



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Andrew M. Jaques, Director
Benzene, Toluene, and Xylene (BTX) VCCEP Consortium
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Jaques:

Thank you for coordinating BTX VCCEP Consortium's sponsorship and assessment activities regarding o-xylene and m-xylene in EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) and for including p-xylene and mixed xylenes in your assessment. EPA appreciates the contributions of the Consortium and the member companies listed on the Tier 1 assessment submission (BP Amoco Chemical Company, Chevron Phillips Chemical LP, ExxonMobil Chemical Company, Flint Hills Resources, L.P., Marathon Petroleum LLC, Shell Chemical LP, Sunoco, Inc., and Total Petrochemicals U.S.A.) to VCCEP.

The purpose of this letter is to inform the Consortium and its member companies of EPA's VCCEP Tier 2 Data Needs Decision for xylenes. In formulating this decision, EPA has considered all available information, including the assessment provided by the Consortium and the report of the VCCEP Peer Consultation Panel that provided comments on the Consortium's assessment for xylenes. EPA has determined that additional data beyond the assessment prepared by the Consortium are needed to characterize the risks of xylenes to children.

EPA has determined that the Tier 1 exposure assessment is complete and EPA does not recommend any Tier 2 exposure studies at this time for VCCEP. EPA has also determined that all Tier 1 toxicity studies have been conducted and that there are no data needs identified for Tier 2 toxicity studies at this time for VCCEP. However, EPA has identified two data needs for Tier 3 toxicity studies: a developmental neurotoxicity study and an adult neurotoxicity screening battery, preferably using mixed xylenes and inhalation exposure. Additional exposure studies may be warranted pending the results of the Tier 3 toxicity studies and the Sponsor's updated assessments. Additional details regarding EPA's data needs are provided in the Enclosure.

EPA's Data Needs Decision document will be posted to the VCCEP website, along with this decision letter, so that other stakeholders are informed of the status of this review.

We encourage the Consortium and its member companies to commit to sponsor xylenes in Tier 3 of VCCEP. The design of VCCEP specifies that sponsor companies make a Tier 3 commitment within four months of receiving EPA's Data Needs Decision. (*See* 65 FR 81700, December 26, 2000).

We look forward to hearing from you on this issue. Please contact Jim Willis, the Director of the Chemical Control Division in EPA's Office of Pollution Prevention and Toxics, if you have any questions or concerns associated with this Data Needs Decision. Jim can be reached at (202) 564-4760.

Sincerely,

A handwritten signature in cursive script, appearing to read "Charles M. Auer".

Charles M. Auer
Director, Office of Pollution Prevention
and Toxics

Enclosure

VOLUNTARY CHILDRENS CHEMICAL
EVALUATION PROGRAM:
DATA NEEDS ASSESSMENT
OF XYLENES

Prepared By
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Office of Pollution Prevention & Toxics
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Preface

Chemicals of potential concern to children's health are the subject of evaluation in the pilot Voluntary Children's Chemical Evaluation Program (VCCEP). VCCEP was developed to ensure that there are adequate publicly available data to assess the impact that industrial chemicals may have on children.

In August 1999, OPPT announced the initiation of a process in which it sought stakeholder input on all aspects of the VCCEP. OPPT held three public meetings and took comments on possible designs for a voluntary program. After considering all the comments of interested stakeholders, the pilot VCCEP was announced in a *Federal Register* notice on December 26, 2000. In the notice, OPPT asked companies that produce and/or import 23 specific chemicals to volunteer to sponsor their evaluation in Tier 1 of a pilot of the VCCEP. Thirty-five companies and ten consortia responded and volunteered to sponsor 20 of the chemicals.

The ultimate objective of the VCCEP is to ensure that there are adequate toxicity and exposure information available to assess the potential risks to children. A tiered approach is being pursued to gather the information, with each subsequent tier, of the three tiers, including more complex toxicology and exposure studies. Information from all three tiers may not always be necessary to adequately characterize the risk to children. The sponsor develops a chemical assessment at each tier of analysis. The assessment includes four sections: a summary of the toxicology information, a summary of the exposure information, a risk characterization, and a data needs assessment. The data needs assessment discusses the need for additional data, which could be provided by the next tier, to fully characterize the risks the chemical may pose to children.

During the public stakeholder meetings, it was proposed that an outside group of scientific experts should have the opportunity to provide comments on the data needs portion of the assessments. The approach adopted involves convening a group of scientific experts with extensive and broad experience in toxicity testing and exposure evaluations, as well as expertise in the specific chemical, referred to as a Peer Consultation Panel. The sponsor provides the assessments to an outside third party who is responsible for seeking input through the Peer Consultation Panel. The outside third party develops a summary of the panel's opinions and makes it available to the sponsor and the public.

OPPT reviews the sponsor's assessment and develops a response to the sponsor specifically on the data needs assessment. The response focuses primarily on whether any additional information is needed to adequately characterize the potential risks to children. EPA's response is sent to the sponsor and made available to the public.

Additional information regarding the Voluntary Children's Chemical Evaluation Program is provided in Appendix A and is available at <http://www.epa.gov/oppt/chemrtk>.

In October 2005, the American Chemistry Council's Benzene, Toluene, and Xylenes VCCEP Consortium (ACC) submitted its Tier 1 assessment of the Xylenes Category (m-xylene, o-xylene, p-xylene, and mixed xylenes) for the Voluntary Children's Chemical Evaluation Program (VCCEP). OPPT has reviewed the four components of the assessment, and where appropriate, has confirmed the accuracy of the toxicology and exposure information. EPA has also reviewed a report of a peer consultation panel that provided comments on the assessment; this report is available at www.tera.org.

The xylenes category for this VCCEP assessment includes individual isomers m-xylene, o-xylene, p-xylene, and mixed xylenes. The treatment of individual xylene isomers and mixed xylenes as a single category is supported by similar physical and chemical properties, hazard effects, and exposure sources.

1.0 Summary of EPA Recommendations for VCCEP

1. The Tier 1 exposure assessment is complete. For VCCEP, EPA does not recommend any Tier 2 exposure studies at this time.
2. All Tier 1 toxicity studies have been conducted. For VCCEP, there are no data needs identified for Tier 2 toxicity studies at this time.
3. EPA has identified two data needs for Tier 3 toxicity studies; a developmental neurotoxicity study and an adult neurotoxicity screening battery, preferably using mixed xylenes and inhalation exposure. EPA will evaluate the need for additional exposure studies pending the results of the Tier 3 toxicity studies.

2.0 Summary of Exposure Assessment

Production, Applications and Fate of Xylenes

The sponsor's submission states that domestic production capacity in 2004 for mixed, o-, m-, and p-xylene was 7939, 503, 268, and 4947 thousand metric tons per year, respectively. Domestic consumption in 2004 for mixed o-, m-, and p-xylene was 6562, 432, 94, and 2909 thousand metric tons, respectively.

The sponsor's submission states that as of 2004, there are 13 companies with a total of 23 plants in the United States (including its territories) that produce one or more xylene isomers, or mixed xylenes. Twenty-one facilities produce mixed xylenes; 4 produce o-xylene; 2 produce m-xylene; and 9 produce p-xylene. Some plants produce more than one isomer.

According to the sponsor's submission, mixed xylenes, which make up the majority of domestic production, are primarily used in the manufacture of individual xylene isomers (o-, m-, and p-xylene,) with a small amount used as a motor fuel additive. The individual xylene isomers are used as a chemical intermediate in the manufacture of fibers, coatings,

plastics, and inks. They are also used as additives in paints, metal cleaning solvents, carburetor cleaners, lubricants, water repellents, wood stains and varnishes, and other consumer products. Xylenes are not permitted for use in cellophane food wrappers, but may appear in adhesives used in food packaging, in compliance with Food and Drug Administration (FDA) guidelines.

The sponsor's submission presents xylenes as an industrial and commercial product, providing a production volume, a list of uses, and the percentage of production derived from certain sources and/or production methods. More than 99% of xylene production is derived from catalytic reforming (82%) or toluene disproportionation (17%). Production of mixed xylenes and the three common xylene isomers is provided for the years 1988-2004; air releases are provided for the years 1988-2003 using data from EPA's Toxics Release Inventory (TRI). In general, during the period shown, production has increased while air emissions have declined. Xylenes are produced at 23 facilities in the United States, including U.S. territories.

The sponsor's submission also presents estimates of xylene releases to air, soil and water. Major activities contributing to air releases are provided in a table, and the reader is referred to a 1994 EPA document for further information about each release activity. Release amounts are not provided for each release activity, but percentages of the total release deriving from four broad release categories (on-road, non-road, major source, and biomass/other) are provided. The report presents releases to air, surface water, groundwater, land, and "transfer to disposal," with a release amount (in millions of pounds per year) for each, using 2003 TRI data.

The sponsor's submission presents a wide range of xylenes release data from 1988 through 2004 from the U.S. Toxic Release Inventory. Included in the submission are air emissions, surface water discharges, underground injections, releases to land, and total on- and off-site releases. The data presented do not show release estimates for facilities that may use xylenes in quantities less than the TRI threshold.

The sponsor's submission does not include a complete list of physical-chemical properties of the xylenes and it does not discuss the environmental fate of the xylenes. The sponsor's submission does include a few physical-chemical properties of a mixture of xylenes isomers; these appear in various places in the submission and appendices:

- Molecular weight = 106.2 (Appendix A, Table A-9-1)
- Octanol-water partition coefficient (log value): not provided.
- Vapor pressure = 8 mm Hg @ 25°C (Appendix A, Table A-9-1)
- Water solubility = "highly soluble in blood" (Section 6.1.1); no other data given.
- Melting point: not provided.
- Boiling range = 131-141°C (Appendix B, Robust Summaries)
- Henry's Law constant: not provided.
- Density: 0.86 g/ml @ 25°C (Table A-8-1)
- Photolysis: not provided.
- Hydrolysis: not provided.

- Biodegradation: not provided.

The sponsor could have used EPI Suite to estimate a variety of physical chemical properties and predict environmental fate. EPI Suite version 3.12 is available at <http://www.epa.gov/opptintr/exposure/docs/episuitedl.htm>

Occupational Exposure

The submission discusses occupational exposure to xylene in three areas: production and processing, use as a feedstock, and use in chemical products (solvents, paints, lacquers, etc.).

The submission presents Industrial Hygiene monitoring (inhalation, airborne concentration) data from 1995-2001 (chemical manufacturing and distribution). These data only cover employees who did not wear respirators.

The submission presented exposure records from American Industrial Hygiene Association journal papers from 1961-1988. The data focused on solvent end-use exposures from 8 end-use scenarios [adhesives, painting (auto body and furniture), general use-electronics, curing, mixing, extruding, and polyurethane molding]. The submission averaged all of the exposures for the end-use activities and presented two Time Weighted Average (TWA) exposures (mean, 95th-percentile). The submission did not provide data for individual activities.

The submission presented results from data searches of the National Library of Medicine PubMed/Medline citation database, NIOSH Health Hazard Evaluations, and OSHA publications (1997-2001). The data were presented in a table that showed the average 8-hour TWA for xylene inhalation exposure for four occupational categories [graffiti removal, aircraft maintenance, municipal firefighter, and painting (including lacquers and stains) during new home construction].

The submission states that determining the dermal contribution to occupational exposure to xylene is difficult due to the potential for simultaneous inhalation and dermal exposure. There was some limited investigation of dermal exposure to xylene during auto body painting. However, researchers found that the data were inconclusive. The submission stated that in manufacturing settings (chemical manufacturing and processing), it is widely accepted that the potential for chemical exposure (dermal and inhalation) is low because of the closed system operations and the inherent physical hazards (fire, explosion) involved.

There is a presentation of modeled dermal exposure (women) to xylenes during activities such as the application of varnishes or stains. For the EASE model cited in the submission [Estimation and Assessment of Substance Exposure], parameters such as skin surface area, frequency of exposure, and concentration of xylene in the end use product are all imperative to the utility of the model. The model assumes exposures to occur under non-occluded skin conditions.

Children's Exposure

The assessment of children's exposures in the sponsor's submission was based on an examination of all sources of xylenes to which children might reasonably be expected to be exposed, including environmental sources and consumer products. Environmental exposures assessed in the submission include inhalation of indoor and outdoor air, consumption of food, and consumption of water. Certain "microenvironments" with potentially high exposures, such as homes where smoking occurs, gasoline-powered motor vehicles, and areas where xylene products are used by consumers, were also assessed. The sponsor's exposure assessment categorized the potentially exposed population as follows: Infant (less than 1 year old); Toddler (1 to 5 years old); Child (6 to 13 years old); Teenager (14 to 18 years old). In addition, a category for adult females aged 19 to 35 was included in order to assess occupational exposure to mothers who could in turn expose infants via nursing. Adverse health effects to children via exposure of prospective fathers were not assessed because xylenes are not associated with male reproductive health effects. The assessment included both typical and high-end exposure calculations. For each scenario and population group, available data were used to derive an exposure concentration and a standard dose equation was used to calculate a dose.

The sponsor's exposure assessment does not include the 10 childhood age groups recommended in EPA's recently published Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants:

Recommended Set of Childhood Age Groups for Agency Exposure Assessments (U.S. EPA 2005)

Age Groups <1 Year	Age Groups ≥ 1 Year
Birth to <1 month	1 to <2 years
1 to <3 months	2 to <3 years
3 to <6 months	3 to <6 years
6 to <12 months	6 to <11 years
	11 to <16 years
	16 to <21 years

The ambient exposure scenarios assessed in the submission include intake of outdoor air in urban and rural settings, indoor air at home and in school, food, and water. Exposure to environmental ("second-hand") tobacco smoke, consumer products, and gasoline sources were also assessed.

Older children (aged 14 to 18) were assessed as users of consumer products, while the three younger age groups were assessed as non-users. Older children (ages 14 to 18) were also included with adult females as potential direct consumers of tobacco smoke.

Rural and urban xylene concentrations in ambient outdoor air were derived from EPA's AirData database. The data are acceptably current (2004). The submitter also considered

the impact of known major emitters of xylenes using EPA's SCREEN3 air dispersion model. The model results indicate that in close (500 meter) proximity to the highest known emitter of xylenes, ambient air concentrations are approximately 10 times the high-end urban xylene concentration determined from the EPA AirData database. Page 88 of the sponsor's submission gives the high-end concentration from the database as $7.7 \mu\text{g}/\text{m}^3$, but this appears to be an error; the value in Table 7.4 that is used in the exposure assessment is $5.9 \mu\text{g}/\text{m}^3$. The modeled value is $64 \mu\text{g}/\text{m}^3$; the submitter states that because only a minuscule portion of the U.S. population is close to the high-emitting facilities, the high-end values from the EPA AirData database are appropriate to characterize exposure among the general population.

Xylene concentrations in indoor air at home, aside from those associated with site-specific activities, were derived from the Agency for Toxic Substances and Disease Registry and from 8 peer-reviewed studies conducted in the United States. Due to limitations in the available data, indoor air concentrations were derived from outdoor air concentrations by inferring a typical and a high-end difference ("delta") between indoor and outdoor air, and applying this delta to the urban and rural outdoor air concentrations obtained from EPA's Air Data database. The delta was $6.6 \mu\text{g}/\text{m}^3$ for typical exposure and $30 \mu\text{g}/\text{m}^3$ for high-end exposure. Table 7-12 of the submission shows the application of these delta values to the outdoor air concentrations, but there appears to be an error; the high-end outdoor urban concentration is $5.9 \mu\text{g}/\text{m}^3$ and the corresponding high-end indoor concentration is presented as $35.7 \mu\text{g}/\text{m}^3$, but the correct value is $35.9 \mu\text{g}/\text{m}^3$ ($5.9 + 30$). This incorrect value is carried forward into the exposure assessment, but is not likely to have a significant impact on the outcome of the assessment.

Xylene concentrations in indoor air at school were estimated using an EPA study of 10 schools and another study that assessed 9 schools. The submitters used the high-end values from the EPA study as the high-end values for indoor air in schools, but used the outdoor urban air concentration as the typical indoor air concentrations in schools based on the results of the second study, which found that indoor school air concentrations were similar to outdoor air concentrations.

Xylene concentrations in food were derived from the FDA's Total Diet Survey and the LifeLine computer-based modeling system. Drinking water was assessed using available data from EPA and the U.S. Geological Survey in conjunction with the LifeLine model. Intakes derived from the model were found to be comparable to those found in a recent study in the United Kingdom.

The presence of xylenes in human milk was simulated using a pharmacokinetic model to estimate VOC intake by infants, given a known nursing schedule and level of exposure experienced by the mother. The model parameters and results are discussed in detail.

The sponsor's submission addresses several microenvironments where exposure to xylenes could be significant. Xylene concentrations in vehicles were estimated using mean values from three studies; the number of samples collected in each study is not provided. Similarly, exposure during refueling is assessed using data from two studies,

with no *n* provided. For the use of consumer products, the submitter used the Multi-Chamber Concentration and Exposure Model to estimate exposure in both the room of product use and other parts of the house. Use patterns for consumer products were estimated using data from EPA-sponsored studies and from EPA's Exposure Factors Handbook.

The sponsor's exposure assessment concludes with an extensive discussion of uncertainty for each of the exposure scenarios investigated. The principal sources of uncertainty were the use of published monitoring data as representative values for the U.S. population and the use of mathematical modeling in cases where measured data were insufficient.

3.0. Summary of Hazard Assessment

Table 1. Summary of Existing Tier 1 Toxicity Studies

Tier 1 Toxicity Studies		m-Xylenes	o-Xylenes	p-Xylenes	Mixed Xylenes*
Acute Toxicity	Oral	✓	✓	✓	✓
	Dermal	✓	X	X	✓
	Inhalation	✓	✓	✓	✓
Genetic Toxicity (In Vitro)	Bacterial	✓	✓	✓	✓
	Cytogenetics	X	X	X	✓
Genetic Toxicity (In Vivo)	Micronucleus or chromosomal aberrations	✓	✓	✓	✓
Repeat-Dose Toxicity		✓	X	✓	✓
Combined Repeat-Dose Toxicity with Reproductive and Developmental Toxicity Screens		✓	✓	✓	✓

* Mixed xylenes consists of the three individual isomers (m-, o-, and p-xylene), as well as ethylbenzene, which is generally in the range of 5-20% by weight. Ethylbenzene exposure is being evaluated separately under VCCEP. ✓ = data available; X = data unavailable.

Toxicokinetics of Xylenes

The absorption, distribution, metabolism, and elimination of xylenes have been extensively studied in rats and mice. The available studies indicate that xylenes are rapidly absorbed following both inhalation and oral exposure. Uptake of xylenes in the respiratory tract is increased by physical exercise. Following absorption, considerable

metabolism occurs, with the liver being the primary site of metabolism. Xylenes are distributed throughout the body, but show the greatest affinity for lipid-rich tissues such as adipose tissue or the brain. Elimination is rapid and occurs primarily in the urine, with the predominant form being the glycine conjugate of methylbenzoic acid (methylhippuric acid). In humans exposed by inhalation, the loss of xylene from the blood has been shown to follow biphasic, first-order kinetics with half-lives of about 0.5–1 hour and 20–30 hours.

Physiologically based pharmacokinetic (PBPK) models for m-xylene inhalation have been developed for both rats and humans. Conceptually, the models consist of five dynamic tissue compartments representing the lung, adipose tissue, slowly perfused tissues, richly perfused tissues, and the liver. Inhalation of m-xylene is represented by addition of m-xylene to the system via the lung component. Because the available models lack an oral input component, they can not be used to extrapolate data between the inhalation and oral routes of exposure.

Toxicity Data in Humans

Available human data on xylenes are limited. EPA's Toxicological Review of xylenes for the IRIS Assessment (dated January 2003) provides a review of occupational epidemiological studies and case reports. Cancer studies reported in the IRIS Assessment did not quantify xylene exposures or specify xylene composition, involved exposures to several other solvents, and involved small numbers of cases, among other limitations. Three noncancer studies in occupational cohorts were described in the IRIS Assessment. One study identified neurological symptoms in workers in a plant in China, based on responses to a subjective symptom questionnaire. The other 2 studies examined pregnancy outcomes in women in the workplace in Finland. The studies on pregnancy outcome in women exposed to xylenes in the workplace were fairly limited in providing information on reproductive toxicity in humans. Among other limitations, exposures were not quantified, the number of cases of spontaneous abortions was small, and other chemicals, including other solvents, were present in the workplace. None of the case reports provided exposure concentrations and exposures to other chemicals took place; however, persons with accidental exposures to xylenes experienced nose, throat, and eye irritation and neurological symptoms (eg. headaches, dizziness, vertigo, seizures, etc.).

The interim AEGL-1 set for xylenes was based on a human study that reported eye irritation during exposure to 400 ppm mixed xylenes after 30 minutes of exposure. The AEGL-1 value is 130 ppm (after applying an intraspecies UF of 3). The sponsor used the interim AEGL-1 to evaluate acute inhalation exposures.

Toxicity Data in Animals

Hazard endpoints in the sponsor's report were based on available animal toxicology data on individual xylene isomers and isomer mixtures. The existing information is too numerous to summarize here in any detail; only the main highlights of this data will be summarized below.

Mutagenicity

Xylenes have been tested for mutagenicity and genotoxicity in a range of *in vitro* and *in vivo* systems. Most test results indicate xylenes are not mutagenic and do not induce chromosomal abnormalities. One study of cultured human lymphocytes, indicates that at high concentrations, xylene exposure can induce DNA fragmentation, probably indirectly by disrupting cell membranes and causing cytotoxicity (14% viability) by the release of active nuclease.

Xylenes were negative in the *Salmonella typhimurium* reverse mutation assays, *E. coli* forward mutation assays, and in a yeast mitotic gene conversion assay using *Saccharomyces cerevisiae*. Using cultured human lymphocytes or cultured Chinese hamster ovary cells, exposure to xylenes did not increase the frequency of sister chromatid exchanges.

Peripheral blood lymphocytes of humans exposed to xylenes *in vivo* did not show increased sister chromatid exchanges, chromosomal aberrations, or micronuclei formation. Similarly, rats and mice exposed *in vivo* by oral administration or injection did not have increased chromosomal aberrations in reticulocytes or bone marrow.

Acute Toxicity

Acute toxicity of xylenes has been studied in laboratory animals, mainly rats and mice. The sponsor summarizes that “mixed xylenes and xylene isomers induce minimal oral (rats and mice), dermal (rabbits), intraperitoneal (rats and mice), or inhalation (rat and mice) acute toxicity. Mixed xylenes, m- and p-xylene are moderate to marked dermal irritants and induce mild to moderate eye irritation in rabbits.”

Reported LD₅₀ for rats exposed orally to mixed xylenes range from 3523 mg/kg to 8600 mg/kg. The NTP studied acute oral toxicity of mixed xylenes in rats and mice exposed by gavage in corn oil. In single-administration studies, groups of five F344/N rats and B6C3F1 mice of each sex received 500, 1,000, 2,000, 4,000, or 6,000 mg/kg. Administration of xylenes caused deaths at 6,000 mg/kg in rats and mice of each sex and at 4,000 mg/kg in male rats. In rats, clinical signs observed within 24 hours of dosing at 4,000 mg/kg included prostration, loss of muscular coordination, and loss of hind limb movement; these effects continued through the second week of observation. Tremors, prone position, and slowed breathing were recorded for mice on day 3, but all mice appeared normal by the end of the 2-week observation period.

Deaths are reported in studies of inhalation toxicity in rodents at concentrations ranging from approximately 2000 ppm (m-xylene in mice, 24-hour exposure) to 6700 ppm (mixed xylene in rats, 4-hour exposure).

Repeated Dose Toxicity

For oral exposure, minimal comparison studies on the toxicity of individual xylene isomers are available. For inhalation exposure, various patterns of toxicity among xylene isomers have been reported. No consistent pattern in toxicity profiles following oral or inhalation exposure has been identified.

Oral

No consistent target organ effects have been observed in the numerous repeat-dose subchronic oral toxicity studies in rats and mice. Among the many effects observed, decreased body weight, observed most consistently in male rats, has been identified as the most sensitive health effect from repeated chronic exposure. In the only animal study of chronic duration, the 2-year NTP study in rats (used to derive the EPA IRIS RfD of 0.2 mg/kg-day), evidence of decreased body weight and possible increased mortality in male rats was observed at doses lower than those that produced effects seen in other studies; decreased body weights and possible increased mortality were observed in male but not female rats exposed to 500 mg/kg-day of mixed xylenes by gavage for 2 years. Increases in liver and kidney weights were also observed, but these effects occurred at dose levels above the lowest levels inducing body weight changes, were seen in the absence of any histopathology, and occurred inconsistently across studies.

Inhalation

Results from studies in rats, mice, and rabbits clearly identify potential persistent neurological impairment as a potential health hazard from repeated inhalation exposure.

A number of subchronic studies in animals provide evidence for neurological effects following repeated inhalation exposures to xylenes; subchronic studies in rats have demonstrated that neurological effects in adult animals are the most sensitive effects of xylenes following repeated inhalation exposures.

At higher exposure levels, changes in body weight have been reported in some studies, but not in others. Similarly, high-dose exposure to xylenes has resulted in changes in liver morphology, weight, and enzymatic functions.

Dermal

No repeat dose toxicity studies by the dermal route are available; only acute toxicity studies by this route were located.

Neurotoxicity

For oral exposures, animal data on neurological effects are limited. A comprehensive examination of persistent changes in neurobehavior (e.g., a functional observational battery) following acute or repeated oral exposure to xylenes has not been conducted, and any gross clinical signs and symptoms of neurological impairment observed in

subchronic oral studies occurred only at exposure levels above the lowest levels associated with body weight changes.

Subchronic studies in rats have demonstrated that neurological effects in adult animals are the most sensitive effects of xylenes following repeated inhalation exposures, with measurable effects in several neurobehavioral endpoints beginning at concentrations as low as 100 ppm m-xylenes, following exposures for 6 hours per day, 5 days per week, for 3 months (used to derive the EPA IRIS RfC of 0.1 mg/m³). Statistically significant changes in motor coordination (impaired rotarod performance and decreased motor activity), altered radial maze performance (spatial learning impairment), and increased sensitivity to pain were reported; tests of these endpoints conducted at least 24 hours after exposure ceased provided some evidence the changes were persistent. Overall results from the rat studies provide evidence that repeated exposure to m-xylene at concentrations \geq 100 ppm (6 hours per day, 5 days per week) may produce persistent changes in several neurological endpoints in adult rats. Supporting evidence for persistent neurologic effects from xylenes exposure includes reports of changes in indices of hearing loss in rats exposed to \geq 800 ppm mixed xylenes 14 hours per day for 6 weeks and in rats exposed to 1000 ppm mixed xylenes 18 hours per day, 7 days per week, for 61 days.

Cancer

No chronic toxicity or cancer studies in animals exposed by inhalation to xylenes are available.

The animal carcinogenicity data base for xylenes is limited to an NTP oral bioassay in rats and mice, and an oral bioassay in rats. The oral NTP study produced no evidence of carcinogenicity in male or female rats exposed to doses up to 500 mg/kg-day, or in male or female mice exposed to doses up to 1000 mg/kg-day. The oral bioassay in rats provided incomplete information regarding tumor incidence data and pathology and was therefore determined to be of limited use in evaluating the carcinogenicity of xylenes. Results from genotoxicity studies have been consistently negative.

Reproductive/Developmental Toxicity

No studies of the reproductive toxicity of xylenes following oral exposures are available.

Results from two animal studies indicate that developmental effects are a potential health hazard from oral exposures to xylenes. Cleft palate formation was reported in the fetuses of mice exposed to 2060 mg/kg-day, but not at 1030 mg/kg-day on gestation days 6-15. Other oral gestational exposures of mice also reported cleft palate formation at 1960 mg/kg-day, but not at 780 mg/kg-day. Maternal toxicity was not sufficiently evaluated in these studies.

A one-generation reproductive toxicity study in rats by the inhalation route has been conducted. In that study, groups of male and female CD rats were exposed to 0, 60, 250,

or 500 ppm mixed xylenes by inhalation for 6 hours per day, 5 days per week, for 131 days prior to mating, with exposure continuing in females on gestation days 1-20 and lactation days 5-20. No adverse effects were noted in F₀ adults. No differences were observed in testes weights or histological examination of reproductive tissue in xylene-exposed males sacrificed after mating when compared with control males. Decreases in the female mating index were not considered by the authors to be treatment-related. The male mating index, pregnancy rate, and fertility index were comparable to controls. The highest exposure level in this study, 500 ppm, was considered a NOAEL for reproductive endpoints. An assessment of developmental effects in the fetuses at gestation day 21 in this study also identified 500 ppm as a NOAEL for maternal and developmental toxicity (including assessment of external, visceral, and skeletal fetal malformations or variations).

A number of studies have examined standard developmental toxicity endpoints in offspring of rats, mice, and rabbits exposed to mixed xylenes or individual xylene isomers following inhalation exposures. These studies identified maternally toxic levels for decreased body weight gain in pregnant rats at doses greater than or equal to 700 ppm o-, p-, or m-xylene 24 hours per day, or 1600 ppm p-xylene 6 hours per day; and for maternal death and abortions in pregnant rabbits exposed to 230 ppm mixed xylenes or p-xylene for 24 hours per day. Pertinent developmental effects in rats such as fetal skeletal and visceral malformations (such as cleft palate) and variations (such as delayed ossification or extra ribs) were reported at concentrations of up to 700 ppm o-, m-, or p-xylene 24 hours per day or 780 ppm mixed xylenes for 24 hours per day. Statistically significant increased incidences of fetuses with delayed ossification or extra ribs were reported in these studies on an exposure-group basis; only one study provided litter-specific information. The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 350 or 700 ppm 24 hours per day or at mixed xylene concentrations of 780 ppm 24 hours per day, and increased abortions in rabbits exposed to 230 ppm 24 hours per day.

A more recent study examining the developmental toxicity of the xylene isomers by the inhalation route has been conducted. In that study, five groups of 20-26 pregnant Sprague-Dawley rats were exposed by whole body inhalation to 0, 100, 500, 1000, or 2000 ppm of either o-, m-, p-xylene, technical xylenes, or ethylbenzene 6 hours/day on gestation days 6-20. Maternal body weights, body weight changes, and corrected weight gain (minus gravid uterine weight) were recorded throughout gestation. Dams were sacrificed on gestation day 21, the uterus was removed and weighed, and the number of corpora lutea, implantation sites, resorptions, and dead and live fetuses recorded. Live fetuses were weighed, sexed, and examined for external anomalies; half of the fetuses from each litter were examined for internal soft tissue changes, the other half for skeletal examination. Signs of maternal toxicity included significant reductions in maternal body weight gain, and decreases in food consumption and corrected weight gain at 1000 and 2000 ppm for the individual xylene isomers, and at 2000 ppm for technical xylene. Reductions in maternal food consumption and corrected weight gain were also observed at doses \geq 1000 ppm ethylbenzene. Signs of developmental toxicity included significant decreases in fetal body weight at 500 ppm for o-xylene or technical xylene, 1000 ppm for

m- or p-xylene, and at 1000 ppm ethylbenzene. Delays in ossification were observed in fetuses exposed to 2000 ppm m-xylene. Increases in skeletal variations were also observed in fetuses exposed to 2000 ppm o- or p-xylene, and 2000 ppm ethylbenzene; however, these skeletal variations occurred at the same rate as in the control group. No other effects were reported. The study authors concluded a NOAEL of 500 ppm for m- and p-xylene for both maternal and developmental toxicity; and for maternal and developmental toxicity, a NOAEL of 500 ppm and 1000 ppm, respectively, for both o-xylene and technical xylene. The results of this study are in contrast to those observed in earlier studies where signs of developmental toxicity were seen at lower concentrations. The study authors suggest that perhaps these differences could be due, in part, to the shorter length of daily exposure (6 hours versus 24 hours). In addition, previous studies examining potential developmental toxicity of xylenes did not give adequate information on the criteria used to assess skeletal effects, and this might also account for the differences observed. The sponsor suggests that the differences are due to the fact that the quality and interpretability of the earlier studies varied considerably and a complete assessment of the results was sometimes difficult due to the absence of key data and reporting. The sponsor selected the more recent study as the key study for the developmental toxicity endpoint because it was the most modern and comprehensive study, concurrently evaluating mixed xylenes, the individual isomers, and ethylbenzene, and provided key data and statistics.

Developmental Neurotoxicity

No available studies have examined the potential effects of oral exposure of xylenes on developmental neurobehavioral endpoints.

A number of studies have examined neurobehavioral endpoints in offspring of animals exposed to mixed xylenes or individual xylene isomers following inhalation exposures during gestation; however, most of these studies had only one exposure concentration tested and only a limited battery of behavioral tests assessed (water maze test, open field performance, air-righting reflex, and rotarod performance). Equivocal evidence exists for impaired neurological development in rat offspring following gestational exposure to inhaled xylenes. Impaired cognitive (but not motor) performance in the Morris water maze test in female but not male offspring of rats exposed to 500 ppm mixed xylenes 6 hours per day on gestation days 7-20 and decreased rotarod performance were observed in offspring in rats exposed to 200 ppm 'technical' xylene 6 hours per day on gestation days 6-20. Deficits in the water maze test were observed only in female rat offspring raised in standard housing and not in female rats raised in enriched housing with various toys. The decreases in rotarod performance were not observed in a later study by the same group of investigators. The findings of the earlier study were in question because it was not conducted by experimenters who were blind to the exposure status of the rats. In addition, offspring of rats exposed to 800 or 1600 ppm p-xylene 6 hours per day on gestation days 7-16 performed similarly to offspring of nonexposed rats in tests of CNS development; an acoustic startle response test on post-natal days 13, 17, 21, and 63 and a figure-eight maze test on post-natal days 22 and 65.

Immunotoxicity

Limited data are available regarding the possible immunotoxic effects in animals following exposure to xylenes.

Inconsistent results for thymus and spleen weights were observed in animals exposed orally to xylenes. Decreases in thymus and spleen weights in the absence of histopathology were observed in male and female rats exposed orally to 2000 mg/kg-day m-, o-, and p-xylene for 10 days. No increases in thymus or spleen weights were observed in rats exposed up to 1500 mg/kg-day mixed xylenes for 90 days, or in rats and dogs exposed up to 13 weeks.

Inhalation exposures in mice to p-xylene concentrations as high as 1200 ppm, 6 hours per day for 4 days did not exhibit adverse effects on splenic natural killer cell activity.

4.0 Risk Characterization

The sponsor used several toxicological indices to calculate the quantitative risk estimates. For oral and dermal exposures, risks were calculated using the EPA oral reference dose (RfD) of 0.2 mg/kg-day. Inhalation exposures were evaluated by the sponsor using a chronic toxicological index, labeled a chronic inhalation health benchmark, of 0.66 mg/m³ instead of the EPA RfC of 0.1 mg/m³. For short-term air exposures, the sponsor used the interim AEGL-1 value of 130 ppm.

The sponsor evaluated the xylene exposures received from everyday background sources in ambient air, water, food and in-vehicle air. The sponsor concluded that except for the nursing infant of an occupationally-exposed mother, aggregated background concentrations result in hazard indices (HIs) that are less than 0.05 at the high-end exposure for all age groups.

The sponsor estimated total xylene exposure to the nursing infant of an occupationally-exposed mother range from a typical exposure of 0.0005 mg/kg-day to a high-end exposure of 0.027 mg/kg-day. The sponsor calculated HQs ranging from 0.003 to 0.13 for this group of children.

The sponsor concluded chronic, source-specific, inhalation exposures to xylenes from tobacco smoking and vehicle refueling pathways do not exceed the sponsor's health benchmark. The sponsor states that HIs range from 0.0009 for a child exposed only to ETS to 0.034 for an adult exposed to ETS and mainstream smoke. The sponsor concludes that HIs do not exceed 0.003 for a high-end exposure during gasoline refueling.

Short term air concentrations of xylenes to which children may be exposed during use of various consumer products are not expected to exceed the interim AEGL-1 value of 130 ppm under typical or high-end exposure conditions.

5.0 Summary of the Sponsor's Data Needs Assessment

The sponsor concludes that no further testing is needed on the VCCEP hazard endpoints. Their rationale is that there are significant margins between the HIs and estimated exposures, and there is extensive data covering the endpoints for the three VCCEP hazard Tiers.

The sponsor acknowledges in general terms that there may be data gaps for exposure of children to xylenes. The sponsor states, however, that the information presented in their submission is adequate to demonstrate that reasonably anticipated exposures to xylenes from environmental sources are not likely to present significant health risks to children. Therefore, the sponsor does not identify specific data gaps or data needs for exposure.

6.0 EPA Response to the Data Needs Assessment

The sponsor's submission for the xylenes category is a Tier 1 Data Summary and contains a hazard assessment, exposure assessment, risk assessment, and data needs assessment. It references the data sources for the exposure estimates considered.

For the exposure assessment, there are areas of the report that EPA believes lack data, additional analyses, or transparent presentation. However, EPA does not believe that these areas would significantly impact the exposure estimates for xylenes and therefore characterizes these exposure areas as data gaps, not data needs.

Although the submission presents Industrial Hygiene monitoring data, these data only cover employees who did not wear respirators. These data may have only limited value since it is likely that the employees who did wear respirators would have had higher potential exposures (since their activities required them to wear respirators). The submission could benefit from additional exposure data for employees wearing respirators who might work in areas where higher airborne concentrations of xylenes exist.

EPA notes that the submission presented exposure records from AIHA journal papers. The data consisted of averaged inhalation exposures for various end-use activities. As a result of the exposures being averaged, it is not possible to determine which end-use activities present the highest potential occupational exposures. The submission could benefit from presenting the inhalation exposures independently so that it may be possible to use Department of Labor statistics to identify the occupations (and subsequently the end-use activities) where women of childbearing age have the highest employment.

EPA notes that the submission presents information on exposures during petrochemical processing. There is potential for worker and general population exposure to xylenes through air emissions from petrochemical processing facilities. The submission includes monitoring data for xylene air concentrations at these facilities. However, allowances exist for these facilities to release "burps" or emergency emissions under certain

circumstances. It is not transparent whether these data include emissions during these events (“burps”). Additional characterization of these emissions and their effect on ambient air concentrations may help to present a more transparent picture of the potential impact on children who live in areas surrounding these facilities.

EPA notes that the submission provides two aggregate exposure data to xylenes (including mean and 95th percentile) during eight end use activities including adhesives, auto body and furniture painting. It may be more transparent to present the exposure data separately for the various end use activities.

EPA notes that there was limited investigation of dermal exposure to xylenes using the EASE model. An explanation of the modeled results, including conservative assumptions (e.g. exposure duration and concentration) and rationale as to why the scenario being assessed should result in the highest exposure among the various scenarios would be beneficial. Also additional dermal data, perhaps from readily available literature, such as the NIOSH Health Hazard Evaluations, for various uses may be available and may help to provide a clearer picture of potential risks from dermal exposure.

The sponsor’s submission would benefit from including a complete list of physical-chemical properties of the xylenes and discussing, at least briefly, the environmental fate of the xylenes.

The sponsor’s exposure assessment would benefit from including more of the childhood age groups recommended in the EPA’s recently published Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants, especially for children less than 12 months old. Several Peer Consultation panelists stated there should be an evaluation of more than four age groups of children and in particular there should be a division of the under 1 year old into multiple groups. Any future exposure assessment by the sponsor should consider exposure of additional age groups.

All Tier 1 toxicity studies and most Tier 2 toxicity studies have been conducted. For Tier 1, acute toxicity studies, mutagenicity studies, a one-generation reproductive toxicity study, and numerous repeat-dose toxicity studies have been conducted. For Tier 2, numerous repeat-dose toxicity studies, developmental toxicity studies in two species, mutagenicity studies, and metabolism and pharmacokinetic studies have been conducted.

EPA has identified two data gaps for Tier 2 toxicity studies; an immunotoxicity study, and a two-generation reproductive toxicity study; however, EPA does not consider these data gaps as data needs for the following reasons. For immunotoxicity, limited data regarding possible immunotoxic effects in animals following exposure to xylenes is equivocal, and none of the numerous repeat-dose toxicity studies provides any evidence that the immune system is a target. For reproductive toxicity, no effects were observed in a one-generation reproductive toxicity study in animals exposed to xylenes by the inhalation route. In addition, a definitive inhalation developmental toxicity study

exhibited effects only at extremely high concentrations (LOAELs of 500 -1000 ppm). Members of the Peer Consultation Panel also stated that a 2-generation study was not warranted. Therefore, EPA contends that it is unlikely that any significant new information would be gained by conducting a two-generation reproductive toxicity study at this time.

EPA has identified several data gaps for Tier 3 toxicity studies (a chronic toxicity/carcinogenicity study by the inhalation route, a complete neurotoxicity screening battery, and a developmental neurotoxicity study). EPA believes that based on available structure-activity relationships and lack of structural alerts, there is a low carcinogenicity concern for xylenes. Given this, in addition to the negative carcinogenicity data by the oral route and consistently negative results from genotoxicity studies, carcinogenicity by the inhalation route is not expected. Therefore, EPA does not consider chronic toxicity/carcinogenicity by the inhalation route a data need at this time. However, EPA does consider the adult neurotoxicity screening battery and the developmental neurotoxicity study as data needs for the following reasons. The sponsor clearly acknowledges and identifies neurotoxicity as the primary health effect and most sensitive endpoint for xylenes in animals and in humans. The sponsor also clearly acknowledges that the available studies (Hass et al., 1995, 1997; Korsak et al., 1994, among others) assessing this endpoint have several limitations including the absence of dose-response data, the lack of definitive NOAEL levels, single-dose studies, and the lack of consistent results. Members of the Peer Consultation Panel also noted that neurobehavioral development was a concern because there were no data from direct dosing during the neonatal and post-natal period to address this endpoint. EPA agrees that there is sufficient evidence to support a concern for neurotoxicity for this class, but feels that the existing data base is inadequate to fully characterize and assess risk for this endpoint for the same reasons articulated by the sponsor. Therefore, EPA has identified adult neurotoxicity and developmental neurotoxicity studies as Tier 3 data needs and recommends that these studies be conducted on the commercial xylene mixture, preferably by the inhalation route.

The sponsor suggests using toxicity data on structurally similar solvents (toluene, benzene, and aromatic naphtha chemicals) where data are lacking on mixed xylenes and individual xylene isomers. In general terms, EPA finds this approach can be a reasonable one. However in the sponsor's xylene report there is not adequate scientific data or argument presented to support the approach, such as presentation of specific neurotoxicity studies of analogs with MOA or metabolism comparisons to xylenes. Therefore, EPA disagrees with the sponsor's statement that analog data contained in the report is sufficient to fill in Tier 3 data needs in the hazard assessment.

There are also uncertainties in the exposure assessment that contribute to the decision to consider the neurotoxicity tests as data needs. As mentioned by members of the peer consultation panel, no data is presented on accidental poisoning or deliberate intoxication with xylene in children. Also as voiced by the panel is the concern that maximum consumer exposures could have been underestimated by using only exposures generated when using products according to labels as maximal, rather than estimation of maximum

reasonably foreseeable use. One panel member stated that he found a much larger number of consumer products contain xylenes than considered in the report.

Finally, there are uncertainties associated with the sponsor's risk calculations. For chronic exposures, the study of Korsak et al. (1994) of rats exposed to *m*-xylene was used as the principal study to calculate IRIS RfC of 0.1 mg/m³ (EPA 2003a). The sponsor used the same study to derive their chronic inhalation health benchmark concentration of 0.66 mg/m³, but does not adequately justify the decrease in adjustment and uncertainty factors compare to the EPA RfC. The sponsor did not refer to any new ADME or toxicological data or models to support their estimates. However, HQs and HIs calculated with the EPA RfC may yield values closer to 1.

In addition, the sponsor used the interim AEGL-1 value of 130 ppm to evaluate short-term air exposures. However, the sponsor does not emphasize the AEGL-1 is intended as a screening level that is designed only for very rare or once-in-a-lifetime exposures of less than 8 hours. Many consumer products contain xylenes, so the expected minimum exposure period to children would be far more frequent than a "once-in-a-lifetime" event. Therefore, a toxicity value based on the developmental toxicity studies or the ATSDR acute inhalation MRL of 2 ppm (for exposure periods up to 14 days) would represent a more appropriate index for evaluating children's risk. It appears that the xylene exposures estimated by the sponsor would be less than these values.

In summary, EPA has identified the adult neurotoxicity screening battery and developmental neurotoxicity studies as Tier 3 data needs based on substantial uncertainties in the existing toxicology database, the exposure assessment, and the resulting risk calculations. This recommendation is consistent with the recommendations of the Peer Consultation Panel.

Reference

U.S. EPA. 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. U.S. Environmental Protection Agency, Washington, D.C. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=146583>