Toluene External Review Draft (December 2003)
CASRN 108-88-3
00/00/00

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Toluene; CASRN 108-88-3; 00/00/00

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. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Toluene

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/0000
Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Toluene
CASRN – 108-88-3
Last Revised -- 00/00/0000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts.

RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An RfD of 0.2 mg/kg-day was previously entered on the IRIS data base in 1990. This value was based on a NOAEL of 223 mg/kg-day for increased relative liver and kidney weights in rats identified by a 13 week NTP gavage study (NTP, 1990). A total uncertainty factor of 1000 was used to account for a combination of inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data. The change in the value of the RfD from the previous IRIS assessment is due primarily to the use of newer methodologies.

___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	1000	0.2 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)

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). Technical Report Series No. 371. Research Triangle Park, NC.

NTP (1990) exposed both sexes of F344 rats and both sexes of B6C3F1 mice to gavage doses of 0, 223, 446, 900, 1800, or 3600 mg/kg-day (duration adjusted) for 5 days/week 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 liver weights were 100, 108, 113, 138, and 135 percent of controls; relative liver weights were 100, 104, 108, 135, and 178 percent of controls; absolute kidney weights were 100, 107, 112, 119, and 113 percent of controls; relative kidney weights were 100, 100, 106, 114, and 146 percent of controls for 0, 223, 446, 900, or

1800 mg/kg-day. 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. 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 (hemorrhages in the two highest dose groups). Liver effects in B6C3F1 mice were less clear, with relative liver weights significantly increased in all treated groups of female mice, but significant increases in absolute weight were evident only at the 223 and 1800 mg/kg-day dose groups. No other significant changes were seen in mice exposed to less than 1250 mg/kg.

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. Only one subchronic study examining oral exposure to toluene in rodents (rats and mice) is available. This study (NTP, 1990) was chosen as the principal study. The critical effect is increased kidney weight. The choice of increased kidney weight as a critical effect is supported by several acute oral and inhalation toxicity studies indicating renal tubule toxicity. A concentration-dependent nephropathy was seen in chronic inhalation cancer bioassays (NTP, 1990; Huff, 2003). One case report following lethal oral exposure to 625 mg/kg (Ameno et al., 1989) noted acute tubular necrosis and acidosis was reported in a nonlethal case report of thinner ingestion (Cavarti and Bjerk, 1997). 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 (Kroege 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 glomerularnephritis 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 RfD was derived by the benchmark dose approach (BDS. Version 1.3). The benchmark response (BMR) was defined as the default of a change of one standard deviation (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 complete 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. This corresponds to a 9% response level (i.e., increase in kidney weight from control). Details of the model results are presented in Appendix B of the Toxicological Review.

___I.A.3. UNCERTAINTY FACTORS (ORAL RfD)

UF = 1000.

A 10-fold uncertainty factor 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.

A 10-fold uncertainty factor for intraspecies differences (UF_H) was used to account for potentially sensitive human subpopulations. This UF was not reduced because of the lack of human oral exposure information.

A 10-fold uncertainty factor was used to account for extrapolating from less than chronic results on experimental animals (UF_s).

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

An oral subchronic study in two species and several immunotoxicity studies are available. A number of studies by both the oral and inhalation routes have demonstrated that toluene does not elicit developmental or reproductive effects except at doses that are significantly higher than those that cause other systemic effects (see Section 4.3 of the Toxicological Review for details). The available 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). Finally, a 2-generation inhalation toxicity study is available which lends support to the oral database in that effects are noted only at high concentrations. For these reasons a data base UF was not needed.

___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 evaluated for use as the principal study. Changes in thymus weight in the Hsieh et al. (1989) study was not considered an adverse effect since no change was observed in a later studies by Hsieh et al. (1990) and Burns et al. (1994). In addition, Luster et al. (1992) have indicated that thymus weights may not be predictive of immunotoxic potential based on an evaluation of studies conducted by NTP.

Additional effects on immunological endpoints were considered as potential critical effects. 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 antibody-forming cell assay (PFC) 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 [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, the host resistance assays by Burns et al. (1994) indicate a lack of immunotoxic response when animals treated with toluene are challenged. Host resistance to challenges with *Listeria monocyogenes*, *Streptococcus pneumoniae*, *Plasmodium yoelii*, or B16F10 melanoma were 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. For these reasons, immunotoxic endpoints are not considered critical effects.

Additional studies by Hsieh et al. (1990a, c, 1991) found statistically significant increases in 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. 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.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Low
Data Base -- Medium
RfD -- Low

Confidence in the principal study is low due to a lack of potential endpoints examined. Confidence in the data base is rated medium due to the lack of human and chronic animal data via the oral route of exposure. There is low confidence in the resulting RfD.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document – U.S. EPA. (2003) Toxicological review of toluene in support of summary information on the Integrated Risk Information System.

This assessment was peer reviewed by external scientists (August 2002). Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2003.

Other EPA Documentation -- none.

Agency Consensus Date -- __/__/__

___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@epamail.epa.gov (email address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

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Last Revised -- 00/00/0000

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An RfC of 0.4 mg/m^3 was previously entered on the IRIS data base in 1992. This value was based on the LOAEL of 88 ppm (332 mg/m^3) for decreased performance in neurological tests identified by the study of Foo et al. (1990). This LOAEL was adjusted to a continuous exposure level of 119 mg/m^3, and a total uncertainty factor of 300 (10 for use of a LOAEL, 10 for intrahuman variability, and 3 for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation) was applied. The current RfC is based on a newer study and uses BMD modeling for the derivation of the point of departure.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	RfC
Alterations in color vision in occupationally-exposed workers	BMCL: 99 ppm (374 mg/m^3) BMCL (ADJ): 130 mg/m^3 BMC: 500 mg/m^3	10	10 mg/m^3

Zavalic et al., 1998

*Conversion Factors and Assumptions -- Assuming 25°C and 760 mmHg, BMCL (mg/m^3) = 99 ppm x 92.15/24.45 = 374 mg/m^3. This is an extrarespiratory effect of a soluble vapor. The BMCL is based on an 8-hour TWA occupational exposure. MVho = 10 m^3/day, MVh = 20 m^3/day. BMCL (HEC) = BMCL (ADJ) = 374 x MVho/MVh x 5 days/7 days = 130 mg/m^3.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

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

Zavalic et al. (1998) examined two groups of Croatian workers occupationally exposed to toluene for effects on color vision relative to a group of unexposed controls. The first exposed group (group E1) consisted of 46 workers (3 men, 43 women) employed gluing shoe soles, while the second group (group E2) consisted of 37 workers (34 men, 3 women) employed in a rotogravure printing press. Mean exposure times were 16.21 ±6.1 (mean ±SD) years for group E1 and 18.34 ±6.03 years for group E2. The control group consisted of 90 workers (61 men, 29 women) who were not occupationally exposed to solvents. For all groups, smoking and alcohol consumption information was collected. Air sampling tubes were fixed onto the work tables or machines at nose height. Air was collected continually throughout the workday. Samples of air were collected at work stations in both the shoe factory and printing press for analysis of airborne toluene concentrations; median concentrations were 32 ppm (121 mg/m^3; range of 11.3-49.3 ppm) for group E1 and 132 ppm (498 mg/m^3; range of 66-250 ppm) for group E2. Samples of venous blood were taken in all three groups on Wednesday before the work shift, and toluene concentrations were determined. Urine samples were taken Wednesday after the work shift and analyzed for *ortho*-cresol and hippuric acid. Samples were taken in the middle of the work week because WHO (1985) determined that, in the case of toluene exposure where low body accumulation occurs, this sampling period gives the best approximation of exposure.

Analysis of color vision was performed using the Lanthony D-15 desaturated panel, which is based on the ability to recombine a set of 15 desaturated color caps according to a definite chromatic sequence. The Lanthony D-15 test was designed to measure small changes in color discrimation and has been used to monitor color vision changes which accompany disease progression or environmental chemical exposure (Iregren et al., 2002; Gobba and Cavalleri, 2003). This test differs from other color

vision tests by its hue saturation and brightness. The colors are pastel (chromal saturation 2 on a scale of 0-14) and bright (value 8 on a scale of 0-10). Its sensitivity for acquired dyschromatopsia is explained by the observation that the first phases of color vision impairment manifest as paling of colors (Lanthony, 1984). The use of pale colors in the panel, contrary to the saturated version, permits the detection of early phases of trichromatic abnormalities.

Subjects who wore spectacles or contact lenses used them. The test was applied for each eye separately. The score index for both eyes was calculated according to a formula developed by Bowman (1982). Color vision was tested on Wednesday morning before the work shift, at least 16 hours after the last exposure to toluene, and on Monday, at least 64 hours after the last exposure to toluene, both in natural sunlight. Results are reported as the color confusion index (CCI) or age- and alcohol intake-adjusted color confusion index (AACCI). The CCI was calculated by dividing the results by an ideal or correct score. AACCI was calculated on the basis of age and alcohol intake influence on CCI in the nonexposed group. Deviation from the ideal score depended on the order in which each subject arranged the caps.

In the high-exposure group (group E2), there were statistically significant correlations between toluene in air (132 ppm with a range of 66 - 250 ppm) and toluene in blood (0.0042 µg/mg with a range of 0.0021 - 0.9422), *ortho*-cresol in urine (0.97 mg/g creatinine with a range of 0.26 - 4.01), and hippuric acid (1.872 g/g creatinine with a range of 0.322 - 2.875) in urine. Correlation between toluene in air and blood for group E1 was positive, but was not statistically significant. CCI scores on both Wednesday and Monday were significantly higher in group E2 (1.29 $\pm$ 0.10 [mean ±SD] and 1.30 $\pm$ 0.11, respectively) relative to both controls (1.15 $\pm$ 0.10 and 1.14 $\pm$ 0.10, respectively) and to group E1 (1.17 $\pm$ 0.08 and 1.18 $\pm$ 0.10, respectively). CCI scores for group E1 were not significantly different from controls at any time examined. In all groups, including controls, a statistically significant correlation between CCI and both age and alcohol consumption was reported. CCI scores for those workers who consumed no alcoholic beverages at all were significantly greater for group E1 (1.17 $\pm$ 0.08 and 1.17 $\pm$ 0.08, respectively) than for non-consumers in the control group (1.13 $\pm$ 0.08 and 1.13 $\pm$ 0.09, respectively); however, age-matching of these two subgroups was not reported. Given the dependence on age and alcohol intake, the AACCI scores are considered more relevant indicators of toluene exposure than CCI scores. AACCI scores for group E2 were significantly correlated with toluene in blood, toluene in air, *ortho*-cresol in urine, and hippuric acid in urine. No statistically significant correlation was established between AACCI scores and any marker of toluene exposure for group E1. The AACCI scores were significantly higher ($p<0.05$) for group E2, but not group E1, compared to controls. Actual data points (or mean ±SD) for AACCI scores were not reported. The results were presented graphically. However, the mean ±SD AACCI scores were obtained from the author and are included in Appendix C (Table C-1) of the Toxicological Review. This study identified a NOAEL of 32 ppm (121 mg/m^3; group E1) and a LOAEL of 132 ppm (498 mg/m^3; group E2) for alterations in color vision in toluene-exposed workers based on AACCI scores.

A number of occupational and animal studies are available which examine the effects of toluene exposure by the inhalation route. The Zavalic et al. (1998) study was chosen as the principal study. Altered color vision is the critical effect. Numerous studies have identified NOAELs in the range of 25-

50 ppm toluene (Cavalleri et al, 2000; Eller et al., 1999; Nakatsuka et al., 1992; Schaper et al., 2003; Stengel et al., 1998; Zavalic et al., 1998; Zupanic et al., 1992). These studies were designed to measure effects on subjective symptoms (e.g., headache, dizziness), color vision, neurological and psychomotor functioning, hearing, and immune function. Other studies have shown statistically significant effects in workers on subjective symptoms, auditory evoked brain potentials, neurobehavioral parameters, neurological functioning, electrophysiological cardiac parameters, and color vision in the range of 83-132 ppm toluene (Abbate et al., 1993; Boey et al., 1997; Eller et al., 1999; Foo et al., 1990; Murata et al., 1993; Zavalic et al., 1998). Conversely, one study found no neurotoxic effects at toluene levels of 68-185 ppm (Antti-Poika et al., 1985), whereas Campagna et al. (2001) found statistically significant effects on color vision in workers exposed to 8 and 36 ppm toluene. In addition, Vrca et al., (1995, 1997) and Yin et al. (1987) found subjective symptoms and alterations in visual- and auditory-evoked brain potentials in workers exposed to 40-60 ppm toluene.

Some of the available studies are confounded by known co-exposure to other contaminants (Nakatsuka et al., 1992; Yin et al., 1987) or inadequate exposure information (i.e., no duration of exposure reported or no direct air sampling) (Antti-Poika et al., 1985; Murata et al., 1993; Nakatsuka et al., 1992; Vrca et al., 1995, 1997) and were not considered further for the principal study. Several studies (Boey et al., 1997; Cavalleri at al., 2000) were of short exposure (5-9 years) duration and were not considered further since there are other studies available of chronic duration which would be more suitable for the derivation of an RfC. A number of studies did not identify an adverse effect (Antti-Poika et al., 1985; Cavalleri et al., 2000; Nakatsuka et al., 1992; Schaper et al., 2003; Stengel et al., 1998; Zupanic et al., 2002), thus making them unsuitable for the principal study when other more suitable studies are available.

The Zavalic et al. (1998) study is an adequate cross-sectional study of chronically-exposed humans. The study utilized two exposed groups and conducted measurements of color vision on Mondays and Wednesdays providing some evidence that the effects were persistent at least over the 64 hour weekend period. Impaired color vision is the critical effect in this study. Effects were correlated with both airborne and blood toluene concentrations. The study of Eller et al. (1999) defined a similar NOAEL (25 to 32 ppm) as that found in the Zavalic et al. (1998) study for decreased performance in neurobehavioral and neuropsychological tests, but the effect levels, exposure durations and exposure levels in this study were less clearly characterized. The Campagna et al. (2001) study shows statistically significant effects on color vision at estimated exposure levels of 8 and 36 ppm toluene. Similar studies of color vision impairment (Cavalleri et al., 2000; Nakatsuka et al., 1992; Zavalic et al., 1998) all found no statistically significant effects at higher doses (30-40 ppm). In addition, the Campagna et al. (2001) study did not measure exposure via blood levels of toluene, whereas the Zavalic et al. (1998a) study found correlations between between color vision impairment, airborne toluene levels and blood toluene levels. While the Foo et al. (1990) study was selected as the principal study for the previous RfC derivation, it contains a single exposure group and a shorter exposure period (i.e., 5.7 ±3.2 years) making it less suitable than the Zavalic et al. (1998a) study which contains two exposure groups and a longer exposure duration. Thus, given the weight of evidence of exposure ranges, observed effects among the available studies and the confounders discussed above, the Zavalic et al. (1998a) study was chosen as the principal study.

The RfC was derived by the benchmark dose approach (BDS. Version 1.3). Benchmark analysis was performed for decreases in the color confusion index as adjusted for age and alcohol consumption (Zavalic et al., 1998). The benchmark response (BMR) was calculated for various increments of standard deviations from the control mean. The upper 98th percentile of the control distribution was taken to describe an upper limit of "normal" values. Details of the model results are presented in Appendix C of the Toxicological Review. In the absence of information on the level of response to consider adverse, a change in the mean equal to one standard deviation from the control mean was used according to the U.S. EPA Benchmark Dose Guidance (U.S. EPA, 2000). A BMCL of 99 ppm (374 mg/m^3) was derived and used as the point of departure. This concentration corresponds to an anticipated 13 percent extra population risk (see Appendix C of the Toxicological Review). Thus, 13 percent of the population exposed at the BMCL would be expected to exceed the 98th percentile of the control distribution of adjusted scores, assuming the data are normally distributed and that the fitted model is plausible.

___I.B.3. UNCERTAINTY FACTORS (INHALATION RfC)

UF = 10

A total uncertainty factor of 10 was applied to this effect level, i.e., 10 for consideration of intraspecies variation (UF_H; human variability).

A 10-fold uncertainty factor for intraspecies differences (UF_H) was used to account for potentially susceptible human subpopulations. Pelekis et al. (2001) have developed a model employing pharmacokinetic information to derive a chemical-specific intraspecies UF for toluene. The result of the effort is an informed quantitation of "normal" human-to-human and adult-to-child variability. The Pelekis model is based solely on the pharmacokinetic differences between adults and children. In the case of intraspecies variability, the differences in humans may be due to lifestage (childhood versus advanced age), genetic polymorphisms, decreased renal clearance in disease states, unknown pharmacodynamic variations in response to toluene exposure, etc. It is not clear that the variability defined in the Pelekis model accounts for the differences in pharmacokinetics and pharmacodynamics of these various human states.

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 was not necessary (UF_s). Workers were chronically exposed to toluene for a mean duration of 16 - 18 years in the Zavalic et al. (1998a) study.

An uncertainty factor was not needed to account for extrapolating from a LOAEL to a NOAEL because NOAEL/LOAEL methodology was not used in the derivation of the point of departure.

The data base 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 and 2-generation inhalation toxicity studies are available.

___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

There is a growing body of literature indicating that chronic exposure to a variety of volatile organic solvents including toluene, styrene, perchloroethylene and carbon disulfide is associated with subtle deficits in visual perception measured either as deficits in color vision or deficits in visual contrast sensitivity (for reviews see Gobba, 2000; Iregren et al., 2002). Occupation-related color vision impairment, like other acquired dyschromatopsias, usually results in impairment of blue-yellow color discrimination or, less frequently, in a combination of blue-yellow and red-green loss. Congenital dyschromatopsias more frequently result in red-green deficits (Hart, 1987, 1992; Mergler et al., 1987, Gobba and Cavalleri, 2003). The mode of action of color vision loss induced by solvents is not known. However, according to "Koller's rule" the impairment of blue-yellow discrimination suggests a retinal location of the effect (Hart, 1992). One possible mechanism may be related to a direct effect of solvents (or metabolites) on cone function (e.g., membrane metabolism), or to an interference with neurotransmitters (like dopamine) (see Gellar and Hudnell, 1997 for a review). Alternatively, color vision loss may be the result of a distal axonopathy of the optic pathway, as suggested by Shaumberg and Spencer (1978) for n-hexane.

Additional ocular effects from toluene exposure have been noted. Visual-evoked potentials have been shown to be altered in printing press workers chronically exposed to high levels (Urban and Lukas, 1990) as well as lower concentrations of toluene (Vrca et al., 1995,1997). Optic neuropathies with dyschromatopsia, blindness, changes in pattern visual-evoked potentials, pendular nystagmus, ocular flutter, opsoclonus, bilateral internuclear ophthalmoplegia and retinal impairment have also been reported in participants who chronically sniffed toluene or toluene-based glue (Hormes et al., 1986; Hunnewell and Miller, 1998; Kiyokawa et al., 1999; Lazar et al., 1983; Poblano et al., 1996; Sasa et al., 1978; Toyonaga et al., 1989; Ehyai and Freemon, 1983).

Impairment of color vision may also be an indicator of additional neurological effects [see Dick et al., 2000; Mergler et al., 1987]. Toluene abusers who have been exposed for long periods of time exhibit a variety of neurologic manifestations, including ataxia, tremor, anosmia, sensorineural hearing loss, dementia, corticospinal tract dysfunction, abnormal brainstem auditory-evoked potentials, and epileptic seizures (Hormes et al., 1986; Lazar et al., 1983; Sasa et al., 1978; Ron, 1986). Abnormal magnetic resonance imaging findings in toluene abusers include generalized cerebral, cerebellar, and brainstem atrophy, atrophy of the corpus callosum, loss of gray-white matter discrimination, multifocal high signal intensity in the cerebral white matter, and hypointensity of the thalami on T2-weighted images (Xiong et al., 1993; Rosenberg et al., 1988a, b). Dick et al. (2000) suggested that color vision loss may be part of a neurological syndrome related to organic solvent exposure, also including coarse tremor, impaired vibration sensation in the legs and cognitive impairment.

A number of animal studies have examined the neurological effects of inhaled toluene; these studies generally reported impaired response 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. 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) or brainstem auditory-evoked responses (elicited by tone pips of differing loudness and frequency and detected by subdural scalp electrodes). Hearing loss, as measured by both techniques, was observed after as few as 2 weeks 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 data base was also 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 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. 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, impaired color vision alone was selected as the critical endpoint in this assessment.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- High
RfC -- Medium

Confidence in the principal study is medium. The Zavalic et al. (1998) study is an adequate cross-sectional study in chronically-exposed humans that examined appropriate endpoints of concern at multiple exposure levels. However, only one effect level was identified, thus limiting the study's ability to describe the exposure-response relationship. Confidence in the database is high. Many chronic studies in humans exist which identify neurological alterations as a sensitive effect of long-term repeated toluene exposure at concentrations in the range of 40-150 ppm. 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. There is medium confidence in the resulting RfC.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document – U.S. EPA. (2003) Toxicological review of toluene in support of summary information on the Integrated Risk Information System.

This assessment was peer reviewed by external scientists (August 2002). Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2003.

Other EPA Documentation -- none.

Agency Consensus Date -- __/__/__

___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@epamail.epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Toluene
CASRN -- 108-88-3
Last Revised -- 00/00/0000

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July. Risk Assessment Forum. http://www.epa.gov/ncea/raf/cancer.htm). The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per µg/L drinking water or

per µg/cu.m air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

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

___II.A.2. HUMAN CARCINOGENICITY DATA

Available studies in toluene-exposed workers have reported very limited or no evidence suggesting carcinogenic effects of toluene exposure (Antilla et al., 1998; Svennson et al., 1990; Wiebelt and Becker, 1999). A cohort mortality study in toluene-exposed workers (Wiebelt and Becker, 1999) did not report an increase in cancer-specific mortality for the entire cohort. A subcohort of highly-exposed workers demonstrated statistically significant increases in mortality from cancers of the bone and connective tissue, but lack of exposure characterization, co-exposure information, and categorization of and adjustment for other confounding factors (age, smoking, etc.) within the subcohort precludes drawing conclusions from these results as to the possible association between toluene exposure and cancer risk. Svennson et al. (1990) similarly did not report increased cancer-specific mortality among rotogravure printers. While an increase in tumors of the respiratory tract was reported, this increase was not statistically significant when only subjects with exposure periods of five years or more were examined, and no dose-response relationships were present for tumor incidence. Antilla et al. (1998) carried out a retrospective cohort analysis of 5301 workers monitored for biological markers of occupational exposure to styrene, toluene, or xylene; no significantly increased incidence rates of cancer could be associated with toluene exposure. Other studies examining the carcinogenicity of toluene in occupationally-exposed humans have failed to adequately account for co-exposure to other compounds.

___II.A.3. ANIMAL CARCINOGENICITY DATA

NTP (1990; Huff, 2003) has conducted a 2-year inhalation carcinogenicity study in F344 rats and B6C3F1 mice, and found no evidence for carcinogenicity in either sex of either species at exposure levels up to 1200 ppm. Another inhalation carcinogenicity study in F344 rats (CIIT, 1980; Gibson and Hardisty, 1983) likewise reported no evidence for carcinogenic effects of toluene at exposure levels up to 300 ppm. A lifetime carcinogenicity study in Sprague-Dawley rats by the oral route (Maltoni et al., 1997) was suggestive of potential carcinogenic effects of toluene, but the dose-response relationships were not well defined (i.e., the 500-mg/kg animals had considerably more tumors than those in the 800-mg/kg group) and study details were inadequately reported.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Available studies examining the genotoxic effects of toluene have generally reported negative results. Toluene was found to be nonmutagenic in reverse mutation assays with *S. typhimurium* (Mortelmans and Riccio, 1980; Nestmann et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981; Connor et al., 1985; Nakamura et al., 1987; NTP, 1990) and *E. coli* (Fluck et al., 1976; Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in *S. cerevisiae*. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Lyapkalo, 1973; Dobrokhotov and Einkeev, 1977) report toluene as effective in causing chromosomal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Forni et al., 1971; Maki-Paakkanen et al., 1980), although a slight increase was noted in workers co-exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This finding is supported by studies of cultured human lymphocytes exposed to toluene *in vitro*; no elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner-Smidt and Friedrich, 1978).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

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

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

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

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document – US EPA. (2003) Toxicological review of toluene in support of summary information on the Integrated Risk Information System.

This assessment was peer reviewed by external scientists (August 2002). Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA (2003).

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

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

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

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CASRN – 108-88-3
Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

Toluene
CASRN – 108-88-3

Date	Section	Description
03/01/1988	I.A.4.	Text revised
09/07/1988	II.	Carcinogen summary on-line
02/01/1989	II.D.3.	Secondary contact's phone number corrected
07/01/1989	I.B.	Inhalation RfD now under review
03/01/1990	VI.	Bibliography on-line
04/01/1990	VI.C.	Combs et al., 1973 citation corrected
06/01/1990	IV.A.1.	Area code for EPA contact corrected
06/01/1990	IV.F.1.	EPA contact changed
07/01/1990	I.A.	Withdrawn; new RfD verified (in preparation)
07/01/1990	VI.A.	Oral RfD references withdrawn
08/01/1990	I.A.	Oral RfD summary replaced; RfD changed
08/01/1990	II.	Text edited
08/01/1990	VI.A.	Oral RfD references revised
09/01/1990	III.A.	Health Advisory on-line
09/01/1990	VI.D.	Health Advisory references added
08/01/1991	VI.C.	Litton Bionetics, Inc., 1981 reference title clarified
01/01/1992	IV.	Regulatory actions updated
04/01/1992	IV.A.1.	CAA regulatory action withdrawn
08/01/1992	I.B.	Inhalation RfC on-line
08/01/1992	VI.B.	Inhalation references on-line

02/01/1994	II.D.3.	Secondary contact's phone number changed
04/01/1994	I.A.7.	Primary contact changed
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
__/__/____	I., II., VI.	New RfD, RfC, and cancer assessment

_VIII. SYNONYMS

Toluene
CASRN – 108-88-3
Last Revised -- __/__/__

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