Toluene; CASRN 108-88-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Toluene

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/23/2005
Inhalation RfC (I.B.)	yes	09/23/2005
Carcinogenicity Assessment (II.)	yes	09/23/2005

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Toluene
CASRN — 108-88-3
Section I.A. Last Revised — 09/23/2005

The RfD is an estimate of an oral exposure, for a given duration, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark dose (BMDL), a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfD is intended for use in risk assessments for health effects known or assumed to be produced

through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Since RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

The previous IRIS assessment utilized the NTP (1990) 13-week rat gavage study as the principal study and changes in liver and kidney weights as the critical effect for derivation of the RfD (0.2 mg/kg-day). The NOAEL was identified as 223 mg/kg-day. A composite UF of 1000 was applied to account for interspecies and intraspecies extrapolations, subchronic-to-chronic extrapolation, and limited reproductive and developmental toxicity data. The current assessment differs due to newer methodologies and consideration of additional data.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Increased kidney weight **13-week gavage study in rats (NTP, 1990)**	BMDL: 238 mg/kg-day BMD: 431 mg/kg-day	3000	0.08 mg/kg-day

* Conversion Factors and Assumptions - BMDL- 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a one standard deviation change in the mean.
BMD - Maximum likelihood estimate of the dose corresponding to a one standard deviation change in the mean.

I.A.2. Principal and Supporting Studies (Oral RfD)

No studies examining the chronic or subchronic effects of oral exposure to toluene in humans are available. A lifetime gavage study in rats (Maltoni et al., 1997) reported only carcinogenic endpoints and is, therefore, not suitable for use as the principal study for derivation of an RfD. One subchronic study (NTP, 1990) examining oral exposure to toluene in rodents (rats and mice) is available and was chosen as the principal study. The critical effect chosen is increased kidney weight. NTP (1990) exposed both sexes of F-344 rats and both sexes of B6C3F1 mice

to toluene by gavage for 13 weeks. In male rats, absolute and relative weights of both the liver and kidney were significantly increased ($p<0.05$) at doses greater than or equal to 446 mg/kg-day. Absolute kidney weights were 100, 107, 112, 119, and 113% of controls; relative kidney weights were 100, 100, 106, 114, and 146% of controls for 0, 223, 446, 900, or 1800 mg/kg-day dose levels. The study in rats established a NOAEL of 223 mg/kg-day for increases in liver and kidney weights of male rats, with a LOAEL of 446 mg/kg-day. Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at doses greater than 2500 mg/kg-day. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Kidney sections were examined in particular for the occurrence of hyaline droplets in the proximal tubules with negative findings. Additional study information can be found in Section 4 of the Toxicological Review (U.S. EPA, 2005). A concentration-dependent nephropathy was also seen in chronic inhalation cancer bioassays (NTP, 1990; Huff, 2003). It should be noted that no increase in kidney weight was seen in the parallel study in B6C3F1 mice, indicating a species difference in the response.

The choice of increased kidney weight as the critical effect is supported by several acute oral and inhalation human toxicity studies, indicating renal tubule toxicity. One case report following lethal oral exposure to 625 mg/kg toluene (Ameno et al., 1989) and a nonlethal case report of thinner ingestion (Caravati and Bjerk, 1997) noted acute tubular necrosis and acidosis. Inhalation of high doses of toluene has caused distal renal tubular acidosis (Taher et al., 1974; Fischman and Oster, 1979) among drug users, sometimes with tubular proteinuria (Kamijima et al., 1994). A case of focal segmental glomerulosclerosis was noted for a leather worker exposed to toluene for 40 years (Bosch et al., 1988). Toluene sniffing has been associated with the formation of renal stones (Kroeger et al., 1980), proteinuria (Streicher et al., 1981), and hepato-renal damage (O'Brien et al., 1971). In addition, a case of anti-glomerular basement membrane antibody-mediated glomerulonephritis has also been reported in a woman who sniffed glue for several weeks (Bonzel et al., 1987). It should be noted that several studies involving painters (Askergren, 1982; Franchini et al., 1983) or printers (Gericke et al., 2001) with toluene exposure have reported no effect on renal function. Askergren (1982) and Franchini et al. (1983) found no effect on excretion of beta-2-microglobulin, and Gericke et al. (2001) found no effect on serum creatinine levels or glomerular filtration rate. The choice of increased kidney weight as a critical effect is based on the above data and the available animal data indicating an increase in kidney weight in the same studies where overt kidney toxicity was observed at higher doses. The available data on postulated modes of action for toluene-induced kidney toxicity are described in Section 4.5.3 of the Toxicological Review (U.S. EPA, 2005).

The RfD was derived by the benchmark dose approach using EPA's (U.S. EPA, 2001) benchmark dose software (BMDS, Version 1.3). The benchmark response (BMR) was defined

as the change of one control standard deviation from the control mean (U.S. EPA, 2000). Benchmark analysis was performed for absolute kidney weight changes in male rats (NTP, 1990). Male rat kidney data were chosen for BMD modeling as these data exhibited a greater response than that seen in female rats (see study description in Section 4.2.1.1 of the Toxicological Review). A BMDL of 238 mg/kg-day was derived and used as the point of departure. The BMDL corresponds to the lower bound on the dose associated with a 10% increase in individuals having a kidney weight greater than the 98th percentile of kidney weights in the control group (and the SD corresponding to 9% increase in kidney weight from control). Details of the model results are presented in Appendix B-1 of the Toxicological Review.

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

Total UF = 3000

A total uncertainty factor (UF) of 3000 was applied to this effect level: 10 for extrapolation for interspecies differences (UF_A; animal to human), 10 for consideration of intraspecies variation (UF_H; human variability), 10 for use of a subchronic study to estimate chronic effects (UF_S; duration of exposure), and 3 for database insufficiencies and contradictions in the immunotoxicity data (UF_D). The total UF = 10 x 10 x 10 x 3 = 3000.

An uncertainty factor of 10 was used to account for laboratory animal-to-human interspecies differences (UF_A). No information is available on differences or similarities in the toxicity of toluene between animals and humans.

An uncertainty factor of 10 was used to account for intraspecies differences (UF_H) including variability in susceptibility in human populations and life-stages. This UF was not reduced because of the lack of human oral exposure information.

An uncertainty factor of 10 was used to account for extrapolating from a subchronic study to estimate chronic exposure conditions (UF_S).

An uncertainty factor was not needed to account for extrapolating from a LOAEL to a NOAEL because BMD modeling was used to identify the point of departure.

An uncertainty factor of 3 was used to account for deficiencies in the toluene database. An oral subchronic study in two species is available. Neurotoxicity has been identified by inhalation studies in humans and animals as a critical endpoint. However, limited neurotoxicity studies by the oral route are available. Several oral exposure high-dose reproductive and developmental toxicity studies are available which indicate toluene does not

generally elicit developmental or reproductive effects except at doses that are significantly higher than those causing other systemic effects (see Section 4.3 of the Toxicological Review for details). A two-generation reproductive toxicity study by the oral route of exposure is not available, however, a two-generation reproductive toxicity study by the inhalation route of exposure is available that possibly lends support to the oral database in that effects are noted at high concentrations. Toxicokinetic information indicates that the absorption kinetics of toluene is similar and extensive following both oral and inhalation exposure. For example, Gospe and Al-Bayati (1994) compared oral and inhalation exposures to toluene in the rat and concluded that oral dosing produces blood toluene levels that are similar to those produced by inhalation (see Section 3.1.2 of the Toxicological Review). It should be noted, however, that differences in metabolism between exposure routes have not been elucidated, nor has a role for metabolites been ascertained in the toxicity of toluene. Immunotoxicity data are available but the results are conflicting. The data to date are inadequate to draw conclusions regarding whether immunosuppression may be a more sensitive endpoint (i.e., an endpoint that would result in a lower point of departure) than kidney toxicity.

A three-fold uncertainty factor for insufficiencies in the database was used to account for the lack of adequate data on endpoints of potential concern for toluene, including neurotoxicity, two-generation reproductive toxicity, and immunotoxicity.

The RfD for toluene was calculated as follows:

RfD = BMDL ÷ UF

= 238 mg/kg-day ÷ 3000

= 0.08 mg/kg-day

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

A number of immunotoxicity studies are available (Hsieh et al., 1989, 1990b, 1991; Burns et al., 1994) and were considered for use as the principal study. Changes in thymus weights in the Hsieh et al. (1989) study were not considered an adverse effect since no change was observed in later studies by Hsieh et al. (1990b) and Burns et al. (1994). Additional effects on immunological endpoints were considered as a potential critical effect from toluene exposure. For example, statistically significant and dose-related decreases in antibody response were noted by Hsieh et al. (1989, 1990b, 1991). There is evidence that the PFC assay is among the most predictive tests available for immunotoxicity (Luster et al., 1992) and that suppression of the antibody response is predictive of decreased resistance to challenge with infectious agents or tumor cells (Luster et al., 1993). An important objective of the use of the PFC assay and

anti-SRBC ELISA in immunotoxicity testing is to determine the ability of the immune system to respond to an antigenic challenge. As such, it tests the ability of three primary immune system cells (i.e., macrophages [phagocytosis and processing of SRBCs], T lymphocytes [which assist B lymphocytes] and B lymphocytes [production and release of anti-SRBC specific antibody]) to respond to this antigen in a coordinated manner leading to the production of antibodies to SRBC.

However, in the same test that Hsieh et al. (1989, 1990b, 1991) showed suppression of the antibody response (the PFC assay), Burns et al. (1994) did not find immunosuppression. The studies were not entirely parallel; Hsieh and Burns used different mouse strains (CD-1 and B6C3F1, respectively), examined different sexes (males and females, respectively), and utilized different exposure durations (28 vs. 14 days, respectively). Furthermore, the host resistance assays by Burns et al. (1994) indicated a lack of immunotoxicity when animals treated with toluene were challenged. Host resistance to challenges with *Listeria monocyogenes*, *Streptococcus pneumoniae*, *Plasmodium yoelii*, or B16F10 melanoma was not affected at a dose of 600 mg/kg-day for 14 days. In addition, a reduced incidence of tumors was observed in mice that were challenged with PYB6 fibrosarcoma. Stefanovic et al. (1987) found no significant changes in immunoglobulin levels after toluene treatment of human sera and also showed no changes in the complement activity parameters studied in the toluene treated sera. The conflicting data between the Hsieh and Burns studies and the lack of suppression of host resistance present an unclear picture of toluene immunotoxicity. For these reasons, immunotoxic endpoints alone are not considered critical effects.

Additional studies by Hsieh et al. (1990a,c) found statistically significant increases in a variety of brain neurotransmitter levels at exposure levels as low as 5 mg/kg-day. The study authors measured levels at one time point immediately at the termination of toluene treatment; it cannot be determined if the effects observed were persistent. Neurotoxicity studies from oral exposure to toluene have not been performed; therefore, the changes in neurotransmitter levels have not been correlated with behavioral, neuropsychological, or neuroanatomical changes and were not considered further. Available reproductive studies (Gospe et al., 1994, 1996; Gospe and Zhou, 1998, 2000) were conducted at higher doses than those used in the studies described above with minimal effects on dams and offspring and, as such, were not considered for the choice of principal study.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The overall confidence in the RfD assessment is medium. Confidence in the principal study is medium. It is an adequate gavage study of subchronic duration. Confidence in the database is rated medium due to the lack of chronic data, neurotoxicity studies, and a two-generation reproductive toxicity study, and uncertainty surrounding the immunotoxicity of toluene. An oral subchronic study in two species and several immunotoxicity studies are available. A number of oral and inhalation studies have demonstrated that toluene does not elicit developmental or reproductive effects except at doses that are significantly higher than those causing other systemic effects. The available toxicokinetic data indicate the absorption of toluene is similar and extensive following both oral and inhalation exposure. A two-generation reproductive inhalation toxicity study is available which lends support to the oral database in that effects are noted only at high concentrations.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA (2005)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Toluene (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***

Agency Completion Date -- 08/26/2005

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Toluene
CASRN — 108-88-3
Section I.B Last Revised — 09/23/2005

The RfC is an estimate of an inhalation exposure, for a given duration, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark concentration (BMCL), a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

The previous IRIS assessment utilized the Foo et al. (1990) occupational study as the principal study and neurological effects as the critical effect for the derivation of the RfC (0.4 mg/m^3). The LOAEL was identified as 332 mg/m^3 (88 ppm), which was converted to a human equivalent concentration of 119 mg/m^3. A composite UF of 300 was used that consisted of a 10-fold UF for intraspecies variability, a 10-fold UF for the use of a LOAEL instead of a NOAEL, and a three-fold UF for database deficiencies, including a lack of animal exposure data evaluating neurotoxicity and respiratory irritation. The current IRIS assessment takes into account a number of newer human studies that are available and incorporates newer methodologies.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	RfC
Neurological effects in occupationally-exposed workers **Multiple human studies (see Table 1 and Figure 1).**	NOAEL (average): 34 ppm (128 mg/m^3) NOAEL (ADJ): 46 mg/m^3	10	5 mg/m^3

*Conversion Factors and Assumptions — See Table 1 for a list of studies used in the derivation of the RfC. Assuming 25 ºC and 760 mm Hg, NOAEL (average) (mg/m^3) = 34 ppm × 92.15/24.45 = 128 mg/m^3. This is an extrarespiratory effect of a soluble vapor. The NOAEL (HEC) is based on an 8-hour TWA occupational exposure. MVho = 10 m^3/day, MVh = 20 m^3/day. NOAEL (HEC) = NOAEL (ADJ) = 128 × MVho/MVh × 5 days/7 days = 46 mg/m^3.

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

A substantial database examining the effects of toluene in subchronic and chronic occupationally exposed humans exists. The weight-of-evidence from these studies indicates neurologic effects (i.e., impaired color vision, impaired hearing, decreased performance in neurobehavioral analysis, changes in motor and sensory nerve conduction velocity, headache, dizziness) as the most sensitive endpoint. Numerous case studies in humans exposed to high concentrations of toluene for abusive purposes have also indicated neurological effects in adults as critical effects of concern. Human studies indicating the potential for adverse effects from toluene exposure other than neurological effects are also available. None of these studies indicated effects at doses lower than those observed for neurological effects. Animal studies (NTP, 1990) have also suggested respiratory irritation as a sensitive effect, but this effect in humans appears to occur at higher exposure concentrations than those resulting in neurologic effects.

All of the available occupational studies were considered for the principal study upon which to base the derivation of the RfC. A discussion of available animal studies is presented in Section I.B.4. Numerous human studies have identified NOAELs in the range of 25-50 ppm toluene for individual neurological effects (Cavalleri et al., 2000; Eller et al., 1999; Nakatsuka et al., 1992; Neubert et al., 2001; Schaper et al., 2003; Zavalic et al., 1998a; Zupanic et al., 2002). These studies were designed to measure effects on subjective symptoms (e.g., headache, dizziness), color vision, neurological and psychomotor functioning, and hearing. Several

studies have shown statistically significant effects in workers in the range of 83-132 ppm on at least one of the following neurological effects: color vision, auditory evoked brain potentials, neurobehavioral parameters, and neurological functioning (Abbate et al., 1993; Boey et al., 1997; Eller et al., 1999; Foo et al., 1990; Neubert et al. 2001; Vrca et al., 1995, 1996, 1997; Zavalic et al., 1998a).

As a whole, the available studies present a substantial body of evidence in humans indicating a relationship between neurological effects and toluene exposure at the lowest occupational exposure levels measured. No single study stands out as the best study on which to characterize neurological effects nor to specify a single critical effect. Thus, in lieu of selecting one study as the principal study, a review of the human database indicated ten studies can be considered adequate. The determination of study adequacy was based on the use of accepted testing procedures for neurological endpoints, chronic exposure duration, inclusion of a measure of exposure, comparison to defined control groups, and no known co-exposure to other solvents in the workplace. Figure 1 and Table 1 summarizes this subset of studies. Response levels of the adequate studies are identified in Table 1 and are calculated as the difference between the reported means from the exposure and reference groups for statistically significant outcomes. This subset of studies presents a cluster of NOAELs for neurological effects which are generally below reported LOAELs for all endpoints. A deficit in neurological function was chosen as the critical effect based on this suite of neurological studies due to the overall preponderance of evidence for this endpoint at low doses.

Potential limitations associated with the studies that were considered adequate are included in Table 1. For additional discussion of the limitations and uncertainties associated with studies that were considered adequate, see Sections 4.1.2.2, 4.5.3 and Appendix A of the Toxicological Review (U.S. EPA, 2005). Not included in the subset are studies with known co-exposure to other solvents (Antti-Poika et al., 1985; Yin et al., 1987; Campagna et al., 2001), studies lacking adequate exposure information (Antti-Poika et al., 1985; Murata et al., 1993), studies without a reference group (Muttray et al., 1995; Morata et al., 1997; Schaper et al., 2003; Tanaka et al., 2003), and studies where questionnaires were the only assessment of toxicity or exposure (Lee et al., 1988; Zupanic et al., 2002; Seeber et al., 2004). These studies contribute qualitatively to the overall weight-of-evidence of the choice of critical effect but are given lesser weight due to the inadequacies described. Orbaek and Nise (1989) was not included in the subset of studies due to the low number of workers tested and uncertainty in the exposure levels. Chouaniere et al. (2002) observed effects on psychomotor performance at doses of 25 and 40 ppm but the doses were estimated based on test results precluding the use of this study for quantitative purposes.

Figure 1. Summary of NOAELs/LOAELs for neurological endpoints for a subset of occupational studies of chronic inhalation exposure to toluene.

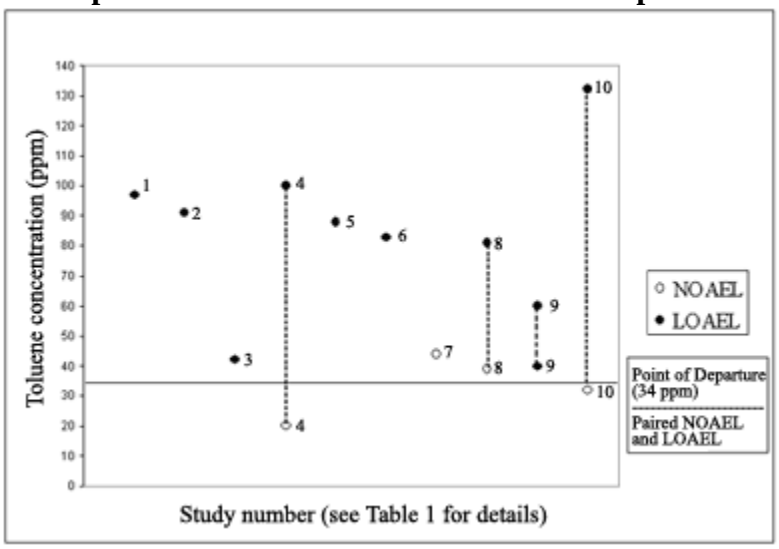

Table 1. Selected subset of occupational studies of neurological effects from toluene inhalation

Study number in Figure 1 and reference	Number of workers and duration of exposure (average years ± SD)	NOAEL (ppm)	LOAEL (ppm)	Effect/test	Response level at the LOAEL (statistically significant response compared to controls)[a]	Noted potential limitations
1. Abbate et al., 1993	Reference (n=40), exposed (n=40) (12-14 years; no SD reported)	None[b]	97	Brainstem response auditory-evoked potential	28% increase of the latency shift for wave-I during passage from 11 to 90 repetitions.	
2. Boey et al., 1997	Reference (n = 29) exposed	None	91	Neuropsychological examination; digit span, visual	Increased time to complete the grooved	Control workers were exposed to 12 ppm toluene

Study number in Figure 1 and reference	Number of workers and duration of exposure (average years ± SD)	NOAEL (ppm)	LOAEL (ppm)	Effect/test	Response level at the LOAEL (statistically significant response compared to controls)[a]	Noted potential limitations
	(n = 29) (4.9 ± 3.5 years; range of 1-13 years)			reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests	pegboard test 7% and 6% for dominant and non-dominant hands respectively, increase in time to complete trail-making test parts A&B, 31% & 28%, respectively; 15% decrease in backward digit span test; 12% and 10% decrease in symbol digit modality test for written and oral sections, respectively.	
3. Cavalleri et al., 2000	Reference (n=16), exposed (n=33) (9.75 years; no SD reported)	None	42	Color vision impairment (Lanthony D-15)	29% increase in CCI and 49% increase in total confusion index (TOCI) (reported as mean of both eyes).	Exposure measured from urinary excretion of toluene: on the basis of previous data, air concentrations estimated to be 42 ppm.
4. Eller et al., 1999	Reference (n=19), low exposure (n=30), high exposure (n=49)	20	>100	Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visuomotor function, computerized	13% increase in performance time on Bourdon Wiersma Test but no increase in the number of missed or incorrect	The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years.

Study number in Figure 1 and reference	Number of workers and duration of exposure (average years ± SD)	NOAEL (ppm)	LOAEL (ppm)	Effect/test	Response level at the LOAEL (statistically significant response compared to controls)[a]	Noted potential limitations
	low exposure (1-12 years; no SD reported) high exposure (>12 years)			neurological examination (CATSYS, TREMOR, and SWAY), subjective assessment	detections; 33% of exposed population reported concentration difficulties.	
5. Foo et al., 1990	Reference (n=30), exposed (n=30) (5.7 ± 3.2 years)	None	88	Neurobehavioral tests: Benton visual retention test, visual reproduction, trail making, grooved pegboard, digit span, digit symbol, finger tapping, and simple reaction time	Increased time to complete the trail-making test parts A&B, 51% & 63%, respectively; 25% decrease in digit symbol test performance; 16% decrease in total digit span test scores (both forward and backward).	Control workers were exposed to 13 ppm toluene for 2.5 ± 3.2 years. The education level was lower in the exposed group. As a result, data from the neurobehavioral tests were adjusted for years of education using a generalized linear model.
6. Murata et al., 1993	Reference (n=10), exposed (n=10) (11 years; range of 1-36 years; no SD reported)	None	83	Electrophysiological analysis of maximial motor and sensory nerve conduction velocity (MCV & SCV)	9% reduction in the MCV in the forearm and 6% reduction in the SCV in the palm.	Exposed workers were matched for age but not alcohol consumption.

Study number in Figure 1 and reference	Number of workers and duration of exposure (average years ± SD)	NOAEL (ppm)	LOAEL (ppm)	Effect/test	Response level at the LOAEL (statistically significant response compared to controls)[a]	Noted potential limitations
7. Nakatsuka et al., 1992	Reference (n=120), exposed (n=174)	44-48	None	Color vision impairment (Lanthony's new color test and Ishihara's color vision test)	No measured effect on color vision.	In lieu of determining exposure duration, groups were age-matched to control for effects of aging on color vision.
8. Neubert et al., 2001	Ref-ex (n=109), ref-int (n=48), exp gp I (n=316), exp gp II (n=535), exp gp III (n=308), exp gp IV (n=65)	39 (exp gp 1)	81 (ex gp IV)	Psychophysiological and psychomotor testing: verbal memory span, visuomotor performance, immediate visual memory, self-rating of feeling, biosensory vigilance, critical flicker fusion frequency test, personality dispositions	5% reduction in ascending flicker fusion frequency.	Exposure was identified as chronic but the duration was not reported.
9. Vrca et al., 1995	Reference (n=59), exposed (n=49) (21.4 ± 7.4 years)	None	40-60	Visual evoked potentials	The amplitudes of visual evoked brain potentials were 24, 43, and 55% higher for N75, P100, and N145, respectively.	Exposure levels were estimated based on urinary levels of metabolites and toluene levels in blood.
10. Zavalic et al., 1998a	Reference (n=90), low exposure (n=46), high exposure (n=37)	32	132	Color vision impairment (Lanthony D-15)	10-14% increase in CCI (both eyes).	The results from this investigation were reported in several publications (Zavalic et al., 1998a,b,c); some reporting

Study number in Figure 1 and reference	Number of workers and duration of exposure (average years ± SD)	NOAEL (ppm)	LOAEL (ppm)	Effect/test	Response level at the LOAEL (statistically significant response compared to controls)[a]	Noted potential limitations
	low exposure (16.21 ± 6.1 years) high exposure (18.34 ± 6.03 years)					discrepancies exist regarding the number of workers in the exposed and control groups and the statistical analyses.

[a] Not all studies examined all neurotoxicity endpoints.
[b] No NOAEL identified in this study.

The subset of studies shown in Figure 1 were weighted equally since none was clearly a stronger study. The highest NOAEL was identified as 44 ppm (Nakatsuka et al., 1992). The lowest LOAELs were identified as 40-42 ppm (Vrca et al., 1995, 1997; Cavalleri et al., 2000). An arithmetic mean of the NOAEL values in Table 1 was chosen to represent an average point of departure. Thus, the average exposure level of 34 ppm is used as the point of departure for the derivation of the RfC. This value is lower than the LOAELs identified above. The range of NOAELs for the suite of neurological effects is 20 to 48 ppm. The average NOAEL is used as a surrogate given concerns about the use of a particular individual NOAEL based on the discussion in Section 5.2.1 of the Toxicological Review (U.S. EPA, 2005). There is some uncertainty in using an average value from a suite of studies with varied endpoints and varied levels of response for the point of departure. However, the uncertainty is expected to be less than that associated with choosing any particular one of the available studies for deriving the point of departure since there were potential limitations associated with many of the available studies and no single study stands out as being of the highest quality. Furthermore, this subset of studies presents a cluster of NOAELs for neurological effects which are generally below reported LOAELs for all endpoints.

The NOAEL (average) of 34 ppm (128 mg/m^3) was adjusted from an occupational exposure scenario to continuous exposure conditions as follows:

NOAEL (adj)	= NOAEL (average) x VEho/VEh x 5 days/7 days
	= 128 mg/m^3 x 10m^3/20m^3 x 5 days/7 days
	= 46 mg/m^3

Where:
VEho = human occupational default minute volume (10 m^3 breathed during the 8 hour workday)
VEh = human ambient default minute volume (20 m^3 breathed during the entire day)

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

UF = 10

A total uncertainty factor of 10 was applied to the adjusted average NOAEL (i.e., 10 for consideration of intraspecies variation). A 10-fold uncertainty factor for intraspecies differences (UF_H) was used to account for potentially susceptible human subpopulations and lifestages. This 10-fold uncertainty factor includes consideration of the Pelekis et al. (2001) model employing pharmacokinetic information to derive a chemical-specific intraspecies UF for toluene that accounts for childhood exposure only. Their analysis suggests an informed quantitation of adult-to-child variability reported to be in the 3-fold range. The Pelekis model is based on the pharmacokinetic differences between adults and children. However, differences in human susceptibility may also be due to lifestage (e.g., advanced age) differences among the adult population, genetic polymorphisms, decreased renal clearance in disease states, and unknown pharmacodynamic variations in response to toluene exposure. Since the variability defined in the Pelekis model may not account for these additional differences in pharmacokinetics and pharmacodynamics, a full factor of 10 is used.

An uncertainty factor to account for laboratory animal-to-human interspecies differences (UF_A) was not necessary because the point of departure is based on human exposure data.

An uncertainty factor to account for extrapolating from less than chronic results (UF_S) was not necessary. Most of the studies used in the analysis were of chronic duration.

An uncertainty factor was not needed to account for extrapolating from a LOAEL to a NOAEL because a surrogate NOAEL, i.e., an average NOAEL from a subset of studies, was used to derive the point of departure.

The database for inhalation exposure to toluene is considered adequate. Numerous human and animal chronic and subchronic studies are available. Animal studies have demonstrated reproductive and developmental effects of toluene at exposure levels higher than those used for the determination of the point of departure. In addition, neurotoxicity studies and a two-generation reproductive toxicity study are available. There is some uncertainty regarding potential immunological effects of toluene via the inhalation route of exposure. These uncertainties arise from the conflicting immunotoxicity data on toluene following oral exposure in animal studies (see Sections 4.2.1.1 and 5.1.1 of the Toxicological Review for study descriptions). Two studies on immunologic effects following inhalation exposure are available. Stengel et al. (1998) assessed several immunological parameters in blood following chronic occupational exposure to 50 ppm toluene but no statistically significant effects were observed. Aranyi et al. (1985) examined the effects of inhalation exposure to toluene on pulmonary host defenses in animals and found transient effects at low doses with a lack of a dose-response relationship. These results indicate additional research may be needed to further evaluate the potential immunological effects of toluene by the inhalation route of exposure but do not warrant an uncertainty factor at this time. A database uncertainty factor is not considered necessary.

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

A number of animal studies have examined the neurological effects of inhaled toluene. These studies were generally carried out at high doses and reported impaired responses in neurologic examinations. For example, Rebert et al. (1989a,b) reported abnormal flash-evoked potentials in rats exposed to a single inhalation exposure of 500-16,000 ppm toluene. Evoked potentials reflect the function of the nervous system. Increases in latencies in evoked potentials can reflect deficits in nerve conduction and are indicators of a potential neurotoxic effect. Wood et al. (1983) exposed rats to toluene levels up to 3000 ppm for 4 hours prior to behavioral evaluation and reported that toluene reduced performance in behavioral tests, particularly at the 1780 and 3000 ppm exposure levels. Von Euler et al. (2000) exposed 30 rats to 80 ppm toluene for 4 weeks and found a selective decrease of approximately 6% in the area of the parietal cortex by magnetic resonance imaging. Autoradiographic analysis revealed a 7-10% decrease of the cerebrocortical area. Inhalation exposure to toluene has also been shown to result in irreversible high-frequency hearing loss in rats. Pryor et al. (1984) evaluated hearing loss by a behavioral technique (avoidance response elicited to an auditory signal) and 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 of exposure to 1000 ppm toluene for 14 hours/day. Hearing loss was irreversible, as evidenced by a failure to return to normal response after 3 months of recovery.

In addition to neurologic effects in humans, the previous RfC on the IRIS database was based on irritation of the upper respiratory tract, specifically the nasal epithelium, as reported in the chronic NTP (1990) study in rats. However, these effects occurred in rats exposed to high concentrations (600 ppm or greater) of toluene and did not show an appreciable increase with increasing concentration (i.e., the incidence of the lesions was greater at 600 ppm than at 1200 ppm). Support that the nasal lesions are a high-exposure phenomenon also comes from the results of a chronic inhalation study in rats performed by CIIT (1980), which reported no effects on the nasal epithelium of animals exposed to 300 ppm toluene. A 28-day inhalation study in rats (30 and 300 ppm) likewise failed to demonstrate treatment-related lesions in the nasal epithelium (Poon et al., 1994). Acute studies in humans have demonstrated that subjective reports of irritation of the nose and/or eyes occurs at exposure levels of 100 ppm or greater (Baelum et al., 1985, 1990; Echeverria et al., 1989; Andersen et al., 1983) but not at exposures below 100 ppm (Echeverria et al., 1989; Andersen et al., 1983). Because neurologic effects are a more sensitive endpoint for exposed humans, neurological deficits were selected as the critical endpoint in this assessment.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — High
RfC -- High

The overall confidence in this RfC assessment is high. Confidence in the database is high. Many chronic studies in humans are available. In addition, numerous animal studies on the reproductive and developmental effects of toluene exist, which identify these effects as occurring at doses higher than that identified as the point of departure. No single study was chosen as the principal study, however, a subset of studies were considered adequate for the determination of the RfC. The overall study confidence is high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA (2005)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Toluene (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***

Agency Completion Date -- 08/26/2005

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Toluene
CASRN — 108-88-3
Section II. Last Revised — 09/23/2005

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is an upper bound on the estimate of risk

per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m^3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), *there is inadequate information to assess the carcinogenic potential* of toluene because studies of humans chronically exposed to toluene are inconclusive, toluene was not carcinogenic in adequate inhalation cancer bioassays of rats and mice exposed for life (CIIT, 1980; NTP, 1990; Huff, 2003), and increased incidences of mammary cancer and leukemia were reported in a lifetime rat oral bioassay at a dose level of 500 mg/kg-day but not at 800 mg/kg-day (Maltoni et al., 1997). In the NTP (1990) and Huff (2003) studies, no neoplasms were noted in male rats, and one nasal, two kidney, and two forestomach neoplasms observed in female rats were considered not to be associated with toluene exposure. No increase in the incidence of neoplasms was observed in mice. Toluene has generally not been genotoxic in short-term testing protocols. The previous IRIS assessment classified toluene as Group D (*not classifiable as to human carcinogenicity*) under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986) based on inadequate data on the carcinogenicity of toluene in humans and inadequate evidence of carcinogenicity in animals. Toluene is not included in the *10th Report on Carcinogens* (NTP, 2002). IARC has classified toluene as Group 3 (*not classifiable as to its carcinogenicity in humans*) with a supporting statement that there is inadequate evidence in humans and evidence suggesting a lack of carcinogenicity of toluene in experimental animals (IARC, 1999).

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Available studies in toluene-exposed workers have reported very limited or no evidence suggesting carcinogenic effects of toluene exposure (Anttila et al., 1998; Svensson et al., 1990; Wiebelt and Becker, 1999). A cohort mortality study in toluene-exposed workers (Wiebelt and Becker, 1999) did not report an increase in cancer-specific mortality for the

entire cohort. A subcohort of highly-exposed workers demonstrated statistically significant increases in mortality from cancers of the bone and connective tissue, but lack of exposure characterization, co-exposure information, and categorization of and adjustment for other confounding factors (age, smoking, etc.) within the subcohort precludes drawing conclusions from these results as to the possible association between toluene exposure and cancer risk. Svensson et al. (1990) similarly did not report increased cancer-specific mortality among rotogravure printers. While an increase in tumors of the respiratory tract was reported, this increase was not statistically significant when only subjects with exposure periods of five years or more were examined, and no dose-response relationships were present for tumor incidence. Anttila et al. (1998) carried out a retrospective cohort analysis of 5301 workers monitored for biological markers of occupational exposure to styrene, toluene, or xylene; no significantly increased incidence rates of cancer could be associated with toluene exposure. Other studies examining the carcinogenicity of toluene in occupationally exposed humans have failed to adequately account for co-exposure to other compounds.

II.A.3. Animal Carcinogenicity Data

NTP (1990) and Huff (2003) have conducted a 2-year inhalation carcinogenicity study in F-344 rats and B6C3F1 mice and found no evidence for carcinogenicity in either sex of either species at exposure levels up to 1200 ppm. Another inhalation carcinogenicity study in F-344 rats (CIIT, 1980; Gibson and Hardisty, 1983) likewise reported no evidence for carcinogenic effects of toluene at exposure levels up to 300 ppm. A lifetime carcinogenicity study in Sprague-Dawley rats by the oral route (Maltoni et al., 1997) was suggestive of potential carcinogenic effects of toluene, but the dose-response relationships were not well defined (i.e., the 500 mg/kg animals had considerably more tumors than those in the 800 mg/kg group) and study details were inadequately reported.

II.A.4. Supporting Data for Carcinogenicity

Available studies examining the genotoxic effects of toluene have generally reported negative results. 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; Connor et al., 1985; Nakamura et al., 1987; NTP, 1990) and *E. coli* (Fluck et al., 1976; 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 (Lyapkalo, 1973; Dobrokhotov and Enikeev, 1977) 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 (Forni et al., 1971; Maki-Paakkanen et al., 1980), although a slight increase was noted in workers co-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).

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

Not applicable. Data are inadequate for an assessment of human carcinogenic potential.

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

Not applicable. Data are inadequate for an assessment of human carcinogenic potential.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA (2005)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Toluene (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)***.

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

Agency Completion Date - 8/26/2005

II.D.3. EPA Contacts (Carcinogenicity Assessment

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Toluene
CASRN — 108-88-3

VI.A. Oral RfD References

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VII. Revision History

Substance Name — Toluene
CASRN — 108-88-3
File First On-Line 01/31/1987

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
07/01/1990	I.A.	Withdrawn; new RfD verified (in preparation)
08/01/1990	I.A.	Oral RfD summary replaced; RfD changed

Date	Section	Description
08/01/1992	I.B.	Inhalation RfC on-line
09/23/2005	I., II., VI.	New RfD, RfC, and cancer assessment.

VIII. Synonyms

Substance Name — Toluene
CASRN — 108-88-3
Section VIII Last Revised — 09/23/2005

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