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Provisional Peer-Reviewed Subchronic Toxicity Values

for Toluene
(CASRN 108-88-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED SUBCHRONIC TOXICITY VALUES FOR TOLUENE (CASRN 108-88-3)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

A streamlined approach was used to derive provisional subchronic RfD and RfC values for toluene. Toluene has chronic RfD, RfC, and cancer assessments on IRIS (U.S. EPA, 2005b), so only subchronic toxicity values are required to support the complex aliphatic and aromatic mixture assessment. Toluene has recently been reassessed by the IRIS program, and a Toxicological Review (U.S. EPA, 2005a) is available. In addition, the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for toluene has been updated recently (ATSDR, 2000). Both the IRIS Toxicological Review and the ATSDR Toxicological Profile contain comprehensive overviews of the toxicology and toxicokinetics information available on toluene. While the IRIS Toxicological Review for Toluene encompassed the exposure duration-relevant literature to 2005, updated literature searches were conducted from January 2004 to July 2007 for studies pertinent to the derivation of subchronic toxicity values for toluene; Appendix B provides a description of the literature search process. No new studies were identified pertinent to the derivation of subchronic provisional toxicity values. As such, given the availability of the recent IRIS and ATSDR reviews, these reports were used to identify the exposure duration-relevant critical studies and endpoints for use in deriving the subchronic values.

The derivation of subchronic toxicity values for toluene is discussed below. Review of the data supporting the chronic toxicity values for toluene currently on IRIS (U.S. EPA, 2005b) indicate that subchronic data were used to derive the chronic values and, thus, are appropriate to serve as the basis for the corresponding subchronic toxicity values. A brief rationale is provided for the selection of the critical study and endpoint, a summary of the critical study is presented, and the subchronic toxicity-value-derivation process is described. For further information on the toxicology and toxicokinetics of toluene, the reader may consult the IRIS record (attached to this report as Appendix A), IRIS Toxicological Review (U.S. EPA, 2005a), or ATSDR (2000) Toxicological Profile for toluene.

REVIEW OF PERTINENT DATA AND DERIVATION OF PROVISIONAL SUBCHRONIC TOXICITY VALUES FOR TOLUENE

Subchronic p-RfD

The chronic RfD for toluene (0.08 mg/kg-day) currently on IRIS (U.S. EPA, 2005b) is based on kidney weight increases in a subchronic rat study (NTP, 1990). It includes an uncertainty factor (UF) of 10 for subchronic-to-chronic extrapolation. The ATSDR intermediate-duration oral Minimal Risk Level (MRL) (0.02 mg/kg-day) was derived in September 2000 (ATSDR, 2000) based on neurological effects in a 28-day mouse drinking water study (Hsieh et al., 1990). In the Toxicological Review, U.S. EPA (2005a) rejected this study as the basis for the chronic RfD because the study did not determine whether the critical effect (increased brain neurotransmitter levels) was persistent (levels were measured immediately after the end of treatment) and because this endpoint had not been correlated with functional neurological changes.

The database supporting the oral RfD for toluene is somewhat limited. In particular, this is due to the lack of comprehensive neurotoxicity testing after exposure by the oral route, particularly considering that neurotoxicity is the critical effect following inhalation exposure. In order to determine whether newer studies that might be in support of or inform the derivation of the subchronic p-RfD have been published, an update literature search (2004−2007) was conducted to search for studies of oral exposure to toluene. The only oral study identified in the literature search appears to have measured limited endpoints (heart rate, blood pressure, core temperature, and motor activity) after acute exposure and was published only as an abstract (Gordon et al., 2006); as such, it is not suitable for use in the derivation of a subchronic p-RfD. As no more suitable studies were identified, the subchronic p-RfD is based on the same critical study (NTP, 1990), endpoint (increased kidney weight), and point of departure (POD) as the chronic RfD—but without a UF for subchronic-to-chronic extrapolation.

A summary of the critical study is excerpted from the U.S. EPA (2005a) Toxicological Review for Toluene and reproduced here for the reader's convenience.

> *The oral toxicity of toluene was investigated in a subchronic gavage study in F-344 rats (NTP, 1990). 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, 5 days/week for 13 weeks. The exposure was for 5 days/week and therefore the dose is adjusted to a 7-day week (e.g., 312 mg/kg × 5/7 = 223 mg/kg-day) resulting in dose estimates of 0, 223, 446, 893, 1786 or 3571 mg/kg-day, respectively. All animals receiving 3571 mg/kg-day died within the first week and were eliminated from further evaluation. There was one female and eight males in the 2500 mg/kg-day group that died, but two of these deaths were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 1786 mg/kg-day, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. A significant decrease ($p < 0.05$) in body weight for males in the 1786 mg/kg-day group was the only significant change. There were no significant changes in hematology or urinalysis for any group of animals. Some biochemical changes, including a significant increase ($p < 0.05$) in serum aspartate aminotransferase (AST) in 1786 mg/kg-day males and an increase in cholinesterase activity in females receiving 1786 mg/kg-day were noted.*

There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder (NTP, 1990). 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 446 mg/kg-day. Absolute liver weights (mean ± SE) in males were 10,490 ± 360 (100%), 11,310 ± 300 (108%), 11,850 ± 390 (113%), 14,440 ± 480 (138%) and 14,130 ± 1220 (135%) milligrams for 0, 223, 446, 893 and 1786 mg/kg-day doses, respectively. Relative liver weights (mean ± SE) in males were 33.3 ± 0.81 (100%), 34.5 ± 0.68 (104%), 35.9 ± 0.68 (108%), 45.0 ± 1.69 (135%), and 59.4 ± 3.28 (178%) grams/100 g body weight for 0, 223, 446, 893 and 1786 mg/kg-day doses, respectively. Absolute kidney weights (mean ± SE) in males were 1084 ± 14 (100%), 1159 ± 34 (107%), 1213 ± 39 (112%), 1292 ± 34 (119%) and 1227 ± 114 (113%) milligrams for 0, 223, 446, 893 and 1786 mg/kg-day doses, respectively. Relative kidney weights (mean ± SE) in males were 3.5 ± 0.06 (100%), 3.5 ± 0.07 (100%), 3.7 ± 0.06 (106%), 4.0 ± 0.06 (114%) and 5.1 ± 0.32 (146%) grams/100 g body weight for 0, 223, 446, 893 and 1786 mg/kg-day doses, respectively. In females, absolute and relative weights of the liver, kidney and heart were all significantly increased at doses greater than or equal to 893 mg/kg-day ($p < 0.01$ for all comparisons except $p < 0.05$ for absolute kidney and heart weights at 893 mg/kg-day).

Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at doses greater than 1786 mg/kg-day (NTP, 1990). 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. 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 1786 mg/kg-day and males at 893 mg/kg-day. In the bladder, hemorrhage of the muscularis was seen in males at 1786 mg/kg-day. The NOAEL in rats for this study is 223 mg/kg-day. The LOAEL is 446 mg/kg-day based on liver and kidney weight changes in male rats.

As noted above, the subchronic p-RfD for toluene is based on the same critical study, endpoint, and POD as the chronic RfD. For the chronic RfD, U.S. EPA (2005b) conducted benchmark dose (BMD) modeling on the absolute kidney-weight changes in male rats in the NTP (1990) study. Modeling resulted in a $BMDL_{1SD}$ (lower confidence limit on the benchmark dose associated with a benchmark response of one standard deviation from the control mean response) of 238 mg/kg-day, which served as the POD for chronic RfD derivation. Further details on the modeling efforts are available in the IRIS record (see Appendix A) and in the Toxicological Review (see U.S. EPA, 2005a). For the chronic RfD, the $BMDL_{1SD}$ was divided by a total UF of 3,000 that included a 10-fold UF for interspecies extrapolation, 10-fold UF for intraspecies variation, a 10-fold UF for extrapolation from subchronic-to-chronic exposure duration, and a 3-fold UF for database deficiencies (reflecting limited neurotoxicological data by the oral route and conflicting immunotoxicity studies). Appendix A contains details of the UF selections.

For the derivation of a subchronic p-RfD, the $BMDL_{1SD}$ of 238 mg/kg-day for absolute kidney-weight changes is divided by a total UF of 300, as shown below:

Subchronic p-RfD = BMDL ÷ UF
= 238 mg/kg-day ÷ 300
= **0.8 or 8×10^{-1} mg/kg-day**

The composite UF of 300 is composed of the following:

- A UF of 10 is applied 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.

- A UF of 10 is applied 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 UF of 1 for extrapolation from a LOAEL to NOAEL (UF_L) is applied because the current approach is to address this extrapolation as one of the considerations in selecting a Benchmark Response (BMR) for BMD modeling. In this case, a BMR corresponding to a change in absolute kidney-weight equal to one control standard deviation from the control mean kidney-weight was selected under an assumption that it represents a biologically significant change.

- A UF of 3 is applied to account for deficiencies in the toluene database (UF_D). 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 that 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 IRIS Toxicological Review of toluene 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 IRIS Toxicological Review for toluene). 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 are inadequate to inform 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. As such, a 3-fold UF for insufficiencies in the database is applied to account for the

lack of adequate data on endpoints of potential concern for toluene—including neurotoxicity, two-generation reproductive toxicity, and immunotoxicity.

As discussed further in the IRIS Summary and Toxicological Review for toluene, confidence in the principal study, an adequate gavage study of subchronic duration, is medium. Confidence in the database is medium reflecting a lack of neurotoxicity studies, and a two-generation reproductive toxicity study, as well as uncertainty surrounding the immunotoxicity of toluene. An oral subchronic study in two species and several immunotoxicity studies are available. A number of oral 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 (please refer to the IRIS Toxicological Review for toluene for details). Confidence in the subchronic p-RfD is medium.

Subchronic p-RfC

The chronic RfC for toluene (5 mg/m^3) on IRIS (completion date August 2005) is based on neurological effects in humans. The NOAEL (34 ppm or 128 mg/m^3; 46 mg/m^3 after adjustment for continuous exposure) used to derive the RfC was based on a number of critical studies; the mean exposure durations in the studies ranged from 4.9 years (Boey et al., 1997) to 21.4 years (Vrca et al., 1995). A composite UF of 10 for human variability was applied to the NOAEL to derive the RfC; no UF for exposure duration was included. There is no intermediate-duration inhalation MRL for toluene. ATSDR (2000) indicated that there were no data suitable for deriving an intermediate duration inhalation MRL for toluene and that the chronic inhalation MRL would be protective for intermediate exposures. The chronic inhalation MRL for toluene is 0.08 ppm (0.3 mg/m^3) and is based on neurological effects (color vision impairment) in humans exposed occupationally (Zavalic et al., 1998a).

For the derivation of the chronic RfC, U.S. EPA (2005a) selected a subset of the available epidemiological studies based on minimum study quality criteria, reported as "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 coexposure to other solvents in the workplace." However, review of Section 5.2.1 (Choice of Principal Study, in the U.S. EPA, 2005a Toxicological Review) indicates that no studies of subchronic duration were rejected on the basis of exposure duration and two studies of subchronic duration (mean exposure $\leq$7 years) were included in the critical studies: Boey et al. (1997; 4.9 years) and Foo et al. (1990; 5.7 years). There were two studies (Nakatsuka et al., 1992 and Neubert et al., 2001) that did not report exposure duration, although Neubert et al. (2001) characterized the exposure as "chronic." LOAELs in the two subchronic studies were 91 and 88 ppm (343 and 332 mg/m^3; Boey et al., 1997 and Foo et al., 1990, respectively), and were of similar magnitude as the LOAELs from the longer-duration studies. NOAELs were not identified in the subchronic studies (U.S. EPA, 2005a).

Because high quality human epidemiological studies focusing on a known critical endpoint of human toxicity (neurological effects) are available, animal data were not considered for use in deriving the subchronic p-RfC. Examination of the effect levels identified for human studies of toluene in the IRIS record (duplicated below as Table 1) indicates that neurological effects in the human studies were observed at similar levels in both the subchronic and chronic studies. Given that the chronic RfC is based on a number of human occupational studies,

including some studies of subchronic duration, and that derivation of the chronic RfC did not include an UF for exposure duration, the chronic RfC for toluene was adopted as the subchronic p-RfC.

A summary of the cocritical studies is excerpted from the U.S. EPA (2005b) IRIS record for toluene and reproduced below. For additional discussion of the limitations and uncertainties associated with studies that were considered adequate, or the POD selected for the chronic RfC, see the Toxicological Review (U.S. EPA, 2005a).

> *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 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.*
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> *All of the available occupational studies were considered for the principal study upon which to base the derivation of the RfC. 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 with which to characterize neurological effects or 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 that 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 summarize 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.

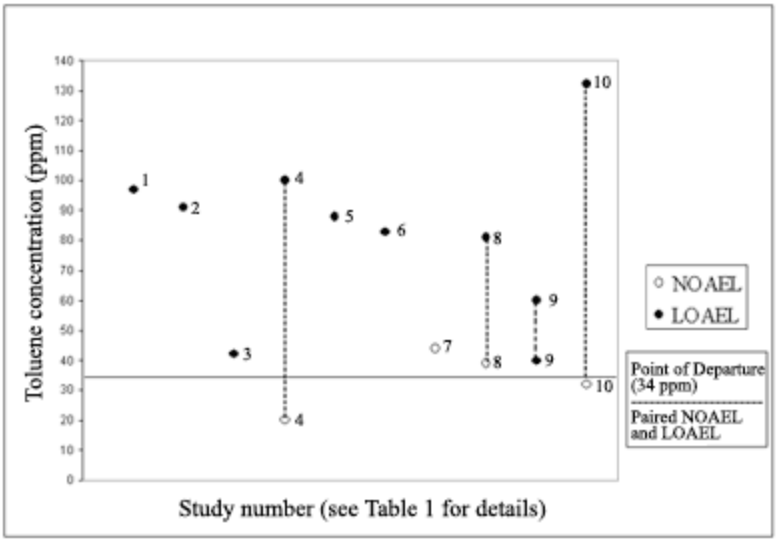

Figure 1. Summary of NOAELs/LOAELs for neurological endpoints for a subset of occupational studies of chronic inhalation exposure to toluene

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 (n = 29) (4.9 ± 3.5 years; range of 1-13 years)	None	91	Neuropsychological examination; digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests	Increased time to complete the grooved pegboard test 7% and 6% for dominant and nondominant 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.	Control workers were exposed to 12 ppm toluene

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) low exposure (1-12 years; no SD reported) high exposure (>12 years)	20	>100	Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visuomotor function, computerized neurological examination (CATSYS, TREMOR, and SWAY), subjective assessment	13% increase in performance time on Bourdon Wiersma Test but no increase in the number of missed or incorrect detections; 33% of exposed population reported concentration difficulties.	The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years.
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 maximal 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.
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) low exposure (16.21 ± 6.1 years) high exposure (18.34 ± 6.03 years)	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 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 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). The range of NOAELs for the suite of neurological effects is 20−48 ppm. An arithmetic mean of the NOAEL values in Table 1 was chosen to represent an average POD. Thus, the average exposure level of 34 ppm is used as the POD for the derivation of the chronic RfC.

The chronic RfC for toluene (5 mg/m^3) is based on neurological effects in human epidemiological studies and includes several of subchronic duration. The NOAEL (46 mg/m^3 after adjustment for continuous exposure) was divided by a composite UF of 10 to derive the RfC; no UF for exposure duration is included (see Appendix A for details regarding UF selection). Thus, the **chronic RfC of 5 or 5 × 10^0 mg/m^3 was adopted as the subchronic p-RfC for toluene.**

As discussed further in the IRIS Summary and Toxicological Review for toluene, many studies in humans are available. No single study was chosen as the principal study, however, a subset of studies was considered adequate for the determination of the RfC, and, in this assessment, the subchronic p-RfC. In addition, numerous animal studies on the reproductive and developmental effects of toluene indicate that these effects occur at doses higher than that identified as the POD. Confidence in the subchronic p-RfC is consistent with the confidence in the IRIS chronic RfC: high.

REFERENCES

Abbate, C., C. Giorgianni, F. Munao et al. 1993. Neurotoxicity induced by exposure to toluene: An electrophysiologic study. Int. Arch. Occup. Environ. Health. 64:389−392.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for Toluene. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services. PB/2000/108028. Online. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=161&tid=29.

Boey, K.W., S.C. Foo and J. Jeyaratnam. 1997. Effects of occupational exposure to toluene: A neuropsychological study on workers in Singapore. Ann. Acad. Med. Sing. 26:84−7.

Cavalleri, A., F. Gobba, E. Nicali et al. 2000. Dose-related color vision impairment in toluene-exposed workers. Arch. Env. Health. 55:399−404.

Eller, N., B. Netterstrom and P. Laursen. 1999. Risk of chronic effects on the central nervous system at low toluene exposure. Occup. Med. 49(6):389−395.

Foo, S.C., J. Jeyaratman and D. Koh. 1990. Chronic neurobehavioural effects of toluene. Br. J. Ind. Med. 47:480−484.

Gordon, C. J., W. Oshiro, T. Samsam, P. Becker, C. Mack, P. Bushnell. 2006. Hypertensive and tachycardic responses to oral toluene in the rat. Neurotoxicology. 27(5):929.

Gospe, S; Al-Bayati, M. 1994. Comparison of oral and inhalation exposures to toluene. Int J Toxicol 13:21−32.

Hsieh, G.C., R.P. Sharma, R.D. Parker et al. 1990. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotoxicol. Environ. Saf. 20:175−184.

Murata, K., S. Araki, K. Yokoyama et al. 1993. Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction. Ind. Health. 31:79−90.

Nakatsuka, H., T. Watanabe, Y. Takeuchi et al. 1992. Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. Int. Arch. Occup. Environ. Health. 64:113−117.

Neubert, D., C. Gericke, B. Hanke et al. 2001. Multicenter field trial on possible health effects of toluene. II. Cross-sectional evaluation of acute low-level exposure. Toxicology. 168:139−183.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B5C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR-371. Research Triangle Park, NC.

Schaper, M., P. Demes, M. Zupanic et al. 2003. Occupational toluene exposure and auditory function: results from a follow-up study. Ann. Occup. Hyg. 47:493−502.

U.S. EPA. 2005a. Toxicological Review of Toluene (CAS No. 108-88-3) in Support of Summary Information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC. EPA/635/R-05/004. Online. http://www.epa.gov/iris/toxreviews/0118tr.pdf.

U.S. EPA. 2005b. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/.

Vrca, A., D. Bozicevic, V. Karacic et al. 1995. Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch. Toxicol. 69:337−40.

Vrca, A., V. Karacic, D. Bozicevic et al. 1996. Brainstem auditory evoked potentials in individuals exposed to long-term low concentrations of toluene. Am. J. Ind. Med. 30:62−66.

Vrca, A., D. Bozicevic, V. Bozikov et al. 1997. Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. Act. Med. Croat. 51:215−219.

Zavalic, M., Z. Mandic, R. Turk et al. 1998a. Quantitative assessment of color vision impairment in workers exposed to toluene. Am. J. Ind. Med. 33(3):297−304.

Zavalic, M., Z. Mandic, R. Turk et al. 1998b. Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits. Occup. Med. 48:175−180.

Zavalic, M., Z. Mandic, R. Turk et al. 1998c. Qualitative color vision impairment in toluene-exposed workers. Int. Arch. Occup. Environ. Health. 71:194−200.

Zupanic, M., P. Demes and A. Seeber. 2002. Psychomotor performance and subjective symptoms at low level toluene exposure. Occup. Environ. Med. 59:263−268.

APPENDIX A. PERTINENT SECTIONS FROM IRIS SUMMARY FOR TOLUENE: CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

Toluene; CASRN 108-88-3; 09/23/2005

Human 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, regional offices, and the Office of Research and Development. Sections I (Chronic Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review 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 at http://www.epa.gov/iriswebp/iris/backgr-d.htm.

STATUS OF DATA FOR Toluene

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/23/2005
Inhalation RfC Assessment (I.B.)	on-line	09/23/2005
Carcinogenicity Assessment (II.)	on-line	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/iriswebp/iris/backgr-d.htm 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:

$$\text{RfD} = \text{BMDL} \div \text{UF}$$

$$= 238 \text{ mg/kg-day} \div 3000$$

$$= 0.08 \text{ mg/kg-day}$$

__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).

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_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 subset of occupational studies of chronic inhalation exposure to toluene.

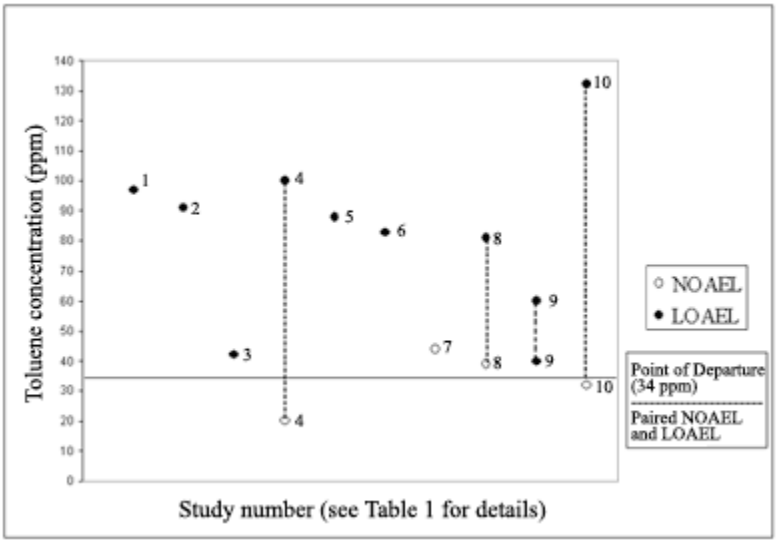

Table 1. Selected subset of occupational studies of neurological effects from toluene inhalation

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 (n = 29) (4.9 ± 3.5 years; range of 1-13 years)	None	91	Neuropsychological examination; digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests	Increased time to complete the grooved pegboard test 7% and 6% for dominant and nondominant 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.	Control workers were exposed to 12 ppm toluene

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) low exposure (1-12 years; no SD reported) high exposure (>12 years)	20	>100	Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visuomotor function, computerized neurological examination (CATSYS, TREMOR, and SWAY), subjective assessment	13% increase in performance time on Bourdon Wiersma Test but no increase in the number of missed or incorrect detections; 33% of exposed population reported concentration difficulties.	The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years.
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 maximal 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.
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) low exposure (16.21 ± 6.1 years) high exposure (18.34 ± 6.03 years)	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 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:

$$\begin{aligned} \text{NOAEL (adj)} &= \text{NOAEL (average) x VEho/VEh x 5 days/7 days} \\ &= 128\ mg/m^3 \times 10m^3/20m^3 \times 5\ days/7\ days \\ &= 46\ mg/m^3 \end{aligned}$$

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).

_VI. Bibliography

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

_VI.A. Oral RfD References

Ameno, K; Fuke, C; Ameno, S; et al. (1989) A fatal case of oral ingestion of toluene. Forensic Sci Int 41:255-260.

Askergren, A. (1982) Organic solvents and kidney function. Adv Mod Environ Toxicol 2:157-172.

Bonzel, KE; Muller-Wiefel, DE; Ruder, H; et al. (1987) Anti-glomerular basement membrane antibody-mediated glomerulonephritis due to glue sniffing. Eur J Pediatr 146:296-300.

Bosch, X; Campistol, JM; Montolie, J; et al. (1988) Myelofibrosis and focal segmental glomerularsclerosis associated with toluene poisoning. Human Toxicol 7:357-361.

Burns, LA; Bradley, SG; White Jr, KL; et al. (1994) Immunotoxicity of mono-nitrotoluenes in female B6C3F1 mice. I. Para-nitrotoluene. Drug Chem Toxicol 17:317-358.

Caravati, EM; Bjerk, PJ. (1997) Acute toluene ingestion toxicity. Ann Emerg Med 30:838-839.

Fischman, CM; Oster, JR. (1979) Toxic effects of toluene: a new cause of high anion gap metabolic acidosis. JAMA 241:1713-1715.

Franchini, I; Cavatorta, A; Falzoi, M; et al. (1983) Early indicators of renal damage in workers exposed to organic solvents. Int Arch Occup Environ Health 52:1-9.

Gericke, C; Hanke, B; Beckmann, G; et al. (2001) Multicenter field trial on possible health effects of toluene. III. Evaluation of effects after long-term exposure. Toxicology 168:185-209.

Gospe, S; Al-Bayati, M. (1994) Comparison of oral and inhalation exposures to toluene. Int J Toxicol 13:21-32.

Gospe Jr, SM; Zhou, SS. (1998) Toluene abuse embryopathy: longitudinal neurodevelopmental effects of prenatal exposure to toluene in rats. Reprod Toxicol 12:119-126.

Gospe Jr, SM; Zhou, SS. (2000) Prenatal exposure to toluene results in abnormal neurogenesis and migration in rat somatosensory cortex. Pediatr Res 47:362-368.

Gospe Jr, SM; Saeed, DB; Zhou, SS; et al. (1994) The effects of high-dose toluene on embryonic development in the rat. Pediatr Res 36:811-5.

Gospe Jr, SM; Zhou, SS; Saeed, DB; et al. (1996) Development of a rat model of toluene-abuse embryopathy. Pediatr Res 40:82-87.

Hsieh, GC; Sharma, RP; Parker, RD. (1989) Immunotoxicological evaluation of toluene exposure via drinking water in mice. Environ Res 49:93-103.

Hsieh, GC; Sharma, RP; Parker, RD; et al. (1990a) Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotoxicol Environ Saf 20:175-184.

Hsieh, GC; Parker, RDR; Sharma, RP; et al. (1990b) Subclinical effects of ground water contaminants. III. Effects of repeated oral exposure to combinations of benzene and toluene on immunologic responses in mice. Arch Toxicol 64:320-328.

Hsieh, GC; Sharma, RP; Parker, RD. (1990c) Subclinical effects of groundwater contaminants. Effects of repeated oral exposure to combinations of benzene and toluene on regional brain monoamine metabolism in mice. Arch Toxicol 64:669-676.

Hsieh, GC; Sharma, RP; Parker, RD. (1991) Hypothalmic-pituitary-adrenocortical axis activity and immune function after oral exposure to benzene and toluene. Immunopharmacol 21:23-31.

Huff, J. (2003) Absence of carcinogenic activity in Fischer rats and B6C3F1 mice following 103-week inhalation exposures to toluene. Int J Occup Environ Health 9:138-146.

Kamijima, M; Nakazawa, Y; Yamakawa, M; et al. (1994) Metabolic acidosis and renal tubular injury due to pure toluene inhalation. Arch Environ Health 49:410-3.

Kroeger, RM; Moore, RJ; Lehman, TH; et al. (1980) Recurrent urinary calculi associated with toluene sniffing. J Urol 123:89-91.

Luster, MI; Portier, C; Pait, DG; et al. (1992) Risk assessment in immunotoxicology. I. Sensitivity and predictability of immune tests. Fund Appl Toxicol 18:200-210.

Luster, MI; Portier, C; Pait, DG; et al. (1993) Risk assessment in immunotoxicology. II. Relationships between immune and host resistance tests. Fund Appl Toxicol 21:71-82.

Maltoni, C; Ciliberti, A; Pinto, C; et al. (1997) Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Ann NY Acad Sci 837:15-52.

NTP (National Toxicology Program). (1990) Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B5C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 371. Available from: National Institute of Environmental Health Sciences, Research Triangle Park, NC.

O'Brien, ET; Yeoman, WB; Hobby, JA. (1971) Hepatorenal damage from toluene in a "glue sniffer." Br Med J 2(752):29-30.

Streicher, HZ; Gabow, PA; Moss, AH; et al. (1981) Syndromes of toluene sniffing in adults. Ann Intern Med 94:758-62.

Taher, SM; Anderson, RJ; MacCartney, R; et al. (1974) Renal tubular acisdosis associated with toluene "sniffing." N Engl J Med 290:765-768.

U.S. EPA. (Environmental Protection Agency). (2000) Benchmark dose technical support document [external review draft]. EPA/630/R-00/001. Available from: http://www.epa.gov/raf/publications/pdfs/BMD-EXTERNAL_10_13_2000.PDF.

U.S. EPA. (2001) Benchmark dose software (BMDS) version 1.3.

U.S. EPA. (2005). Toxicological review of toluene in support of summary information on the Integrated Risk Information System (IRIS).

_VI.B. Inhalation RfC References

Abbate, C; Giorgianni, C; Munao, F; et al. (1993) Neurotoxicity induced by exposure to toluene: an electrophysiologic study. Int Arch Occup Environ Health 64:389-392.

Andersen, I; Lundqvist, GR; Molhave, L; et al. (1983) Human response to controlled levels of toluene in six-hour exposures. Scand J Work Environ Health 9:405-418.

Antti-Poika, M; Juntunen, J; Matikainen, E; et al. (1985) Occupational exposure to toluene:neurotoxic effects with special emphasis on drinking habits. Int Arch Occup Environ Health 56:31-40.

Aranyi, C; O'Shea, WJ; Sherwood, RL; et al. (1985) Effects of toluene inhalation on pulmonary host defenses of mice. Toxicol Lett 25:103-10.

Baelum, J; Andersen, I; Lundqvist, GR; et al. (1985) Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand J Work Environ Health 11:271-280.

Baelum, J; Lundqvist, G; Molhave, L; et al. (1990) Human response to varying concentrations of toluene. Int Arch Occup Environ Health 62:65-71.

Boey, KW; Foo, SC; Jeyaratnam, J. (1997) Effects of occupational exposure to toluene: a neuropsychological study on workers in Singapore. Ann Acad Med Singapore 26:84-7.

Campagna, D; Stengel, B; Mergler, D; et al. (2001) Color vision and occupational toluene exposure. Neurotoxicol Teratol 23:473-480.

Cavalleri, A; Gobba, F; Nicali, E; et al. (2000) Dose-related color vision impairment in toluene-exposed workers. Arch Env Health 55:399-404.

Chouaniere, D; Wild, P; Fontana, JM; et al. (2002) Neurobehavioral disturbances arising from occupational toluene exposure. Am J Ind Med 41:77-88.

CIIT (Chemical Industry Institute of Toxicology). (1980) A twenty-four month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. Conducted by Industrial Bio-Test Laboratories, Inc., Decatur, IL, and Experimental Pathology Laboratories, Inc., Raleigh, NC, for CIIT, Research Triangle Park, NC.

Echeverria, D; Fine, L; Langolf, G; et al. (1989) Acute neurobehavioral effects of toluene. Br J Ind Med 46:483-495.

Eller, N., B. Netterstrom and P. Laursen. (1999) Risk of chronic effects on the central nervous system at low toluene exposure. Occup. Med. 49(6): 389-395.

Foo, SC; Jeyaratnam, J; D. Koh, D. (1990) Chronic neurobehavioral effects of toluene. Br J Ind Med 47:480-484.

Lee, B; Lee, S; Lee, K; et al. (1988) Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. Ind Health 26:11-23.

Morata, TC; Fiorini, AC; Fischer, FM; et al. (1997) Toluene-induced hearing loss among rotogravure printing workers. Scand J Work Environ Health 23:289-98.

Murata, K; Araki, S; Yokoyama, K; et al. (1993) Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction. Ind Health 31:79-90.

Muttray, A; Wolters, V; Mayer-Popken, O; et al. (1995) Effect of subacute occupational exposure to toluene on color vision. Int J Occup Med Environ Health 8:339-45.

Nakatsuka, H; Watanabe, T; Takeuchi, Y; et al. (1992) Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below exposure limits. Int Arch Occup Environ Health 64:113-117.

Neubert, D; Gericke, C; Hanke, B; et al. (2001) Multicenter field trial on possible health effects of toluene. II. Cross-sectional evaluation of acute low-level exposure. Toxicology 168:139-183.

NTP (National Toxicology Program). (1990) Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B5C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 371. Available from: National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Orbaek, P; Nise, G. (1989) Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. Am J Ind Med 16:67-77.

Pelekis, M; Gephardt, LA; Lerman, SE. (2001) Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile compounds. Regul Toxicol Pharmacol 33:12-20.

Poon, R; Chu, IH; Bjarnason, S; et al. (1994) Inhalation toxicity study of methanol, toluene, and methanol/toluene mixtures in rats: effects of 28-day exposure. Toxicol Ind Health 10:231-245.

Pryor, GT; Rebert, CS; Dickinson, J; et al. (1984) Factors affecting toluene-induced ototoxicity in rats. Neurobehav.Toxicol Teratol 6:223-238.

Rebert, CS; Matteucci, MJ; Pryor, GT. (1989a) Acute electrophysiologic effects of inhaled toluene on adult male Long-Evans rats. Pharmacol Biochem Behav 33:157-165.

Rebert, CS; Matteucci, MJ; Pryor, GT. (1989b) Multimodal effects of acute exposure to toluene evidenced by sensory-evoked potentials from Fischer-344 rats. Pharmacol Biochem Behavior 32:757-768.

Schaper, M; Demes, P; Zupanic, M; et al. (2003) Occupational toluene exposure and auditory function: results from a follow-up study. Ann Occup Hyg 47:493-502.

Seeber, A; Schaper, M; Zupanic, M; et al. (2004) Toluene exposure below 50 ppm and cognitive function: a follow-up study with four repeated measurements in rotogravure printing plants. Int Arch Occup Environ Health 77:1-9.

Stengel, B; Cenee, S; Limasset, JC; et al. (1998) Immunologic and renal markers among photogravure printers exposed to toluene. Scand J Work Environ Health 24:276-284.

Tanaka, K; Maeda, T; Kobayashi, T; et al. (2003) A survey of urinary hippuric acid and subjective symptoms among occupational low toluene exposed workers. Fukushima J Med Sci 49:129-39.

U.S. EPA. (Environmental Protection Agency). (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Available from: National Technical Information Service (NTIS), Springfield, VA; PB2000-500023, and http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993.

U.S. EPA. (2005). Toxicological review of toluene in support of summary information on the Integrated Risk Information System (IRIS).

Von Euler, M; Pham, TM; Hillefors, M; et al. (2000) Inhalation of low concentrations of toluene induces persistent effects on a learning retention task, beam-walk performance, and cerebrocortical size in the rat. Exp Neurol 163:1-8.

Vrca, A; Bozicevic, D; Karacic, V; et al. (1995) Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch Toxicol 69:337-40.

Vrca, A; Karacic, V; Bozicevic, D; et al. (1996) Brainstem auditory evoked potentials in individuals exposed to long-term low concentrations of toluene. Am J Ind Med 30:62-66.

Vrca, A; Bozicevic, D; Bozikov, V; et al. (1997) Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. Acta Medica Croatica. 51:215-219.

Wood, RW; Rees, DC; Laties, VG. (1983) Behavioral effects of toluene are modulated by stimulus control. Toxicol Appl Pharmacol 68:462-472.

Yin, S; Li, G; Hu, Y; et al. (1987) Symptoms and signs of workers exposed to benzene, toluene or the combination. Ind Health 25:113-130.

Zavalic, M; Mandic, Z; Turk, R; et al. (1998) Quantitative assessment of color vision impairment in workers exposed to toluene. Am J Ind Med 33:297-304.

Zavalic, M; Mandic, Z; Turk, R; et al. (1998b) Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits. Occup Med 48:175-180.

Zavalic, M; Mandic, Z; Turk, R; et al. (1998c) Qualitative color vision impairment in toluene-exposed workers. Int Arch Occup Environ Health 71:194-200.

Zupanic, M; Demes, P; Seeber, A. (2002) Psychomotor performance and subjective symptoms at low level toluene exposure. Occup Environ Med 59:263-268.

APPENDIX B. DESCRIPTION OF LITERATURE SEARCH PROCESS FOR TOLUENE

The IRIS Toxicological Review (U.S. EPA, 2005) contained a thorough review of oral toxicity data on toluene, so searches were limited to studies published since 2004. The search for additional studies of toluene included terms to identify human exposure studies (epidemiologic, occupational) and animal studies for all relevant noncancer endpoints. The search included health effects and toxicity information available from the U.S. EPA (IRIS), ATSDR, and other relevant federal, state, or international governmental or quasi-governmental agencies, including, but not limited to ACGIH, NIOSH, OSHA, NTP, IARC, WHO, and CalEPA. In addition, electronic databases, including CURRENT CONTENTS, MEDLINE, TOXLINE, BIOSIS/TOXCENTER, TSCATS/TSCATS2, CCRIS, DART/ETIC, GENETOX, HSDB, and RTECS, were searched. Results of the electronic searches of these databases are shown in Table B-1. An electronic listing of all results of the gross literature review (including titles, references and abstracts) and a tabular summary of the search results were provided to U.S. EPA.

A toxicologist screened the literature searches based on review of abstracts and titles for studies pertaining to the health effects from subchronic oral exposure to toluene in humans and animals. Decisions about whether to further consider a particular citation were based on the scientific judgment of the toxicologist, based on reading the abstract provided in the literature search output. Studies that were not considered pertinent were not retrieved. Citations may also have been excluded after retrieval and review of the article by the toxicologist. A study may have been excluded if its scope was outside the scope of the use under consideration, if it was not relevant or appropriate, if its study design was inadequate, or if the study showed inadequacy of quality control or flaws in the interpretation of results.

No new pertinent studies were identified.

Table B-1. Summary of Electronic Database Searches for Toluene

Chemical/ CASRN/ 108-88-3	**PUBMED + PubMed cancer subset = replaces CANCERLIT**	**TOXLINE Special (on TOXNET)**	**BIOSIS (STN) update**	**TSCATS 2**	**CCRIS**	**DART/ETIC (not PubMed)**	**GENE-TOX**	**HSDB**	**RTECS**	**Current Contents (file 440 DIALOG) SF=CLIN, LIFE and AGRI) AND NOT dt=contents**
Dates Searched	2004−2007	2004−2007	UP >19991231 AND PY>2003	TSCATS2 only	not date limited	2004−2007	not date limited	not date limited	not date limited	last 6 months (ud=20070101 :20070808)
Toluene 108-88-3	Tox stg used **183** others downloaded—downloaded (**27** for in vitro/genotox* separated out—less relevant) **PLUS** **78** for in process/publisher—and toluene in title only	no new toluene studies	387 cites were found after eliminating PubMed dupes and using TOX stg downloaded only those **199 TITLES** only that were indexed to /animal (including human)	0 received by EPA since 2004	**DO NOT NEED**	**7** but some are not toluene itself	**DO NOT NEED**	**LARGE HSDB record down-loaded health sections only**	**1**	Removed dupes with Medline—no toc records and limited to 3 subfiles **2** titles only downloaded