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

Substance code
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 __/__/__

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	Online	
Inhalation RfC Assessment (I.B.)	Online	
Carcinogenicity Assessment (II.)	Online	

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

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

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, 1990a). A total uncertainty factor of 1000 was used to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data. Individual uncertainty factors were not identified. Two studies by Hsieh et al. (1989, 1990) discussed in the reassessment below were not discussed in the previous assessment of the RfD for toluene.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Immunological effects: decreased thymus weights 4-week drinking water study in mice Hsieh et al., 1989	BMDL: 41 mg/kg-day BMD: 66 mg/kg-day	1000	1	0.04 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 subchronic or chronic 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 key study for an RfD.

Two subchronic studies examining oral exposure to toluene in rodents exist. Hsieh et al. (1989) exposed groups of male CD-1 mice (five animals/group) to 0, 17, 80, or 405 mg toluene/liter of drinking water for 4 weeks. Based on body weight and water consumption data, the authors calculated average daily toluene doses of 0, 5, 22, or 105 mg/kg-day, respectively. Animals were weighed once per week, and food and water consumption were monitored continuously. Water toluene concentration was determined daily, and fresh solutions were made every three days. After 28 days, the animals were sacrificed, and body, spleen, thymus, liver, and kidney weights were determined. Gross pathological examinations were performed on all mice.

Total erythrocytes and leukocytes were determined, and differential leukocyte counts were measured. Splenocyte suspensions were prepared, and the lymphoproliferative responses to the T-cell mitogens phytohemagglutinin (PHA) and concanavalin A (Con A), the B-cell mitogen *E. coli* lipopolysaccharide (LPS), and the combined mitogen pokeweed mitogen (PWM) were measured. Separate groups of animals were similarly exposed, and were sensitized by intraperitoneal injection of sheep red blood cells (SRBC) 4 days before the end of toluene exposure. The titer of anti-SRBC antibody in the serum collected was used in the plaque-forming colony (PFC) assay. Toluene exposure did not result in increased mortality or clinical signs in any exposed group. No significant changes in food or water consumption were noted, and no gross lesions of the liver, kidney, spleen, heart, thymus, lung, or brain were seen in any treatment group. No changes in body weight (mean ±SE) were seen as a result of toluene exposure. Relative liver weights of toluene-exposed rats were significantly increased (5.67 ±0.07, 6.09 ±0.11, 6.32 ±0.17, and 6.73 ±0.14 g/100 g body weight for 0, 5, 22, and 105 mg/kg-day treatment groups, respectively) and relative thymus weights (mean ±SE) were significantly decreased (0.019 ±0.02, 0.18 ±0.01, 0.18 ±0.02, and 0.13 ±0.02 g /100 g body weight for 0, 5, 22, and 105 mg/kg-day treatment groups, respectively) at 105 mg/kg-day compared to controls, but not at lower doses. The changes in organ weights at the highest dose correspond to a 19% increase in liver weight and a 32% decrease in thymus weight relative to controls. No changes were found in relative spleen and kidney weights at any dose. No significant changes in hematological parameters or spleen cellularity were reported. Splenocyte cultures from animals in all treated groups showed significant reductions in proliferative response, measured by [^{3}H]TdR uptake, when cultured in the absence of mitogen, or in response to PWM. At the highest two dose levels, the proliferative response was also significantly decreased in response to LPS, PHA, and Con A. The biological significance of these effects is unknown. PFC response (both PFC/10^6 spleen cells and PFC/spleen) to SRBC was significantly reduced (46% and 63%, respectively) following exposure to 105 mg/kg-day. The 105 mg/kg-day dose group represents a LOAEL for this study for increased relative liver weight, decreased relative thymus weight, and immunological effects [reduced PFC response (>40%) to SRBC]; the NOAEL is 22 mg/kg-day.

The oral toxicity of toluene was also investigated in a subchronic gavage study in F344 rats (NTP, 1990a). 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. All animals receiving 5000 mg/kg died within the first week. One female and 8 males in the 2500 mg/kg group 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 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ($p<0.05$) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ($p<0.05$) in SGOT in 2500 mg/kg males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ($p<0.05$) at doses greater than or equal to 625 mg/kg. In females, absolute and relative

weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ($p<0.01$ for all comparisons except $p<0.05$ for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL in rats for this study is 223 mg/kg-day (312 mg/kg) based on liver and kidney weight changes in male rats at 446 mg/kg-day (625 mg/kg). The toxicologic significance of these organ weight changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses. Because the exposure was for 5 days/week, the dose is adjusted (e.g., 312 x 5/7 = 223 mg/kg-day).

NTP (1990) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 (4 males, 4 females) receiving 2500 mg/kg also died. Clinical signs seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ($p<0.05$) lower than controls; no significant changes in body weights were seen in female mice. In male mice, absolute kidney weight, but not relative kidney weight, was decreased in the 2500 mg/kg group. Relative brain and liver weights were increased and relative right testis weight was decreased in animals exposed to 1250 mg/kg-day or greater; the absolute weights for these organs were not significantly different from controls. In female mice, absolute liver weights were increased in the 312 and 2500 mg/kg groups, but not in the other treated groups; relative liver weights were increased in all treated groups. No other changes in organ weights were seen in female mice. Several small but statistically significant changes occurred in hematologic parameters, but did not appear to be related to toluene exposure. No histologic changes in the liver, brain, kidneys, or bladder of any group were reported.

Despite its shorter duration and examination of only one sex of animals, the Hsieh et al. (1989) study was selected as the principal study for derivation of the RfD. Decreased thymus weight (32% decrease compared to controls) and decreased antibody response (>40%) were observed in the Hsieh et al. (1989) study at a dose of 105 mg/kg-day. The biological relevance of immunological effects bioassays is difficult to gauge and is the subject of some debate (Luster et al. 1992). However, given that thymus weight and antibody response was significantly decreased, coupled with the observed effects on host defenses following inhalation exposure (Aranyi et al., 1985), immunological effects were identified as the primary effect with decreased thymus weight as the critical effect. Decreased antibody response was not chosen as the critical effect due to a lack of confidence that the dose-response relationship is representative of chemical-induced immunological effects. Both the NTP (1990) and Hsieh et al. (1989) studies identified NOAEL and LOAEL values for altered relative liver weight, but the LOAEL of 105 mg/kg-day and NOAEL of 22 mg/kg-day identified by Hsieh et al. (1989) is lower than the NOAEL of 223 mg/kg-day defined by NTP (1990). However, the changes in liver weight were not correlated

with any histological or anatomical alterations, thus this endpoint is not considered a critical effect.

An additional factor that supports the use of the Hsieh et al. (1989) study is that the method of oral exposure, i.e., ingestion via drinking water, is considered preferable to exposure via gavage that was utilized in the NTP (1990) study. For these reasons, and because data are inadequate to determine which species (rat or mouse) or which mouse strain (B6C3F1 or CD-1) is a more appropriate model for oral toluene toxicity in humans, the study with the most conservative (i.e., health protective) NOAEL, that from Hsieh et al. (1989), was selected for derivation of the RfD.

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, 2000d). Benchmark analysis was performed for thymus weight changes as an indicator of potential immunological effects. A BMDL of 41 mg/kg-day was derived and used as the point of departure. Details of the model results are presented in Appendix B of the Toxicological Review.

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

UF – 1000.

A total uncertainty factor of 1000 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), and 10 for use of a subchronic study to estimate chronic effects (UF_S; duration of exposure). The total UF = 10 x 10 x 10 = 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; there is a lack of human oral exposure data.

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 when there are no useful long-term human data (UF_S).

An uncertainty factor was not needed to account for extrapolating from a LOAEL to a NOAEL because a NOAEL was available.

Because 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, an additional database

uncertainty factor was not deemed necessary. In addition, a 2-generation inhalation toxicity study is available which lends support to the oral database.

MF – 1.

An additional modifying factor was not necessary.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

In a later study, Hsieh et al. (1990) exposed groups of male CD-1 mice for 28 days as described above. At the end of the exposure, six discrete brain sections of the animals were tested for endogenous levels of norepinephrine (NE), dopamine (DA), and serotonin (5-HT), as well as their primary metabolites. No changes in body weight or clinical signs were observed. Toluene exposure induced increases in all of the biogenic amines examined at all dose levels, with the response generally peaking in the mid-dose group and decreasing in the high-dose group. Significant increases of norepinephrine and its metabolite, 3-methoxy-4-hydroxymandelic acid, were found in the midbrain of all dose groups. Significant increases in serotonin levels, but not its metabolite (5-hydroxyindoleacetic acid), were also seen in the midbrain of all dose groups. The unknown implications of changes in neurotransmitter levels, differences in the effects seen in various brain sections, and the biphasic dose-response make determinations of biological significance difficult. A NOEL of 5 mg/kg-day was identified.

Wolf et al. (1956) administered groups of 10 female Wistar rats gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg-day. Hematologic, behavioral, gross, and histopathologic examinations were conducted with no toxic effects being reported at any dose. A NOEL of 84 mg/kg-day was identified.

___I.A.5. CONFIDENCE IN THE ORAL RfD

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

Confidence in the principal study is low, because while the study examined what appears to be the most sensitive endpoint, the study was of only 28 day duration and in a single species and sex. Confidence in the data base is rated medium due to the lack of chronic animal data and uncertainties regarding potential discrepancies between the NTP 13 week study and the Hsieh 28 day study. There is low confidence in the resulting RfD.

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

Source Document – US EPA. (2002) Toxicological review of toluene in support of summary information on the Integrated Risk Information System (IRIS).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as appendix – _____.

Other EPA Documentation -- _____

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 (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris@epamail.epa.gov (email address).

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

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

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. While the Foo et al. (1990) study was selected as the key study for the previous RfC derivation, a number of other studies provided evidence that neurological alterations would occur at toluene concentrations at or near the 88 ppm LOAEL. In addition, the Foo et al. (1990) study does not address co-exposure to other solvents and workers were exposed for a shorter period of time (i.e., 5.7 ±3.2 years).

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Alterations in color vision in occupationally-exposed workers Zavalic et al., 1998	NOAEL: 32 ppm (121 mg/m^3) NOAEL(ADJ): 43 mg/m^3 NOAEL(HEC): 43 mg/m^3 LOAEL: 132 ppm (498 mg/m^3) LOAEL(ADJ): 178 mg/m^3 LOAEL(HEC): 178 mg/m^3	10	1	4 mg/m^3

*Conversion Factors and Assumptions -- Assuming 25^{o}C and 760 mmHg, NOAEL (mg/m^3) = 32 ppm x 92.15/24.45 = 121 mg/m^3. This is an extrarespiratory effect of a soluble vapor. The NOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 m^3/day, MVh = 20 m^3/day. NOAEL(HEC) = NOAEL(ADJ) = 121 x MVho/MVh x 5 days/7 days = 43 mg/m^3. Similarly the LOAEL of 132 results in a LOAEL(ADJ) of 178 mg/m^3.

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

A substantial data base examining the effects of toluene in chronically-exposed humans exists. These studies have identified neurologic effects (i.e., impaired color vision, impaired hearing, decreased performance in neurobehavioral analysis, headache, dizziness) as the most sensitive endpoints, though in many cases, it cannot be determined whether these effects are transient, persistent, or contain both transient and persistent components. Animal studies (NTP, 1990a) have also suggested respiratory irritation as a sensitive effect, but this effect in humans appears to occur only at higher exposure concentrations than those resulting in neurologic effects.

Two studies (Zavalic et al., 1998a; Eller et al., 1999) have identified no-effect levels in occupationally-exposed humans. Eller et al. (1999) reported no neurobehavioral effects in workers exposed to 25 to 32 ppm toluene for 1 to 12 years, while workers exposed to greater concentrations ($\geq$ 100 ppm) showed statistically significant neurologic impairment. Zavalic et al. (1998a) reported a NOAEL of 32 ppm and a LOAEL of 132 ppm for alterations in color vision in exposed workers. A number of additional studies (see Table 1), however, have identified effect levels for neurologic endpoints in exposed humans at levels between 40 and 100 ppm. The available studies each have a number of limitations. However, when considered jointly, these studies indicate that humans repeatedly exposed to toluene concentrations ranging from 40 to 132 ppm have an increased risk of developing neurologic effects.

Zavalic et al. (1998a) 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. 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. Analysis of color vision was performed using the Lanthony 15 Hue desaturated panel, which is based on the ability to recombine a set of 15 desaturated color caps according to a definite chromatic sequence. Results are reported as the color confusion index (CCI) or age- and alcohol intake-adjusted color confusion index (AACCI). 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.

In the high-exposure group (group E2), there were 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 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 ($p<0.05$) 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. 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.

Further analysis of color vision loss in the same groups of workers described above (Zavalic et al. 1998a) was carried out to compare loss in the blue-yellow and red-green ranges (Zavalic et al. 1998b). Both blue-yellow and red-green color confusion were significantly increased in printers, but there was no significant difference in the prevalence of either type of color confusion between exposed and unexposed workers.

Color vision impairment was also evaluated in another group of 45 male workers exposed to mean concentrations of about 120 ppm toluene (Zavalic et al. 1998c). Color vision, assessed by the age and alcohol intake adjusted color confusion score (AACDS), was significantly impaired in exposed workers compared with unexposed controls. Statistically significant correlations were noted between impaired color vision and air toluene, blood toluene, and urinary hippuric acid concentrations. A comparison of color vision assessments made on Monday and Wednesday mornings showed no significant difference. This suggests that color vision impairment results from chronic rather than acute exposure to toluene.

The study of Zavalic et al. (1998a) was selected as the principal study for derivation of an inhalation RfC. It is an adequate cross-sectional study of chronically-exposed humans which identified both a NOAEL (32 ppm) and LOAEL (132 ppm) for neurologic effects (impaired color vision). Impaired color vision is the critical effect. 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) for decreased performance in neurobehavioral and neuropsychological tests, but the effect levels in this study were less clearly characterized. Both of these NOAEL values lie slightly below the 40 to100 ppm range where available data (see Section 4.5.2, Table 1) suggest that persistent neurological effects in humans chronically-exposed to toluene begin to manifest.

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

Total UF –10.

A total uncertainty factor of 10 was applied to this effect level.

A 10-fold uncertainty factor for intraspecies differences (UF_H) was used to account for potentially sensitive human subpopulations.

An uncertainty factor to account for laboratory animal-to-human interspecies differences (UF_A) was not necessary because the NOAEL 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 exposed to toluene for a mean duration of 16 - 18 years.

An uncertainty factor was not needed to account for extrapolating from a LOAEL to a NOAEL because a NOAEL was available.

The data base for inhalation exposure is considered adequate. A single study of reproductive effects of humans occupationally exposed to toluene (Plenge-Bönig and Karmaus,

1999) reported no effects on male fertility, but a significant association between female exposure and reduced fertility was found. However, exposure levels for this study were not quantified, and confounding variables were not distributed evenly among the control and exposed groups, which hindered statistical adjustment. Numerous animal studies have demonstrated reproductive and developmental effects of toluene only at exposure levels which result in maternal toxicity (e.g., decreased maternal bodyweight). In addition, a 2-generation inhalation toxicity study is available.

MF – 1.

An additional modifying factor was not necessary.

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

Eller et al. (1999) reported on the neurological effects of 98 male rotogravure printers chronically exposed to toluene. Exposed workers were divided into workers exposed for 1-12 years (Group 1; n=30) or workers exposed for greater than 12 years (Group 2; n=49); the control group consisted of 19 workers not exposed to toluene. Workers exposed for 12 years or under were exposed to levels estimated at 25-32 ppm (94-121 mg/m^3), though some procedures still involve higher exposure levels for short periods of time. Workers exposed for greater than 12 years may have been exposed to levels exceeding 100 ppm (377 mg/m^3) for up to 27 years. For the scores of self-reported symptoms, the controls and Group 1 were found to be similar, while Group 2 showed a statistically significantly higher incidence of symptoms relative to controls, even after correction for age and alcohol consumption. In neurological tests, no differences between Group 1 and controls were noted. Group 2 showed a statistically significantly poorer performance, relative to the other groups, on 1 of 7 neurological tests and 2 of 5 sets of neuropsychological tests; the tests which were significantly altered were left hand finger tapping, retention times in the number learning test, and total time in the Bourdon-Wiersma test. This study identified a NOAEL of 25-32 ppm and a LOAEL of 100 ppm for increases in subjective symptoms and decreased performance in neurologic tests. The results of this study support the choice of the principal study of Zavalec et al. (1998a).

Foo et al. (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene levels reported in the study were from personal sample monitoring and reported as an 8-hour time-weighted average (TWA), although the number of samples taken and the actual sampling period were not given. No historical exposure values were given. Co-exposure to other solvents was not addressed in the study. The exposed and control cohorts were matched for age, ethnicity, and use of medications. Members of these cohorts did not use alcohol and were nonsmokers. Medical histories were taken to eliminate any histories of central or peripheral nervous system disorders. The average number of years (± SD) worked by the exposed population was 5.7 ± 3.2 and by the controls was 2.5 ± 2.7. Personal air samplers indicated that exposed workers breathed mean toluene air levels of 88 ppm (332 mg/m^3) as a TWA and control workers breathed a mean of 13 ppm (49 mg/m^3) (TWA). A battery of eight neurobehavioral tests were administered to all exposed and control workers. The tests were performed midweek, before the workers reported to

their stations for the day. Group means revealed statistically significant differences in 6/8 tests; all tests showed that the exposed workers performed poorly compared with the control cohort. When individual test results were linearly regressed against personal exposure concentrations, the slopes of the regression lines were all significantly nonzero. However, there was considerable scatter among the data sets, with correlation coefficients ranging from 0.44 to 0.30. Irritation effects were not evaluated in this study, and no clinical signs or symptoms were reported. This study identified a LOAEL of 88 ppm of toluene (332 mg/m^3) for neurobehavioral changes from chronic exposure to toluene. The previous RfC (IRIS, 1992) was based on this study.

In addition to neurologic effects in humans, the previous RfC 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 endpoints are a more sensitive endpoint for exposed humans, they alone were selected as the critical endpoint for derivation of the inhalation RfC.

___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. (1998a) 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 subtle 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 of the reproductive and developmental effects of toluene exist, which identify these effects only at exposure to much greater toluene concentrations. There is medium confidence in the resulting RfC.

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

Source Document – US EPA. (2002) Toxicological review of toluene in support of summary information on the Integrated Risk Information System (IRIS).

This assessment was peer reviewed by external scientists. 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 _____.

Other EPA Documentation -- _____

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 (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris@epamail.epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Toluene
CASRN -- 108-88-3
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Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a 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. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

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

Under the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), toluene is classified in Group D (*Not Classifiable as to Human Carcinogenicity*), based on inadequate data on the carcinogenicity of toluene in humans and inadequate evidence of carcinogenicity in

animals. This classification remains the same as in the previous IRIS entry (1988). Under the draft revised cancer guidelines (U.S. EPA, 1999), *data are considered inadequate for an assessment of the human carcinogenic potential*, because studies of humans chronically-exposed to toluene are inconclusive, and toluene was not carcinogenic in adequate inhalation cancer bioassays of rats and mice exposed for life (CIIT, 1980; NTP, 1990a). 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). Toluene has generally not been found to be genotoxic in short-term testing.

According to the National Toxicology Program (NTP, 1990b), there is no evidence of carcinogenic activity for male or female F344/N rats exposed to toluene during two-year inhalation studies at concentrations of 600 ppm or 1200 ppm. There is no evidence of carcinogenic activity for male or female B6C3F1 mice exposed by inhalation to toluene at concentrations of 120, 600, or 1200 ppm for 2 years. IARC states that toluene is not classifiable as to its carcinogenicity to humans (group 3); 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) 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, 1990a) 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. (2002) Toxicological review of toluene in support of summary information on the Integrated Risk Information System (IRIS).

This assessment was peer reviewed by external scientists. 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 _____.

___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 (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris@epamail.epa.gov (email address).

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

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

__VI.A. ORAL RfD REFERENCES

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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

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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