IRIS SUMMARY

0270
Xylenes; CASRN 1330-20-7; 00/00/0000

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 Xylenes

File First On-Line 09/30/1987

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

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name – Xylenes
CASRN – 1330-20-7
Last Revised – 00/00/00

The oral Reference Dose (RfD) is based on the assumption that thresholds generally exist for non-cancer effects. 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 (U.S. EPA, 2002). 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.

This RfD replaces a previous RfD value of 2 mg/kg/day entered on September 30, 1987, and is based on a reassessment of the existing database. The previous and new RfD values are based on data generated from the same study (NTP, 1986). The previous assessment, which is based on

the chronic component of the NTP study, identified hyperactivity, decreased body weight, and increased mortality in male rats as critical effects.

As the name implies, mixed xylenes is a mixture of the three isomers (o-, m-, p-) of xylene and ethylbenzene. For the most part, studies cited in this assessment are conducted on mixed xylenes. For this reason, it may not be possible to associate the observed effects with an individual isomer or with xylenes as opposed to ethylbenzene.

__I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Neurological effects in the form of lethargy, unsteadiness, tremors and paresis	NOAEL : 1000 mg/kg/day (710 mg/kg/day)*	1000	1	0.7 mg/kg/day
Subchronic rat oral study (gavage)	LOAEL: 2000 mg/kg/day			
(NTP, 1986)				

*Conversion Factors and Assumptions - Dose adjusted for gavage schedule (5 days/week)

__IA.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). (1986) NTP Technical Report on the Toxicology and Carcinogenesis of Xylenes (mixed) (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, and 9.1% o-xylene) in F344/N Rats and B6C3F1 mice (gavage studies). U.S. DHHS, PHS, NIH, Research Triangle Park, NC. NTP TR 327, NIH Publ. No. 86-2583

NTP (1986) conducted toxicology and carcinogenesis studies on mixed xylenes by the oral route of exposure. To ensure accurate administration of the chemical the gavage method was used. The battery of tests involved single dose administration, fourteen day studies, thirteen week studies and two year studies on male and female Fisher 344 rats and $B6C3F_1$ mice. Chronic studies in mice gavaged to doses of 1,000 mg/kg/day provided no evidence of pathological lesions. The authors noted hyperactivity in all high dose mice of both sexes 5-30 minutes following dosing from the fourth week of the study through week 103, but provided no additional characterization of the response. The authors reported that rats in the chronic study had a higher incidence of mortality but also a higher incidence of gavage related deaths. The authors speculate that the higher mortality could be due to increased resistence from gavaging but no notes were taken of the animals behavior during administration. Evidence of chemical-related effects in the chronic studies is limited. In the 13-week study, the authors report that body weight of rats dosed with 1,000 mg/kg/day were 15% and 8% lower at the end of the study compared with that of the vehicle controls but there are no other effects reported. In mice, the authors report neurobehavioral effects in the animals with the onset 5-10 minutes following administration and lasting for 15-60 minutes. The onset and duration of these effects track the pharmacokinetics of xylene (U.S. EPA, 2002).

The critical effect selected for generation of the RfD is the behavioral effect and the principal study is the subchronic component of the NTP (1986) study in mice. In this study male and female $B6C3F_1$ mice were treated with mixed xylenes. Groups of 10 mice of each sex were administered 0, 125, 250, 500, 1,000, and 2,000 mg/kg/day in corn oil by gavage, 5 days/week for 13 weeks. Two female mice in the high dose group died prematurely although gavage error cannot be ruled out as the cause. At 2,000 mg/kg/day, starting 5-10 minutes after dosing and lasting for 15-60 minutes, the animals exhibited lethargy, short and shallow breathing, unsteadiness, tremors, and paresis. Mean body weight of the mice in the high dose group was 7% lower than the vehicle control for males and 17% lower for females. There was no chemical-related gross or microscopic pathologic lesions seen in this study.

__IA.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000

Uncertainty factors are applied as follows: intraspecies uncertainty factor = 10; interspecies uncertainty factor = 10; database insufficiency uncertainty factor = 10; subchronic to chronic extrapolation uncertainty factor = 1; and LOAEL to NOAEL uncertainty factor = 1.

A full uncertainty factor of 10 is applied for intraspecies extrapolation to account for sensitive subpopulations.

A full uncertainty factor of 10 is applied to account for interspecies extrapolation because the RfD is derived from animal studies. Although the metabolic processes involved with the absorption, distribution, metabolism and excretion are similar in animals and humans (Bray et al., 1949; Riihimaki and Savolainen, 1980; David et al., 1979) information on the relative rates is limited.

A data base insufficiency uncertainty factor of 10 is applied to account for the lack of neurotoxicological, developmental, and reproductive studies by the oral route. There are data that are suggestive of developmental effects in rodents but are of limited value given the manner of reporting. For reasons noted above, the data base could be significantly improved with a complete neurotoxicity battery.

An uncertainty factor is not applied to account for a subchronic to chronic extrapolation. The neurological effects that were noted in the subchronic studies were not apparent at the slightly lower doses used in the chronic studies. This may reflect the metabolism and excretion of xylenes following ingestion. Therefore, it is reasonably anticipated that extended exposure will not lead to more pronounced effects or onset of effects at lower doses. Additionally, other factors including body weight decrements were less pronounced in the chronic portion of the NTP (1986) study than in the subchronic.

The RfD is based on a NOAEL and so an uncertainty factor to account for a LOAEL to NOAEL is unnecessary.

No modifying factor is applied because the existing uncertainties in this study are accounted for by the uncertainty factors.

__IA.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

There are a number of studies in which endpoints are identified. In addition to the neurotoxic effects mentioned above liver effects, reduction in body weight or body weight gain, mortality, and developmental effects have also been reported following oral exposure to xylenes. Most studies examining systemic effects following exposure to xylenes report changes in organ weights, most prominently liver weights. Increase in the mass of livers was noted in both oral and inhalation studies. In studies where liver effects were investigated, the authors found a corresponding increase in liver enzymes or morphological changes such as proliferation of the endoplasmic reticulum which, in the opinion of the study authors, are consistent with adaptation to exposure to a foreign substance and most likely reflect initiation of metabolic processes. These effects do not appear to constitute an adverse effect (Condie et al., 1988; Bowers et al., 1982; Ungvary, 1990). Following termination of exposure the liver returned to size comparable with controls indicating that the effect is transient.

The most consistent finding of exposure to xylenes is decreased body weight or body weight gain which is reported in studies through both oral administration or inhalation exposure. Overall, the reports do not provide explanation or mechanism for this effect. In some studies, lower body weight is reported along with decreased food consumption (Wolfe, 1988a) which is consistent with human data relating xylenes exposure to lower appetite (Uchida et al., 1993). In other studies in which food consumption is reported, the response corresponded to increased food consumption (Wolfe, 1988b; Tatrai and Ungvary, 1980; Tatrai et al., 1981). The biological significance of the body weight decrements remains unclear. For the most part, these effects have not been found in association with other possible toxicological effects.

Some studies employing oral gavage administration report increases in the mortality of animals (NTP, 1986; Wolfe, 1988a; b). Mortality in the NTP (1986) study occurred in the chronic study, but not in the subchronic portion of the study. Several, but not all, of the deaths are attributed to gavage error. The authors indicate that the rats may have resisted gavaging although they do not report on activity of the animals during gavaging. In both Wolfe studies (1988a; b) necropsy of the dead rats revealed foreign material in the lungs of the animals that died prematurely. The author notes that the animals in the high dose group exhibited "excessive" salivation prior to dosing, but offers no additional information on the behavior of the animals. Therefore, it is not clear whether mortality was the direct result from administration of xylenes or a response to irritation from gavaging with a noxious chemical.

Developmental studies report increases in skeletal malformations in xylenes-treated offspring (Marks et al., 1982; Nawrot and Staples, 1980). Overall, the nature of the effects varies and the incidence is low compared with vehicle controls. These studies report the data in fetal incidence and not litter incidence: a method that does not allow one to identify whether the effect was limited to a single litter, and therefore reflect a genetic anomaly or reflective of effects seen in several litters.

__IA.5. CONFIDENCE IN THE ORAL RfD

Study – Low to Medium
Data Base – Low to Medium

RfD – Low to Medium

Confidence in the study is low to medium. Data from the principal and supporting studies indicate that xylenes is a neurotoxic chemical. The principal study is a battery of tests designed to identify systemic toxicity in rats and mice ranging from acute to chronic exposures, and where the shorter studies were conducted to establish a dose range for a life-time cancer assay. While the responses seen in animals in the principal study are consistent with neurotoxicity, the study was not designed to evaluate neurotoxic effects in animals. Therefore, it is not known if the effects seen in the animals constitute the most sensitive endpoint. Furthermore, rats used in the study exhibited increased mortality. Although several of the deaths are attributed to gavage error, the cause of the other deaths was not characterized.

Confidence in the data base is low to medium. The data base includes a well-conducted chronic study including the prechronic studies in two species. Although the critical effect is neurotoxicity, the data base for xylenes does not include a functional observational battery or other tests for neurotoxicity by the oral route which could better characterize the nature of the effects. The data base would also be significantly improved with the availability of developmental and reproductive studies including 2-generational study to address possible developmental effects discussed in the Toxicological Review (2002).

Confidence in the RfD is low to medium. The RfD could be significantly improved by a more comprehensive data base including neurotoxicity, reproductive, and developmental toxicity studies.

__IA.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document – U.S. EPA, 2002

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 U.S. EPA, 2002.

Agency Consensus Date – 00 /00/0000

__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)

Substance Name – Xylenes
CASRN – 1330-20-7
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 non-cancer effects. 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.

As noted in I.A. mixed xylenes is composition of the chemical to which the general public is most commonly exposed. Mixed xylenes is comprised of all three isomers of xylenes and commonly contains ethylbenzene. However, the principal study was conducted on the m-xylene isomer. A discussion of the relative toxicity of individual isomers is included in the Toxicological Review (U.S. EPA, 2002).

The previous data base did not include an RfC. The inclusion of one is derived from a study reported following the previous revision September 30, 1987.

__I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
impaired motor coordination (decreased rotarod performance)	NOAEL: 50 ppm (adjusted to 39 mg/m^3)	300	1	0.1 mg/m^3
subchronic inhalation study in male rats	LOAEL: 100 ppm (adjusted to 78 mg/m^3)			
Korsak et al., 1994				

*Conversion Factors and Assumptions - MW = 106.17. Assuming 25C and 760 mmHg, $NOAEL_{(mg/m^3)}$ = 50 ppm x 106.17/24.45 = 217 mg/m^3. $NOAEL_{[ADJ]}$ = 217 mg/m^3 x 6 hours/day, 5 days/week = 38.75 mg/m^3. The $NOAEL^*_{[HEC]}$ was calculated for extrarespiratory effects of gases in Category 3. $(H_{b/g})_A/(H_{b/g})_H = 1$. $NOAEL^*_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g})_A/(H_{b/g})_H$ = 38.75 mg/m^3.

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

Korsak, Z; Sokal, J A; Górny, R. (1992) Toxic effects of combined exposure to toluene and m-xylene in animals. III. Subchronic inhalation study. Polish J Occup Med Environ Health. 5:27-33.

Korsak, Z.; Wisniewska-Knypl, J.; Swiercz, R. (1994) Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int J Occup Med Environ Health. 7:155-166.

Hass, U; Jakobsen, BM. (1993) Prenatal toxicity of xylene inhalation in the rat: a teratogenicity and postnatal study. Pharmacol Toxicol. 73:20-23.

Hass, U; Lund, SP; Simonsen, L; Fries, AA. (1995) Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Neurotoxicol Teratol. 17:341-349.

Hass, U; Lund, SP; Simonsen, L. (1997) Long-lasting neurobehavioral effects of prenatal exposure to xylene in rats. Neurotoxicology. 18:547-551.

Rosengren, L E; Kjellstrand, P ; Aurell, A; Haglid, K G (1986) Irreversible effects of xylene on the brain after long term exposure: a quantitative study of DNA and the glial cell marker proteins S-100 and GFA. NeuroToxicology 7: 121-136.

There are no human studies that are suitable for deriving an RfC and therefore, the RfC is derived from animal studies. There are a number of animal studies which identify possible effects for the derivation of an RfC. The two most prominent candidates are developmental toxicity and neurotoxicity. Data on developmental toxicity are limited by the method of reporting including citing effects as fetal incidence rather than litter incidence (Bio/dynamics Inc., 1983). Neurotoxic effects have been seen in a number of studies. Some of the studies are limited by the use of a single dose by the inhalation route of exposure (Hass and Jakobsen, 1993; Hass et al., 1995). Of the remaining studies, the one with the lowest effect level is an inhalation study by Korsak et al. (1994) in which a rotarod study supports a finding neurotoxicity following a three month exposure to m-xylene.

Groups of 12 male Wistar rats were exposed to 50 or 100 ppm m-xylene or n-butyl alcohol, or their 1:1 mixture at 50:50 ppm or 100:100 ppm for 6 hours/day, 5 days/week for 3 months (purity of chemicals not provided; Korsak et al., 1994). Exposure to 50 or 100 ppm m-xylene alone resulted in decreased rotarod performance starting at 1 month of exposure and remaining at the same level until the end of the 3-month exposure, with the decreases being statistically significant in the 100 ppm exposure group. The study authors employed the rotarod test as a measure of motor coordination disturbances from exposure to m-xylene. The rotarod test involves placing the subject animals on a rotating rod and evaluating the ability of the animals to remain on the rod for a period of 2 minutes. The animals are trained to perform the task, exposed to chemical or control gas, and evaluated at defined intervals. In this study, the authors presented the data in graphical form and, therefore, precise numerical values are not provided. The percentage of failures was roughly 8% and 33% for the 50 and 100 ppm groups, respectively, vs. 0% for the controls. Rats exposed to 50 or 100 ppm m-xylene alone also had statistically increased sensitivity to pain at the end of the 3-month exposure as determined by the hot plate behavior test (in which latency of the paw lick response is measured: was 8.7 and 8.6 seconds, respectively, vs. 12.2 seconds for the controls). No exposure-related changes in body weight gain; absolute or relative organ weights; hematology parameters; or in hepatic microsomal monooxygenase, lipid peroxidation, or triglyceride levels were noted. Although a statistically increased sensitivity to pain was noted as measured by the hot plate behavior test in the xylene-exposed groups, the LOAEL is not based on this endpoint because the response did not reflect a

dose-response relationship. Therefore, the LOAEL is 100 ppm based on decreased rotarod performance, and the NOAEL is 50 ppm.

In a similar study by Korsak et al. (1992), decreased rotarod performance and decreased spontaneous activity were observed in groups of 12 male Wistar rats exposed for 6 hours/day, 5 days/week to 100 ppm m-xylene for 6 months or 1000 ppm for 3 months as compared with controls.

In a study by Hass et al. (1995), pregnant rats were exposed by inhalation to 0 or 500 ppm xylenes for 6 hr/day on GD 7-20 and were allowed to litter. The litters were split into standardized housing and "enriched" housing (containing toys) and tested for rotarod, open field, and Morris maze test at about 3 months of age. No differences were observed in open field test. The decreased rotarod performance in exposed female pups reported by the study authors was not statistically significant. Offspring from xylene-exposed rats that were raised in the enriched environment showed no difference in the Morris maze test compared with controls. Offspring from exposed rats that were raised in the standard housing, however, had impaired performance. Testing at 12 weeks showed a nonsignificant trend for increased latency for finding the platform in the beginning of the learning test. At 16 weeks, the treated animals raised in standard housing required more time to find a platform hidden in the center of the pool. These animals demonstrated no difference in swim speed but required more time to find the platform. In a followup study to test the persistence of these effects, the offspring were tested at 28 and 52 weeks. At 28 weeks the animals took a longer period of time to find the underwater platform in the first of three trials compared with the control group. At 52 weeks there was no difference between the two groups.

Groups of four male and four female Mongolian gerbils were exposed by continuous inhalation to xylene at 0, 160, or 320 ppm for 3 months, followed by a 4-month post-exposure solvent-free period (Rosengren et al., 1986). Xylene exposure caused regional increases in the brain concentrations of GFA protein (glial fibrillary acidic protein; a main component of astroglial filaments), S-100 protein (found in fibrillary astrocytes), and DNA. The authors state that these findings are compatible with the presence of astrogliosis. No other evaluations, including a recording of clinical signs, were mentioned.

Pregnant Wistar rats were exposed to air containing 0 or 200 ppm of technical grade (composition not provided) xylene for 6 hours/day during GD 6-20 (Hass and Jakobsen, 1993). In the postnatal study, statistically decreased rotarod performance was observed in female pups on postnatal days 22 and 23, and in male pups on postnatal day 23. This study is limited by the fact that only one concentration was used, a limited battery of tests were used, and that the testers were not blind to the exposure status of the animals.

In a study designed to investigate the persistence of the decreased Morris water maze test performance of the offspring from the xylene-exposed (Mol:WIST) female rats, the female offspring raised in the standard housing were continued on the study and evaluated at 28 and 52 weeks (Hass et al., 1997). At 28 weeks, an increased latency for finding a platform that was moved to a new position was observed in the female offspring from exposed rats only during the first trial of a testing block, while the next two trials resulted in similar latencies between exposed and control rats. The increased latency again corresponded with increased swimming

length. No other significant differences were observed for other testing situations in the Morris maze test. At 55 weeks, no statistically significant differences were observed between groups.

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

UF = 300

Uncertainty are applied as follows: Intraspecies uncertainty factor = 10; Intraspecies uncertainty factor = 3; extrapolation from subchronic to chronic duration = 3; and uncertainty factor for data base insufficiency = 3. There was no need for an uncertainty factor to extrapolate from a LOAEL to a NOAEL. (10 x 3 x 3 x 3 = 300)

Uncertainty factor of 10 is applied for intraspecies extrapolation to account for sensitive individuals in the populations.

Uncertainty factor of 3 is applied for interspecies extrapolation because dosimetric adjustments were made.

An uncertainty factor of 3 is applied for extrapolation of a subchronic exposure to a chronic exposure. Human data indicate that neurological effects noted were mild and transient. Data on the principal study indicate that the nature of the effect may be transient. Xylenes is readily metabolized into nontoxic metabolites and excreted from the body. Xylenes are not expected to bioconcentrate or persist in the body.

An uncertainty factor of 3 is applied for database insufficiency. As noted there are a number of studies which address neurotoxicity endpoints; however, the data base could be substantially improved with the inclusion of a functional observational battery and other neurotoxicological studies. Additionally, inhalation studies are suggestive of developmental toxicity. A well conducted 2-generation study would benefit the data base.

The effect is based on a NOAEL and therefore an extrapolation from a LOAEL to a NOAEL is not needed.

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

Chronic human data are limited to the study by Uchida et al. (1993) which identifies a "concentration-related" (exposure intensity broken into 1-20 ppm and > 21 ppm) increase in reports of eye irritation, sore throat, and a floating sensation during the work shift. Poor appetite was the only symptom to occur outside of the workplace in the previous 3 month period, however, indicating that the other effects are transient in nature and most likely due to the irritating properties of xylenes. Reports of acute exposures humans are also available, and again demonstrate only transient effects (Klaucke et al., 1982).

The choice of a study in which exposure is limited to m-xylene alone as opposed to the isomeric mixture or to one of the other individual isomers is not expected to affect the RfC derivation. Although differences in toxicity appear to exist among the isomers, no consistent,

significant differences in the potency of the isomers following oral or inhalation exposure are identified (U.S. EPA, 2002).

Data from inhalation studies on pregnant rats indicate a tendency for developmental effects at high levels of exposure. In a one-generational study, groups of male and female CD rats were exposed to 0, 60, 250, or 500 ppm mixed xylenes by inhalation for 6 hours/day, 5 days/week for 131 days prior to mating, with exposure continued in females during GD 1-20 and lactation days 5-20 (Bio/dynamics Inc., 1983). In separate groups, only female rats were exposed to 500 ppm. Potential pup exposure was only through the milk. At the high dose there was a slight but statistically significant increase in the number of resorption sites and mean percentage of resorptions to implants. There were no dams with whole litter resorption. While there are no definitive treatment-related external, visceral, or skeletal malformations, the report states that high-dose fetuses had a slightly higher incidence of unossified sternebrae and incompletely ossified cervical vertebral transverse processes. These are reported as fetal incidence and not litter incidence. Therefore, no LOAEL/NOAEL is established.

Pregnant Wistar rats were exposed to air containing 0 or 200 ppm of technical grade (composition not provided) xylene for 6 hours/day during GD 6-20 (Hass and Jakobsen, 1993). No maternal toxicity is noted. The only effect in fetuses from exposed dams was an increased incidence of delayed ossification of the *os maxcillare* in the skull with 18/26 exposed litters affected compared with 2/22 control litters. The results are reported in fetal incidence rather than litter incidence which limits the utility of the data.

__I.B.5. CONFIDENCE IN THE INHALATION RfC

Study – Medium
Data Base – Medium
RfC – Medium

Confidence in the Korsak et al. (1994) study is medium. Only males were investigated, and only two tests from a multitude of standardized neurotoxicity tests were used to assess the neurotoxicity of inhaled xylene in rats. Therefore, it is unknown if the pain sensitivity test and the rotarod test are the most sensitive for detecting neurological effects following xylene exposure. Despite this insufficiency, however, the LOAEL and NOAEL identified in this study are at concentrations below those identified in other studies.

Confidence in the overall database is medium. Studies available included a chronic toxicity study in rats, a one-generation reproductive study in rats, developmental toxicity studies in rats, and subchronic toxicity studies in rats and dogs. Database deficiencies include a two-generation reproductive study, and a developmental toxicity study in a second species other than rats.

The overall confidence in this RfC assessment is medium.

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

Source Document – U.S. EPA, 2002

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 U.S. EPA, 2002.

Agency Consensus Date – 00 /00/00

__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

Substance Name – Xylenes
CASRN – 1330-20-7

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 µg/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/600/887/045) 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 (U.S. EPA, July 1999). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

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

Classification – Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), xylenes is classified into cancer weight-of-evidence group D, *not classifiable as to human carcinogenicity*. Under the Review Draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), the weight of evidence classification is that *data are inadequate for an assessment of human carcinogenic potential due to conflicting evidence.*

The data base on the carcinogenicity of xylenes is mixed. Human epidemiological studies have found statistically increased incidence of cancer, but the quality of the studies is limited by such factors as the low number of subjects in the cohort, low number of occurrences, and confounded by exposures to other solvents (Arp et al., 1983; Wilcosky et al., 1984; Gerin et al., 1998). The data base on animal studies of xylenes is mixed. An NTP (1986) oral carcinogenicity study found *no evidence* of carcinogenicity of xylenes in rats or mice of either sex. However, a

second study by Maltoni et al. (1983, 1985) found an increase in malignant tumors following exposure to xylenes. The second study is incompletely reported and not amenable to developing a dose response. Genotoxicity studies are consistently negative.

Data on structural analogues are also mixed. Data indicate that chemicals of similar structure to xylenes that have tested positive for carcinogenicity require the metabolism of the parent substance to a more reactive metabolite. For benzene, this involves the formation of an epoxide that is subsequently metabolized to catechol and benzoquinones (U.S. EPA, 2000). This process requires the presence of two adjacent nonsubstituted carbons, a condition, based on its structure, that is less prevalent with xylenes. Metabolism of xylenes proceeds by a different metabolic pathway. These data indicate that metabolism of xylenes involves oxidation of the alkyl group to an acid, as opposed to the formation of an epoxide and diols. The acid is subsequently conjugated with glycine thereby reducing the reactivity of the metabolites compared with benzene. The presence of less reactive intermediates reduces concern for carcinogenicity of xylenes relative to other aromatic chemicals.

__II.A.2. HUMAN CARCINOGENICITY DATA

Insufficient.

Occupational exposure to xylenes are found in association with an increased risk of leukemia (Arp et al., 1983; Wilcosky et al., 1984), non-Hodgkin's lymphoma (Wilcosky et al., 1984), and cancer of the rectum (Gérin et al., 1998), colon (Gérin et al., 1998), or nervous system (Spirtas et al., 1991). Despite these associations, however, a number of limitations preclude the usefulness of these data, including: small sample sizes, no quantified exposure concentrations, and/or concurrent exposures to other solvents.

__II.A.3. ANIMAL CARCINOGENICITY DATA

Insufficient.

In a National Toxicology Program (NTP, 1986) chronic toxicity and carcinogenesis bioassay, groups of 50 male and 50 female Fischer 344 rats, and 50 male and 50 female B6C3F1 mice were administered mixed xylenes (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, and 9.1% o-xylene) in corn oil by gavage at dosages of 0, 250, or 500 mg/kg/day (rats) and 0, 500, or 1000 mg/kg/day (mice) for 5 days/week for 103 weeks. Animals were killed and examined histologically when moribund or after 104-105 weeks. Mortality in males exhibited an apparent dose-related increase, with the increase statistically significant in the high-dose males. Interstitial cell tumors of the testes could not be attributed to administration of the test compound observed in male rats (43/50 control, 38/50 low-dose, and 41/49 high-dose). NTP (1986) report no significant nonneoplastic or neoplastic effects in rats or mice. The authors conclude that there was "no evidence for carcinogenicity" of mixed xylenes for rats or mice of either sex at any dosage tested.

Maltoni et al. (1983; 1985) exposed groups of 40 male and 40 female Sprague-Dawley rats to 0 or 500 mg xylenes/kg BW (mix of o-, p-, and m-xylenes; proportion of each isomer not stated) in olive oil orally by gavage 4-5 days/week for 104 weeks, followed by discontinuation of

dosing to study termination at 141 weeks. Although Maltoni et al.(1985) reported an increase in the overall number of malignant tumors in both treated males (14/40 vs. 11/50 for controls) and females (22/40 vs. 10/50 for controls), further study data, such as survival rates and specific tumor types, were not provided. The study noted that the time to first tumor was 33 weeks. The decision to report the incidence of animals with tumors and not describe the types of tumors and target organ increases the uncertainty associated with the study. The use of a single high dose raises questions about the ability to extrapolate to a low dose.

The Maltoni et al. (1983; 1985) study has significant limitations including incomplete reporting of the composition of the test material; use of a single dose, relatively high incidence of tumors in the control groups, and inadequate reporting of the tumor types.

__II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The genotoxicity of commercial xylene and all 3 individual isomers has been extensively tested and the results are almost uniformly negative. All studies that have been evaluated by the GENTOX panel and cited in the GENTOX database were negative except for one study for which no conclusion was drawn (GENTOX, 1999). Xylene was found to be not mutagenic in bacterial test systems with *Salmonella typhimerium* (Bos et al., 1981; Florin et al., 1980; NTP, 1986) and *Escherichia coli* (McCarroll et al., 1981) or in cultured mouse lymphoma cells (Litton Bionetics, 1978). Xylene also did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (Anderson et al., 1990) or cultured human lymphocytes (Gerner-Smidt and Friedrich, 1978), chromosomal aberrations in rat bone marrow (Litton Bionetics, 1978), micronuclei in mouse bone marrow (Mohtashamipur et al., 1985), or sperm head abnormalities in rats (Washington et al., 1983). Technical grade xylene, but not o- and m-xylene, was weakly mutagenic in *Drosophila* recessive lethal tests (Donner et al., 1980). No increase in the frequency of sister chromatid exchanges were observed in peripheral lymphocytes from individuals exposed to xylene in an occupational setting (Haglund et al., 1980; Pap and Varga, 1987) or an experimental setting (Richer et al., 1993).

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

Not applicable. Data are insufficient for generation of a dose response.

__IIC. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable. Data are insufficient for generation of a dose response.

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

__II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA, 2002

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 U.S. EPA, 2002.

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

Agency Consensus Date – 00/00/00

__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]

__VI. BIBLIOGRAPHY

Substance Name – Xylenes
CASRN – 1330-20-7

Last Revised – 00/00/00

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__VII. REVISION HISTORY

Substance Name – Xylenes
CASRN – 1330-20-7

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
07/01/1989	I.B.	Inhalation RfD now under review
07/01/1989	VI.	Bibliography on-line
03/01/1991	II.D.3.	Primary contact changed
03/01/1991	IV.F.1.	EPA contact changed
01/01/1992	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
08/01/1995	II.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September 1995.
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
00/00/0000		Revised RfD, RfC, Cancer assessment

__VIII. SYNONYMS

Substance Name – Xylenes
CASRN – 1330-20-7
Last Revised – 00/00/0000

108-38-3

1330-20-7
106-42-3
95-47-6
dimethylbenzene
1,2-dimethylbenzene
1,3-dimethylbenzene
1,4-dimethylbenzene
mixed xylenes
m-xylene
meta-xylene
o-xylene
ortho-xylene
p-xylene
para-xylene
xylenes