.33 mg/kg/day (Hudak and Ungvary, 1978), obtained by multiplying the continuous exposure level of 500 mg/m^3 by the mouse inhalation rate of 0.05 m^3/day and dividing by the estimated body weight of a mouse (0.03 kg). In rats, the retarded skeletal development was judged to be a FEL and occurred at a dose of 247.6 mg/kg/day (Hudak and Ungvary, 1978), obtained by multiplying the intermittent exposure level by 1/3 (8 hours/day) and the rat inhalation rate (0.26 m^3/day) and dividing by the

estimated body weight of a rat (0.35 kg). Following the same dose conversion methods, a dose of 278.6 mg/kg/day was reported to be a NOEL in the rat (Litton Bionetics, Inc., 1978a).

Other subchronic inhalation studies from which a NOAEL or NOEL could be derived were not located, Ungvary et al. (1980) and American Petroleum Institute (1980) and Pryor et al. (1983a,b), provide insufficient information on results and experimental design for adequate evaluation and risk assessment. However, the chronic inhalation data from the CIIT (1980) study can be used. The concentration of toluene in air, 1130 mg/m^3, is multiplied by 6/24 and 5/7 to correct for an exposure of 6 hours/day, 5 days/week, and the result is multiplied by 0.26 m^3/day (an assumed respiratory volume in rats) and divided by 0.35 kg (the assumed body weight of rats). A dose of 149.90 mg/kg/day is calculated. Application of an uncertainty factor of 100 (10 to afford greater protection for sensitive individuals and 10 for interspecies extrapolation) and multiplying by 70 kg, the assumed average body weight of humans, results in an AIS of 104.9 mg/day. This is the same value estimated for chronic exposure. Since toluene is rapidly metabolized and cleared, cumulative effects would not be anticipated. Therefore, it is not unreasonable to estimate the same value for both AIS and AIC exposures.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. It is suggested that the U.S. EPA (1985) ADI of 20.3 mg/day be adopted as an interim oral AIC. This value is based on an inhalation NOAEL in rats of 1130 mg/m^3 (CIIT, 1980). Since the U.S. EPA (1985) based an oral ADI on inhalation data, a route-to-route extrapolation was required.

This was accomplished by expanding the exposure (1130 mg/m³) from 6 hours/day, 5 days/week to continuous exposure, and multiplying by 20 m³ (an assumed daily respiratory volume for humans) and by 0.5 to reflect an assumed 50% absorption factor. Application of an uncertainty factor of 100 (10 to afford greater protection for sensitive individuals and 10 for interspecies extrapolation) results in an ADI of 20.3 mg/day for oral exposure to toluene. This value should be reviewed when chronic oral data are available. For corroborative purposes, U.S. EPA (1985) also projected ADIs based upon human inhalation data (Hanninen et al., 1976; Seppalainen et al., 1978) (projected ADI 41 mg/day); as well as the TLV (projected ADI 135 mg/day). They also cite the subchronic oral NOAEL of 590 mg/kg in the rat (Wolf et al., 1956) as supporting data.

6.2.2. Inhalation. Considerable information is available regarding the CNS effects on humans of chronic inhalation exposure to toluene (see Table 3-1). None of the human studies taken individually are suitable for use in human risk assessment because they involve a relatively small number of subjects, inadequately document exposure levels or durations, or do not consider the potential role of concomitant exposure to other toxicants. Collectively, however, the human studies provide a relatively consistent pattern of dose-response relationships for CNS effects.

An AIC for inhalation can be calculated from the chronic (106 week) data in rats (CIIT, 1980). The calculations are based on the rat NOAEL of 1130 mg/m³, and are identical to those in Section 6.1.2. An AIC of 104.9 is calculated.

An RQ for toluene was derived by U.S. EPA (1983b) based on the accumulated data in humans in the workplace summarized in Section 3.2.2. Although none of these studies is by itself suitable for derivation of an RQ, collectively, they consitute a considerable body of data on humans and provide a

fairly consistent pattern of dose-response relationships. Although the CIIT (1980) chronic inhalation experiment defined an effect at 300 ppm in rats, the uncertainty involved in extrapolating from an experimental animal to humans makes selection of the human data a more prudent choice for calculation of a CS.

Consideration of the intermittent subchronic/chronic inhalation exposure data and the supporting acute exposure data leads to the conclusion that exposure periods of $\leq$8 hours to toluene concentrations <100 ppm may result in mild subjective symptoms (fatigue of headache), but are not likely to induce observable effects. Concentrations >100 ppm may cause impaired reaction time, and concentrations of $\geq$300 ppm would be expected to cause gross signs of incoordination. Based on all of the available data, 300 ppm (1130 mg/m^3) can be regarded as an unequivocal effect level in humans. Since this effect level is applicable to intermittent occupational exposures that are assumed to occur 5 days/week, an MED can be calculated by expanding the exposure from 5 to 7 days/week, and assuming that a human breathes 10 m^3 of air/workday with an absorption efficiency of 50% for toluene (SRC, 1981). This calculation gives an MED of 57.6 mg/kg/day, or 4036 mg/day for a 70 kg man. The RV_d associated with a human MED of 4036 mg/day is 1, since log MED is >3. An appropriate RV_e reflecting the (reversible) CNS dysfunction is 7. The CS would therefore be 7, which corresponds to an RQ of 1000.

6.3. CARCINOGENIC POTENCY (q_1*)

There are no data pertaining to the carcinogenicity of toluene by oral exposure to either humans or animals. An inhalation bioassay in rats (CIIT, 1980) yielded decidedly negative results. Quantitative carcinogenic risk assessment is therefore not appropriate.

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APPENDIX

Summary Table for Toluene

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	rat	1130 mg/m³	NOAEL	104.9 mg/day	CIIT, 1980
AIC	rat	1130 mg/m³	NOAEL	104.9 mg/day	CIIT, 1980
Maximum composite score	human	300 ppm (1130 mg/m³) occupational (RV_d=1)	CNS dysfunction (RV_e=7)	7	SRC, 1981; U.S. EPA, 1983b
Oral					
AIS	rat	590 mg/kg	NOEL	30 mg/day	Wolf et al., 1956
AIC	rat	1130 mg/m³	NOAEL	20.3 mg/day*	CIIT, 1980

*This oral AIC is based on an inhalation study as proposed by U.S. EPA (1984).