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- HOME
- SEARCH IRIS
- MULTIPLE SUBSTANCE REPORTS
- WHAT IS IRIS?
- WHAT'S NEW?
- LINKS
- HELP

## IRIS SUMMARY

[view QuickView](#)

Select a Substance

- [QuickView](#)
- [Full IRIS Summary](#)

### Toluene (CASRN 108-88-3)

#### MAIN CONTENTS

[Reference Dose for Chronic Oral Exposure \(RfD\)](#)

0118

#### Toluene; CASRN 108-88-3

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

#### STATUS OF DATA FOR Toluene

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	04/01/1994
Inhalation RfC Assessment (I.B.)	on-line	08/01/1992
Carcinogenicity Assessment (II.)	on-line	02/01/1994

### I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

#### \_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Toluene  
 CASRN -- 108-88-3  
 Last Revised -- 04/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

#### \_I.A.1. Oral RfD Summary

#### SUBSTANCE SUMMARY INDEX

[Chronic Health Harards for Non-Carcinogenic Effects](#)

[Reference Dose for Chronic Oral Exposure \(RfD\)](#)

- [Oral RfD Summary](#)
- [Principal and Supporting Studies](#)
- [Uncertainty and Modifying Factors](#)
- [Additional Studies/Comments](#)
- [Confidence in the Oral RfD](#)
- [EPA Documentation and Review](#)

[Reference Concentration for Chronic Inhalation Exposure \(RfC\)](#)

- [Inhalation RfC Summary](#)
- [Principal and Supporting Studies](#)
- [Uncertainty and Modifying Factors](#)
- [Additional Studies/Comments](#)
- [Confidence in the Inhalation RfC](#)
- [EPA Documentation and Review](#)

[Carcinogenicity Assessment for Lifetime Exposure](#)

[Evidence for Human Carcinogenicity](#)

- [Weight-of-Evidence Characterization](#)
- [Human Carcinogenicity Data](#)
- [Animal Carcinogenicity Data](#)
- [Supporting Data for Carcinogenicity](#)

[Quantitative Estimate of Carcinogenic Risk from Oral Exposure](#)

- [Summary of Risk Estimates](#)
- [Dose-Response Data](#)
- [Additional Comments](#)
- [Discussion of Confidence](#)

[Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure](#)



9888

Critical Effect	Experimental Doses*	UF	MF	RfD
Changes in liver and kidney weights	NOAEL: 312 mg/kg converted to 223 mg/kg/day	1000	1	2E-1 mg/kg/day
13-Week Rat Gavage Study	LOAEL: 625 mg/kg converted to 446 mg/kg/day			
NTP, 1989				

- Summary of Risk Estimates  
 - Dose-Response Data  
 - Additional Comments  
 - Discussion of Confidence

EPA Documentation, Review and Contacts

- Bibliography
- Revision History
- Synonyms

\*Conversion Factors: Dose adjusted for gavage schedule of 5 days/week.

### \_\_I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of toluene in F344/N rats and B6C3F1 mice. Technical Report Series No. 371. Research Triangle Park, NC.

The oral toxicity of toluene was investigated in this subchronic gavage study in F344 rats. Groups of 10 rats/sex/group were administered toluene in corn oil at dosage levels of 0, 312, 625, 1250, 2500, or 5000 mg/kg for 5 days/week for 13 weeks. All animals receiving 5000 mg/kg died within the first week. One female and 8 males in the 2500 mg/kg group died, but 2 of these were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ( $p < 0.05$ ) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ( $p < 0.05$ ) in SGOT in 2500 males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ( $p < 0.05$ ) at doses greater than or equal to 625 mg/kg. In females, absolute and relative weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ( $p < 0.01$  for all comparisons except  $p < 0.05$  for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL for this study is 312 mg/kg/day based on liver and kidney weight changes in male rats at 625 mg/kg. The toxicologic significance of these organ weight changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses. Because the exposure was for 5 days/week, this dose is converted to  $312 \times 5/7 = 223$  mg/kg/day. The LOAEL is 625 mg/kg, which is 446 mg/kg/day when converted.

NTP (1989) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 receiving 2500 mg/kg also died. Signs of toxicity seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ( $p < 0.05$ ) lower than controls. No other significant changes were reported for any group, including macroscopic observation, organ weight means, or clinical pathology parameters. The NOAEL for mice in this study was 1250 mg/kg.

The subchronic study by Wolf et al. (1956) is supportive of the NTP studies. Groups of 10 female Wistar rats were administered gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg/day.

Hematologic, behavioral, gross and histopathologic examinations were conducted with no toxic effects being reported at any dose. Therefore, the highest dose of 422 mg/kg/day is considered to be the NOAEL for this study. However, this study is not used as the basis for the RfD because the LOAEL of 446 mg/kg/day identified by NTP (1989) is too close to the NOAEL identified by Wolf et al. (1956). Also, the NTP study indicated that male rats are more sensitive to toluene and the Wolf study utilized only female rats.

#### I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- An uncertainty factor of 1000 was applied to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data.

MF -- None

#### I.A.4. Additional Studies/Comments (Oral RfD)

Kostas and Hotchin (1981) exposed NYLAR mice pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80, or 400 ppm. Effects were noted in all dosed groups on rotorod performance, measured at 45 to 55 days of age, but there was an inverse dose-response relationship. No effects of toluene exposure were seen on maternal fluid consumption, offspring mortality rate, development of eye or ear openings, or surface-righting response. This study is not suitable for use in risk assessment because only 6 to 9 pregnancies/dose group were obtained, and because the dose-response relationship was inverse.

In an abstract providing limited information, Nawrot and Staples (1979) reported an increase in embryonic lethality in mice exposed to toluene from days 6 to 15 of gestation. Pregnant CD-1 dams were administered 0.3, 0.5, or 1.0 mL/kg bw, 3 times/day (equivalent to approximately 780, 1300, or 2600 mg/kg/day). Maternal toxicity was not observed at any dose level, but toluene was shown to be teratogenic at the high dose and embryo-lethal at the low dose. These levels are higher than the NOAEL demonstrated by the NTP (1989) study.

Several subchronic and chronic inhalation studies have been performed on toluene but are not considered to be suitable for deriving an oral RfD. These studies are summarized nicely in the introduction to the 2-year inhalation bioassay by NTP, 1989. The studies identify the following potential target organs: kidney (male rat); hematologic effects (mice); central nervous system (rats, mice, primates); developmental toxicity (rats, rabbits). It is beyond the scope of this oral RfD summary sheet to describe each of these studies, but the two chronic (2 year) inhalation studies are summarized briefly below.

In a 2-year inhalation study by NTP (1989), F344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm toluene and B6C3F1 mice (60/sex/group) to 0, 120, 600, or 1200 ppm toluene for 6.5 hours/day, 5 days/week. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity of nonneoplastic lesions of the nasal cavity of exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1200 ppm. There were no significant differences in survival among any group of animals during the 2-year study. Mean body weights were generally similar for all groups throughout the study. Nephropathy was seen in almost all rats with the severity somewhat increased in exposed rats. There were also effects on the olfactory and respiratory epithelia of exposed rats. No biologically important lesions were seen in any groups of mice. There was no evidence of carcinogenicity for any group of animals in this study.

A chronic inhalation study in rats performed by CIIT (1980) failed to produce an adverse effect. Groups of 40 F344 rats/sex were exposed to 30, 100, or 300 ppm toluene for 6 hours/day, 5 days/week for 24 months. An unexposed group of 120 rats/sex served as a control. Clinical chemistry, hematology, and urinalysis testing were conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene. The highest dose of 300 ppm was considered to be a NOAEL.

**\_\_I.A.5. Confidence in the Oral RfD**

Study: High  
Database: Medium  
RfD: Medium

Confidence in the principal study is high because a sufficient number of animals/sex were tested in each of six dose groups (including vehicle controls) and many parameters were studied. The same protocol was tested in both mice and rats, with rats being identified as the more sensitive species. The data base is rated medium because it is supported by a 6-month oral study. It is not higher than medium because there is no reproductive study. Also, the oral studies are all subchronic, with the critical study being only 13 weeks in duration. Medium confidence in the RfD follows.

**\_\_I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- None

Agency Work Group Review -- 05/20/1985, 08/05/1985, 08/05/1986, 05/17/1990, 06/20/1990

Verification Date -- 06/20/1990

**\_\_I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or [Hotline.IRIS@epamail.epa.gov](mailto:Hotline.IRIS@epamail.epa.gov) (internet address).

[Back to top](#)

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**\_\_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name -- Toluene  
CASRN -- 108-88-3  
Last Revised -- 08/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

**\_\_I.B.1. Inhalation RfC Summary**

Critical Effect	Exposures*	UF	MF	RfC
Neurological effects Occupational Study	NOAEL: None	300	1	4E-1 mg/cu.m
Foo et al., 1990	LOAEL: 332 mg/cu.m (88 ppm) LOAEL(ADJ): 119 mg/cu.m LOAEL(HEC): 119 mg/cu.m			
Degeneration of nasal epithelium	NOAEL: None			
2-Year Rat Chronic Inhalation Study	LOAEL: 2261 mg/cu.m (600 ppm) LOAEL(ADJ): 437 mg/cu.m LOAEL(HEC): 79 mg/cu.m			

NTP, 1990

\*Conversion Factors: MW = 92.15.

Foo et al., 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 88 ppm x 92.15/24.45 = 332 mg/cu.m. This is an extrarespiratory effect of a soluble vapor. The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = LOAEL(ADJ) = 332 x MVho/MVh x 5 days/7 days = 119 mg/cu.m.

NTP, 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 600 ppm x 92.15/24.45 = 2261 mg/cu.m. LOAEL(ADJ) = LOAEL (mg/cu.m) x 6.5 hours/24 hours x 5 days/7 days = 437 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa = 0.24 cu.m/day, MVh = 20 cu.m/day, Sa (ET) = 11.6 sq.cm, Sh (ET) = 177 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 0.18. LOAEL(HEC) = 437 x RGDR = 79 mg/cu.m.

### I.B.2. Principal and Supporting Studies (Inhalation RfC)

Foo, S., J. Jeyaratnam and D. Koh. 1990. Chronic neurobehavioral effects of toluene. *Br. J. Ind. Med.* 47(7): 480-484.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice (inhalation studies). NTP- TR-371. 253 p.

In humans, toluene is a known respiratory irritant with central nervous system (CNS) effects. Because available studies could not provide subthreshold (NOAEL) concentrations for either of these effects, the LOAELs for both effects need to be considered in developing the RfC. Consequently, the study of Foo et al. (1990) was used for the CNS effects, and that of the National Toxicology Program (NTP, 1990) for the irritant effects. Because the CNS effect was judged to be a more severe and relevant endpoint, the LOAEL for this effect was used for deriving the RfC. Further, this effect is supported by a number of other occupational studies that show effects around 100 ppm.

Foo et al. (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene levels reported in the study were from personal sample monitoring and reported as an 8-hour TWA, although the number of samples taken and the actual sampling period were not given. No historical exposure values were given. Co-exposure to other solvents was not addressed in the study. The exposed and control cohorts were matched for age, ethnicity, and use of medications. Members of these cohorts did not use alcohol and were nonsmokers. Medical histories were taken to eliminate any histories of central or peripheral nervous system disorders. The average number of years (+/- SD) worked by the exposed population was 5.7 +/- 3.2 and by the controls was 2.5 +/- 2.7. Exposed workers breathed toluene air levels of 88 ppm (332 mg/cu.m) as a TWA and control workers 13 ppm (49 mg/cu.m) (TWA); both of which are averages of the individual personal samples. A battery of eight neurobehavioral tests were administered to all exposed and control workers. The tests were performed midweek, before the workers reported to their stations for the day. Group means revealed statistically significant differences in 6/8 tests; all tests showed

that the exposed workers performed poorly compared with the control cohort. When individual test results were linearly regressed against personal exposure concentrations, poor concentration-response relationships resulted for the six tests, with correlation coefficients ranging from 0.44 to 0.30. Irritation effects were not evaluated in this study, and no clinical signs or symptoms were reported. The paucity of exposure information, coupled with the small size of the cohort, limits the interpretation of this study, although the results were essentially confirmed in a clinical study in which the toluene concentrations were carefully controlled (Echeverria et al., 1989) at levels bracketing 88 ppm. Although the data in Echeverria et al. (1989) were generated from short-term exposures (3-7 hours over a period of 142 days), the results may be considered relevant to longer-term exposures as several studies indicate the absence of a duration-response relationship in toluene-induced symptomatology. Fornazzari et al. (1983) noted the absence of a duration-effect relationship among toluene abusers when they were segregated into neurologically impaired vs. unimpaired ( $p = 0.65$ ). The human studies of Iregren (1982), Cherry et al. (1985), Baelum et al. (1985), and the principal study of Foo et al. (1990) all report this lack of a duration-response relationship and confirm the occurrence of CNS effects. Foo et al. (1990) indicate a LOAEL of 88 ppm toluene (332 mg/cu.m) for neurobehavioral changes from chronic exposure to toluene.

In a 2-year bioassay, Fischer 344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/cu.m, respectively) toluene vapors, 6.5 hours/day, 5 days/week (duration-adjusted to 0, 437, and 875 mg/cu.m, respectively) for 103 weeks (NTP, 1990). To generate toluene vapor, the liquid material was heated, and the vapor diluted with nitrogen and mixed with the chamber ventilation air. An interim sacrifice was carried out at 15 months on control and 1200-ppm groups (10/sex/group) to conduct hematology and histopathology of the brain, liver, and kidney. Body weights were measured throughout the study. Gross necropsy and micropathology examinations were performed at the end of the study on all major organs including the nasal passage tissues (three sections), lungs, and mainstem bronchi. Mean body weights in both exposed groups were not different from controls for either sex. No exposure-related clinical signs were reported, and survival rate was similar for all groups. At the interim sacrifice, there was a mild-to-moderate degeneration in the olfactory and respiratory epithelium of the nasal cavity in 39/40 rats of the 600- and 1200-ppm groups compared with 7/20 controls. At the end of 2 years, there was a significant ( $p < 0.05$ ) increase in the incidence of erosion of the olfactory epithelium (males: 0/50, 3/50, and 8/49; females: 2/49, 11/50, and 10/50; at 0, 600, and 1200 ppm, respectively) and of degeneration of the respiratory epithelium (males: 15/50, 37/50, and 31/49; females: 29/49, 45/50, and 39/50; at 0, 600, and 1200 ppm, respectively) in the exposed animals. The females exposed to 600 and 1200 ppm also exhibited a significant increase in inflammation of the nasal mucosa (27/49, 42/50, and 41/50 at 0, 600, and 1200 ppm, respectively) and respiratory metaplasia of the olfactory epithelium (0/49, 2/50, and 6/50 at 0, 600, and 1200 ppm, respectively). A LOAEL of 600 ppm toluene was determined for the concentration-dependent increase in erosion of the olfactory epithelium in male rats and the degeneration of the respiratory epithelium in both sexes. No NOAEL could be derived from this study.

### I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF -- An uncertainty factor of 10 is used to account for intraspecies variability and another factor of 10 for the use of a LOAEL. An additional factor of 3 is applied for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation.

MF -- None

### I.B.4. Additional Studies/Comments (Inhalation RfC)

Toluene-induced neurotoxicity has been documented in humans over a broad spectrum of severity that correlates well with concentration. Numerous case studies on chronic toluene abusers [repeatedly exposed to greater than 30,000 ppm (113,000 mg/cu.m)] have demonstrated functional deficits of the CNS accompanied by abnormal morphology of cerebellar and cortical areas of the brain. Under acute exposure conditions [short exposures to greater than 10,000 ppm (37,690 mg/cu.m)], toluene produces CNS narcosis [American Conference of Governmental Industrial Hygienists (ACGIH), 1991]. Lower concentrations, i.e., 800-400 ppm (3015-1508

mg/cu.m), have been associated with worker complaints of CNS-related effects (ACGIH, 1991). Clinical studies using controlled exposure to toluene have demonstrated concentration-related occurrence of complaints such as drowsiness, ataxia, visual impairment, and headache. A number of occupational studies indicate that these same effects are present in exposed worker populations at concentrations lower than 400 ppm (1508 mg/cu.m) although deficiencies in most of these studies preclude confirming this finding unequivocally. Descriptions of a number of these studies follow. The preponderance of the literature showing CNS effects and the well-known proclivity for solvents to affect CNS processes in humans leave little doubt that the brain is a principal target organ for toluene toxicity in humans.

In cases of inhalation abuse of toluene, Rosenberg et al. (1988) demonstrated diffuse cerebral, cerebellar, and brainstem atrophy in 3 of 11 toluene abusers who also had neurological abnormalities. Filley et al. (1990) were able to correlate neuropsychological impairment with the degree of white matter abnormality ( $p < 0.01$ ). Cerebellar and cortical functions were classified as impaired in 15/24 individuals who had abused toluene daily (425 +/- 366 mg/day) for extended periods (6.3 +/- 3.9 years) (Fornazzari et al., 1983). In a limited case study, Metrick and Brenner (1982) demonstrated brainstem atrophy through computerized tomographic scans and abnormal brainstem auditory-evoked potentials in 2/2 chronic toluene abusers (12-16 years of admitted, continuous abuse). These studies confirm the occurrence of severe CNS damage in response to highly abusive concentrations of toluene.

Several studies that have investigated the occurrence of neurotoxicity at lesser concentrations, such as occupational situations, have not demonstrated significant neurological or other effects. Hanninen et al. (1987) performed a battery of 11 psychological tests on 43 printing workers who had been occupationally exposed to approximately 117 ppm (441 mg/cu.m) toluene for an average of 22 years and found only mildly adverse effects in 2/11 tests. The control and exposed cohorts in this study were, however, mismatched in several areas, most notably alcohol use. Iregren (1982) examined the psychological performance of 38 printers who had been occupationally exposed to 50-150 ppm (188-565 mg/cu.m) toluene for an average of 16.3 years (range 3-32 years). No effects were seen, although the cohorts in this study were apparently matched only by age. In a cohort study, Cherry et al. (1985) attempted to better match the control and exposed cohorts and considered alcohol use. Although no differences between the cohorts were statistically significant, the exposed workers performed worse than the nonexposed workers on 10/13 psychological tests. The 52 workers in this study were not, however, rigorously matched, and the concentrations listed in the study ranged up to greater than 500 ppm (1884 mg/cu.m). The cohorts in the study of Foo et al. (1990) were well matched for a number of confounders, including alcohol use, and statistically significant psychological effects were seen.

In the occupational study conducted by Yin et al. (1987), 94 solvent workers (38 men and 56 women; average employment duration, 6.8 years) and 138 controls (48 men and 90 women) were examined for exposure using diffusion dosimeters, subjective symptoms by questionnaire, hematology, and urinalysis. Exposure concentration (7-hour mean TWA) in the workers was estimated at 42.8 ppm (161 mg/cu.m) toluene with a maximum measurement of 123 ppm (464 mg/cu.m). Workers were co-exposed to 1.3 ppm benzene. No exposure-related effects were noted in any of the biochemical tests examined. In considering the prevalence of subjective symptoms (sore throat, headaches, and dizziness) workers were subgrouped into low (6-39 ppm,  $n = 28$ ) and high (40-123 ppm,  $n = 29$ ) categories. Although the prevalence of subjective symptoms was significantly higher in the exposed workers compared with the control cohort ( $p < 0.01$ ), a concentration-response relationship was not discernable among the groups. No other treatment-related effects were reported. The study was limited because the exposed and unexposed groups were not matched to control for confounding effects (e.g., age, smoking, alcohol consumption, exposure duration). Based on these results, exposure to an average of approximately 42.8 ppm toluene produced no biochemical abnormalities, although neither respiratory irritation nor psychological performance was directly evaluated in these workers.

In the occupational study by Lee et al. (1988), prevalence of subjective symptoms was categorized with respect to exposure levels. The study population (193 women and 65 controls) completed a questionnaire. The exposures were reported as 8-hour TWAs, and workers were grouped in exposure categories of nonexposed, 1-50 ppm, 51-100 ppm, 101-150 ppm, and more than 151 ppm (duration of exposures was not reported). A concentration-dependent increase in prevalence was reported for 25/67 symptoms with increases in complaints over controls occurring at around 100 ppm (348

mg/cu.m). Similar to the Yin et al. study (1987) reported above, symptomatology included headaches, sore throats, and dizziness. Although an effect level in humans of around 100 ppm is indicated by this study, no objective measures of toxicity were examined.

A number of acute human studies have focused on toluene effects. In general, these studies corroborate subjective CNS effects such as headaches and dizziness reported in other longer-term occupational studies (Yin et al., 1987; Lee et al., 1988) and also document irritation effects. The study of Echeverria et al. (1989) correlates the occurrence of these subjective effects with substantial neurological symptoms.

Forty-two college students (21 female and 21 male) were exposed to 0, 74 ppm (279 mg/cu.m), or 151 ppm (569 mg/cu.m) toluene for 7 hours over 3 days (Echeverria et al., 1989). This exposure sequence was repeated for a total of 42 exposures over a 3-month period. The odor of toluene was masked. A battery of performance tests was administered to each participant prior to starting the exposures and again at 4 and 7 hours during the exposure; the initial test served as a control for those tests performed during the exposure. A 5-10% decrement in performance was considered significant if consistent with a linear trend. Test results for visual perception differed from control values for both exposure levels. Results of a manual dexterity test differed from control values at the higher but not the lower exposure level. Psychomotor test results were unaffected by toluene exposure. Subjective symptomatology increased with exposure with increasing numbers of complaints of eye irritation, headache, and somnolence. A NOAEL of 74 ppm (279 mg/cu.m) is indicated for these results. The duration-adjusted value is 122 mg/cu.m for these acute effects.

Andersen et al. (1983) exposed 16 subjects (average age of 24 years) to 0, 10, 40, or 100 ppm (0, 38, 151, or 377 mg/cu.m) toluene for 6 hours on each of 4 consecutive days. Individuals were tested for nasal mucous flow, lung function, subjective response, and psychometric performance. At 100 ppm, irritation was experienced in the eyes and nose, but no effect on nasal mucous flow or lung function was observed. The subjects frequently reported headaches, dizziness, and a feeling of intoxication. These effects were not reported by the 10- or 40-ppm exposure groups. No effects were seen in performance tests. This study indicates an effect level of 100 ppm, and a NOAEL of 40 ppm (151 mg/cu.m).

The acute study by Baelum et al. (1990) evaluated 32 males and 39 females exposed to 0 or 100 ppm (0 or 377 mg/cu.m), or to varying exposures of 50-300 ppm (188-1131 mg/cu.m) (TWA = 102 ppm), for 7 hours. Volunteers exercised on an ergometer cycle for 3 periods of 15 minutes each during the exposure. No significant differences were found in the performances between the exposed and control groups in a battery of tests for performance, visual attention, and reaction times. Exposed subjects reported an increase over nonexposed subjects ( $p < 0.1$ ) in nose and lower respiratory irritation, feelings of intoxication, dizziness, increased coughing, and headaches. Differences were not noted between the group exposed to a constant level (100 ppm) and the group exposed to the same TWA, but with peaks of up to 300 ppm.

Baelum et al. (1985) investigated the effects of a 6.5-hour toluene exposure to 43 printers with a long-term occupational exposure to a mixture of solvents including toluene and 43 controls with no history of exposure to solvents or other chemicals. The duration of employment for the workers ranged from 9-25 years. Each individual was exposed only once to either 0 or 100 ppm (0 or 377 mg/cu.m) toluene during a 6.5-hour exposure period, preceded by a 1-hour acclimatization period. These subjects were then subgrouped into printers exposed to toluene ( $n = 20$ ), printers exposed to air ( $n = 23$ ), controls exposed to toluene ( $n = 21$ ), and controls exposed to air ( $n = 22$ ). All subjects carried out a battery of tests for psychometric performance, visual perception, and vigilance evaluation. Both printers and controls complained of nasal and eye irritation, unacceptable air quality, and unacceptable odor level during the toluene exposure. Signs of neurotoxicity, including moderate fatigue, sleepiness, headaches, and a feeling of intoxication, were likewise similarly reported for both groups. A significant decrease in performance was found for the pegboard visual motor function test in the exposed printers, but not in the controls exposed to 100 ppm toluene. A decrease in psychometric performance, primarily in visual perception and accuracy, was observed in toluene-exposed individuals. Acute exposure to toluene resulted in a lower performance in 4/10 tests conducted, 3 of these 4 evaluated visual perception. The most profound difference between subjects exposed to 100 ppm toluene and those exposed to clean air was observed in the color discrimination test; this difference was seen in both exposed vs. nonexposed printers and exposed vs. nonexposed controls.

This study indicates that little tolerance develops to the irritative and central effects in humans exposed to toluene and that 100 ppm (377 mg/cu.m) is the effect level for these symptoms.

Von Oettingen et al. (1942) exposed 3 humans to 100 or 200 ppm (377 or 754 mg/cu.m) toluene vapors for 8 hours. At 200 ppm, the subjects experienced muscular weakness, confusion, impaired coordination, and dilated pupils, with after-effects including fatigue, general confusion, and moderate insomnia. In 1 subject exposed to 100 ppm toluene, moderate fatigue, sleepiness, and headaches were reported.

Hepatotoxicity has also been examined as a toxicologic endpoint of toluene exposure in humans. Fornazzari et al. (1983) described moderate elevation of serum AP levels in 13/24 (and SGOT in 7/24) toluene abusers upon admission to a clinic. These elevated levels were normal after 2 weeks of solvent abstinence, although the accompanying CNS effects were only minimally improved. In a cross-sectional study of 181 printing workers in which toluene exposures were less than 200 mg/cu.m, no adverse effects were apparent as judged from serum liver enzymes (Boewer et al., 1988). In another cross-sectional occupational study conducted by Guzelian et al. (1988) that involved 289 printing factory employees, 8 workers were found who had an increase described as "marked" in the ratio of ALT/AST enzyme serum activity. Biopsies revealed mild pericentral fatty livers in each of the eight cases. Based on environmental data (probably area monitors) the levels of toluene to which these workers were exposed was less than 200 mg/cu.m., 2-8 hours/day.

Fischer 344 rats (120/sex/group) inhaled 0, 30, 100, or 300 ppm (0, 113, 377, or 1130 mg/cu.m, respectively) toluene (99.9% purity), 6 hours/day, 5 days/week (duration-adjusted to 0, 20, 67, or 202 mg/cu.m, respectively) for 106 weeks (CIIT, 1980; Gibson and Hardisty, 1983). Vapor, generated by bubbling clean air through toluene, was passed through the air supply duct and mixed with air by turbulent flow to produce the desired concentration. Hematology, blood chemistry, and urinalysis were conducted in all groups at 6 (5/sex), 17 (5/sex), 18 (10-20/sex), and 24 months (10/sex). Histopathology was evaluated only in the control and 300-ppm groups at 6 (5/sex), 12 (5/sex), and 18 months (20/sex). At 24 months, histopathological examinations were conducted in organs of all surviving animals, including the respiratory system and sections through the nasal turbinates (number not indicated). No treatment-related non-neoplastic effects were observed in the exposed animals. Although the male rats exposed to 300 ppm had a significant increase in body weight compared to controls, no concentration-response was evident. At the end of the exposure period, the female rats exposed to 100 or 300 ppm exhibited a slight but significant reduction in hematocrit; an increase in the mean corpuscular hemoglobin concentration was also noted but only in the females exposed to 300 ppm. The highest concentration examined in this study, 300 ppm, is designated as a NOAEL for toxicity remote from the respiratory tract in rats. CIIT (1980) reported that the technical and raw data were not audited by their quality assurance group during the study period, although CIIT did conduct a quality assessment procedure to review the data. The available pathology reports containing these data indicate that at least the lower respiratory tract was examined. Communication with the testing sponsor has provided information indicating that only one section was examined from the nasal cavity of these test animals. It is not clear whether this single section would have been sufficient to elucidate the areas of lesions noted in the NTP (1990) study. Consequently, the designation of the 300-ppm exposure level as a NOAEL for respiratory lesions (see NTP, 1990) is problematic.

Fischer 344/N rats (10/sex/group) were exposed to toluene vapors at 0, 100, 625, 1250, 2500, and 3000 ppm (0, 377, 2355, 4711, 9422, and 11,307 mg/cu.m, respectively) 6.5 hours/day, 5 days/week (duration-adjusted to 0, 73, 455, 911, 1823, and 2187 mg/cu.m, respectively) for 15 weeks (NTP, 1990). Organ weights were measured and histological examinations were performed only on controls, 2500- and 3000-ppm groups, and animals that died before the end of the study. Eight of 10 males exposed to 3000 ppm died, all during the 2nd exposure week. No females died at any exposure level. Compared to the controls, final body weights were 15 and 25% lower in the males and 15 and 14% lower in the females of the 2500- and 3000-ppm groups, respectively. There was a concentration-related increase in the relative liver weight, significant at 1250, 2500, and 3000 ppm in males and at 2500 and 3000 ppm in females. The relative weights of the heart, lung, kidney, and right testis were also significantly elevated in the 2500- and 3000-ppm animals compared to those of the controls, although no histopathology was observed in any exposure group. Toxic effects noted in a concurrently conducted gavage study (urinary bladder hemorrhages

in the two highest exposure groups) were not noted in this subchronic inhalation study. A LOAEL of 2500 ppm [LOAEL(HEC) = 1823 mg/cu.m] was determined for the decrease in body weight gain in both males and females, and the NOAEL for this effect was 1250 ppm [NOAEL(HEC) = 911 mg/cu.m].

Toluene has been suspected to cause congenital defects in infants born to mothers who were exposed to or who abused toluene during pregnancy. In a case report study, Hersh et al. (1985) describes clinical and morphometric characteristics common to 3 children whose mothers had abused toluene (but apparently not alcohol or any other substance) for a period of 4-5 years including during their pregnancies with the affected children. Clinical findings common to these three children included microcephaly, CNS dysfunction, attention deficits, and developmental delay/mental deficiency. Phenotypic similarities included a small midface, deep-set eyes, micrognathia (smallness of the jaws), and blunting of the fingertips. A retrospective cohort study was conducted by McDonald et al. (1987) who examined the history of exposure to chemicals of 301 women who had recently given birth to an infant with an important congenital defect. An identical number of women (referents) who had given birth to normal children were matched with respect to age, employment (hours/week), date of delivery, and educational level. In initial matched-pair analysis, chemical exposure was higher in the cases than in the referents (63 cases:47 referents) due to excess cardiac and miscellaneous defects. In further analysis by chemical categories, only exposure to aromatic solvents showed a clear excess of defects, mostly in the urinary tract. Details of these cases (n = 19) showed that toluene was identified as the solvent in 11 of these cases.

Hudak and Ungvary (1978) exposed three groups of pregnant CFY rats to toluene during different periods of gestation and for different durations of exposure. Two of the groups had their own control group exposed to air only and matched for period and daily duration. The first of these (n = 19) was exposed to 1500 mg/cu.m for 24 hours/day during gestational days 9 to 14. Two dams died during these exposures. No details on the deaths are given but no other maternal toxicity was observed. Fetotoxicity was also in evidence as sternebral alterations (6% vs. 1% in controls), extra ribs (22% vs. 0% in controls), and the presence of fetuses with missing tails (2/213, none observed in 315 controls) were recorded. Under these exposure conditions, 1500 mg/cu.m is a LOAEL for fetotoxicity and a frank effect level (FEL) for maternal toxicity. The second group (n = 14) received this same concentration continuously but on days 1-8 of gestation. Five dams died under these exposure conditions although toxicity parameters of the surviving dams were identical with the controls from the first group (gestational days 9-14). Slight hydrocephaly was noted in 4 fetuses (all from the same litter), and 17% growth retardation was noted vs. 7% in the controls. Thus these exposure conditions are a FEL for maternal toxicity and a LOAEL for fetotoxicity. A third group was exposed to 1000 mg/cu.m for 8 hours/day from the 1st to the 21st day of gestation. No maternal deaths or toxicity occurred. Minor skeletal retardation was present in the exposed fetuses at a higher incidence rate (25%) than in concurrent controls (0%). These results indicate that 1000 mg/cu.m is a LOAEL for developmental effects under these exposure conditions. This concentration is also a NOAEL for maternal effects. These workers also exposed groups of pregnant CFLP mice (n = 11-15) to either air or 1500 or 500 mg/cu.m toluene continuously during days 6-13 of pregnancy. All mice exposed to the high concentration died within 24 hours of the beginning of exposure. No dams died in the lower exposure group. In this group, the average fetal weight decreased to 0.96 g from the average control weight of 1.07 g, and the percentage of weight-retarded fetuses (less than 0.9 g) increased to 27.6% from 6.5% in the controls. No difference in incidence of skeletal malformations or anomalies was noted between these and control fetuses. For mice, 1500 mg/cu.m is an FEL and 500 mg/cu.m is a mild LOAEL. Since duration adjustment is not performed for developmental effects, this concentration is also the LOAEL(HEC).

B6C3F1 mice (60/sex/group) were exposed to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/cu.m, respectively) toluene 6.5 hours/day, 5 days/week (duration-adjusted to 0, 87, 47, and 875 mg/cu.m, respectively) for 2 years (NTP, 1990). Mean body weights were not significantly different among groups and no treatment-related clinical signs were observed. Deaths (moribund and natural) occurred in all exposure groups but were not related to exposure and were not greater than the control rates. An excess incidence of non-neoplastic inflammatory lesions of the urinary and genital system was observed in all the groups of male mice. At the 15-month interim sacrifice, minimal hyperplasia in the bronchial epithelium was observed in 4/10 females exposed to 1200 ppm. At the end of the study, there was a concentration-dependent

increase in the incidence of splenic pigmentation in the exposed males (9/60, 11/60, and 18/59 at 120, 600, and 1200 ppm, respectively) compared to controls (4/60). In the females, the incidence was 37/50, 33/50, 34/49, and 28/47 at 0, 120, 600, and 1200 ppm, respectively. The occurrence of endometrial hyperplasia was present in 14% of the animals exposed to the highest concentration but only in 4% in the low-exposure groups and controls. No differences were noted between the exposed and control mice of either sex in the incidence of degeneration of either the olfactory or respiratory epithelium. No other non-neoplastic lesions were observed in exposed mice. As no adverse effects were noted in this study, the highest concentration, 1200 ppm was designated as a NOAEL in mice for this chronic study [NOAEL(HEC) = 875 mg/cu.m].

Sprague-Dawley rats (15/sex/group) were exposed to cumulative mean exposures of 0, 100, or 1481 ppm (0, 377, or 5653 mg/cu.m) toluene vapors, 6 hours/day, 5 days/week (duration-adjusted to 0, 67, and 1009 mg/cu.m, respectively) for 26 weeks (API, 1981). On weeks 9, 18, and 27, neurohistopathological examinations were conducted in 3-5 rats/sex/group. Hematology, clinical chemistry, and urinalysis parameters were evaluated after 13 and 26 weeks of exposure. Body weights were measured weekly. No significant treatment-related effects were reported. Therefore, a NOAEL of 1481 ppm [NOAEL(HEC) = 1009 mg/cu.m] toluene was determined for systemic effects in rats. The study was limited because there were no other neurohistopathological examinations or organ weight measurements conducted on the animals.

Inhalation exposure to toluene has been shown to result in irreversible high-frequency hearing loss in rats. Pryor et al. (1984) exposed young male Fischer 344 rats to a variety of exposure concentrations and durations. Hearing loss was evaluated by a behavioral technique (avoidance response elicited to an auditory signal) or brainstem auditory-evoked responses (elicited by tone pips of differing loudness and frequency and detected by subdural scalp electrodes). Hearing loss, as measured by both techniques, was observed after as few as 2 weeks exposure to 1000 ppm toluene for 14 hours/day. Lower concentrations of 700 ppm for 14 hours/day were without effect after 16 weeks of exposure. Intermittent exposure to 3000 ppm for 30 minutes/hour for 8 hours/day caused hearing loss within 2 weeks, whereas a similar exposure schedule for only 4 hours/day was without effect after 9 weeks. These data define a NOAEL for hearing loss in rats of 700 ppm [NOAEL(HEC) = 2638 mg/cu.m]. The duration-adjusted HEC (assumed 5 days/week) would be 14/24 hours x 5/7 days = 1100 mg/cu.m. Although these results clearly document hearing loss in young adult rats, their direct significance to humans remains unclear. Among chronic toluene abusers there is only a single report of adverse effects on hearing; Metrick and Brenner (1982) claimed that the abnormal auditory-evoked potentials recorded in two chronic toluene abusers was evidence of brainstem abnormalities.

Pregnant Wistar rats and hamsters (group size not indicated) inhaled 0 or 800 mg/cu.m toluene vapors 6 hours/day on gestational days 14-20 (rats) or gestational days 6 to 11 (hamsters) (DaSilva et al., 1990). In the exposed rats, there was a significant ( $p < 0.05$ ) increase in the number of litters with one or more low birth weight pups (less than 4.9 g), from 10% in the controls to 54% in the exposed dams. A decrease ( $p < 0.05$ ) in the number of live pups at birth was also noted in the litters of exposed dams. No evaluation of malformations or anomalies was performed. The neurobehavioral development of the offspring of the exposed rats was assessed using tests of spontaneous alternation, rim escape, and avoidance responses. The only effect noted in the rats, a shortened first trial latency in choosing one side of a maze, was minimal and its significance unclear. No comparable reproductive deficits occurred in the exposed hamsters. The only effect noted in the neurobehavioral tests of the hamster offspring was an equivocal effect in rota-rod performance. No neurobehavioral effect levels were designated from this study, although it appears that the rat developmental processes are more sensitive than those of the hamster, exhibiting adverse effects at 800 mg/cu.m.

Ungvary and Tatrai (1985) exposed New Zealand rabbits (8-10/group) to 0, 500, or 1000 mg/cu.m toluene, 24 hours/day, on gestational days 7-20, and CFLP mice (15 females/group) to 0, 500, 1000, or 1500 mg/cu.m toluene, also continuously, on gestational days 6-15. The control groups consisted of 115 mice and 60 rabbits. All the female mice exposed to 1500 mg/cu.m died. In the mice exposed to 1000 mg/cu.m, there was an increase in fetuses with retarded weight (29%, level of retardation not indicated) and in fetuses with skeletal retardation (12%) compared to 7% and 5%, respectively, in the controls, which did not differ from the animals exposed to 500 mg/cu.m. Of the 8 pregnant rabbits exposed to 1000 mg/cu.m, 2 died, 4 had

spontaneous abortions, and the remaining 2 had total litter resorption. No deaths occurred in the 10 rabbits exposed to 500 mg/cu.m but 1/10 rabbits had a spontaneous abortion (as compared to 0/60 reported for the controls). A NOAEL(HEC) of 500 mg/cu.m toluene was determined for reproductive effects in mice. For rabbits, the 500 mg/cu.m concentration is designated as a LOAEL. These results indicate that pregnant mice may be a sensitive population to the effects of toluene.

Pregnant Charles River CD-1 mice (15-16 females/group) inhaled filtered air or 200 or 400 ppm (754 and 1508 mg/cu.m) toluene 7 hours/day on gestational days 7-16 (Courtney et al., 1986). The relative liver weight in the exposed dams was reported to be significantly lower in the two exposed groups compared to the controls, although no data were presented. A statistically significant increase in lactate dehydrogenase activity in the brain of the dams exposed to 400 ppm was also reported. The exposed pregnant mice did not exhibit any significant differences in the number of implantation sites, number of live fetuses, fetal deaths, or fetal body weight compared to the control values. A statistically significant increase over controls in the incidence (both per litter and per fetus) of enlarged renal pelves was noted in dams exposed to 200 ppm but not 400 ppm. A statistically significant alteration from controls in the rib profile (percentage of fetuses with 1 or 2 additional/fewer ribs) was reported for fetuses from dams exposed to 400 ppm but not 200 ppm. The toxicological significance of this finding is not clear. As no clearly significant toxicological effects were observed, the highest concentration used, 400 ppm [NOAEL(HEC) = 1508 mg/cu.m] is designated as a NOAEL for reproductive and developmental effects in mice.

A 2-generation inhalation reproductive study was conducted in CD rats (10- 40 males, 20-80 females/group) (API, 1985). Animals were exposed by whole- body inhalation to toluene at 0, 100, 500, or 2000 ppm (0, 377, 1885, or 7538 mg/cu.m, respectively) 6 hours/day, 7 days/week for 80 days and a 15-day mating period. The mated females were then exposed to the same concentrations during days 1-20 of gestation and days 5-20 of lactation. After weaning, the pups in this generation (F1) were exposed 80 times and then randomly mated with members of the same exposure group (2 females/1 male) to produce the second generation (F2). Mean male body weights were slightly reduced (maximum of 10%) in the first 2 weeks of the exposure in the animals exposed to 500 and 2000 ppm, although the size of the reduction was not related to exposure. No differences were observed in male or female fertility indices, length of gestation, mean numbers of viable and nonviable pups at birth, or pup survival indices during lactation. No abnormal histopathology was noted in organs examined. A significant decrease ( $p < 0.05$ ) in weight relative to controls was observed in the first generation offspring. The decrease was maintained throughout the lactation period in the pups from dams exposed to the highest exposure and in those from the ancillary group in which females exposed to the 2000 ppm concentration were mated with males having no exposure. No data were available in the report about the F2 generation. Based on the effects on the pups of the first generation (F1), a LOAEL of 2000 ppm [LOAEL(HEC) = 7538 mg/cu.m] is designated, the NOAEL being 500 ppm [NOAEL(HEC) = 1885 mg/cu.m].

#### I.B.5. Confidence in the Inhalation RfC

Study -- Medium  
Database -- Medium  
RfC -- Medium

The study of Foo et al. (1990) indicates adverse neurological effects of toluene in a small worker population. These effects are consistent with more severe CNS effects occurring at abusive concentrations of toluene and could not have been confounded by alcohol as the control and exposed populations did not use alcohol. However, the paucity of exposure information and identification of only a LOAEL is not sufficient to warrant a higher confidence than medium for this study.

Other studies indicate that irritation may occur at around the same concentration, 100 ppm (Baelum et al., 1985; Echeverria et al., 1989). In regard to this effect, the NTP (1990) rat chronic inhalation study was well conducted, established the rat as the most sensitive species, examined an adequate number of animals, and performed histopathology on all major organs, including the brain and the respiratory tract. The sensitive endpoint was the concentration-dependent degeneration of the nasal epithelium characterized by the erosion of the olfactory epithelium and degeneration

of the respiratory epithelium in male rats. The NTP study is also given medium confidence, however, as it did not establish a NOAEL.

Although this data base has a complement of chronic laboratory animal studies, long-term data in humans are not available for either the neurotoxicity or irritation endpoints. The reproductive/developmental studies in three species were not comprehensive in endpoint evaluation but do identify the rabbit as the most sensitive species. The data base is thus given a medium confidence rating. A medium confidence rating for the RfC follows.

#### **\_\_ I.B.6. EPA Documentation and Review of the Inhalation RfC**

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984, 1985

Agency Work Group Review -- 04/21/1988, 05/26/1988, 02/16/1989, 03/21/1989, 05/18/1989, 08/15/1991, 12/11/1991

Verification Date -- 05/18/1989, 12/11/1991

#### **\_\_ I.B.7. EPA Contacts (Inhalation RfC)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or [Hotline.IRIS@epamail.epa.gov](mailto:Hotline.IRIS@epamail.epa.gov) (internet address).

[Back to top](#)

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## **\_\_ II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name -- Toluene  
CASRN -- 108-88-3  
Last Revised -- 02/01/1994

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### **\_\_ II.A. Evidence for Human Carcinogenicity**

#### **\_\_ II.A.1. Weight-of-Evidence Characterization**

Classification -- D; not classified

Basis -- No human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays.

### II.A.2. Human Carcinogenicity Data

None.

### II.A.3. Animal Carcinogenicity Data

A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT, 1980). A total of 960 rats were exposed by inhalation for 6 hours/day, 5 days/week to toluene at 0, 30, 100, or 300 ppm. Groups of 20/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals.

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenic response (Poel, 1963). One drop of toluene (about 6 mL) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al., 1973). No increase in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 mL/mouse, twice weekly for 56 weeks (Doak et al., 1976). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16- 20 uL per drop for 72 weeks (Lijinsky and Garcia, 1972). It is not reported whether evaporation of toluene from the skin was prevented during these studies.

### II.A.4. Supporting Data for Carcinogenicity

Toluene was found to be nonmutagenic in reverse mutation assays with *S. typhimurium* (Mortelmans and Riccio, 1980; Nestmann et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981) and *E. coli* (Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in *S. cerevisiae*. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhotov, 1972; Lyapkalo, 1973) report toluene as effective in causing chromosomal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al., 1980; Forni et al., 1971), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This finding is supported by studies of cultured human lymphocytes exposed to toluene in vitro; no elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner- Smidt and Friedrich, 1978).

[Back to top](#)

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### II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

[Back to top](#)

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### II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

[Back to top](#)

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document -- U.S. EPA, 1987

The values in the 1987 Drinking Water Criteria Document for Toluene have received peer and administrative review.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review -- 09/15/1987

Verification Date -- 09/15/1987

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or [Hotline.IRIS@epamail.epa.gov](mailto:Hotline.IRIS@epamail.epa.gov) (internet address).

[Back to top](#)

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## **VI. Bibliography**

Substance Name -- Toluene  
CASRN -- 108-88-3  
Last Revised -- 08/01/1992

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[Back to top](#)

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[Back to top](#)

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[Back to top](#)

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## **\_VII. Revision History**

Substance Name -- Toluene  
CASRN -- 108-88-3

Date	Section	Description
03/01/1988	I.A.4.	Text revised
09/07/1988	II.	Carcinogen summary on-line
02/01/1989	II.D.3.	Secondary contact's phone number corrected
07/01/1989	I.B.	Inhalation RfD now under review
03/01/1990	VI.	Bibliography on-line
04/01/1990	VI.C.	Combs et al., 1973 citation corrected
06/01/1990	IV.A.1.	Area code for EPA contact corrected
06/01/1990	IV.F.1.	EPA contact changed
07/01/1990	I.A.	Withdrawn; new RfD verified (in preparation)
07/01/1990	VI.A.	Oral RfD references withdrawn
08/01/1990	I.A.	Oral RfD summary replaced; RfD changed
08/01/1990	II.	Text edited
08/01/1990	VI.A.	Oral RfD references revised
09/01/1990	III.A.	Health Advisory on-line
09/01/1990	VI.D.	Health Advisory references added
08/01/1991	VI.C.	Litton Bionetics, Inc., 1981 reference title clarified
01/01/1992	IV.	Regulatory actions updated
04/01/1992	IV.A.1.	CAA regulatory action withdrawn
08/01/1992	I.B.	Inhalation RfC on-line
08/01/1992	VI.B.	Inhalation references on-line
02/01/1994	II.D.3.	Secondary contact's phone number changed
04/01/1994	I.A.7.	Primary contact changed
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
02/22/2001	I., II.	This chemical is being reassessed under the IRIS Program.

[Back to top](#)

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## VIII. Synonyms

Substance Name -- Toluene  
 CASRN -- 108-88-3  
 Last Revised -- 01/31/1987

108-88-3  
 ANTISAL 1a  
 BENZENE, METHYL  
 METHACIDE  
 METHYL-BENZENE  
 METHYLBENZOL  
 NCI-C07272  
 PHENYL-METHANE  
 RCRA WASTE NUMBER U220  
 TOLUEEN  
 TOLUEN  
 Toluene  
 TOLUOL  
 TOLUOLO  
 TOLU-SOL  
 UN 1294

[Back to top](#)

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