United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7508C)

September 26, 2005

Reregistration Eligibility Decision for Xylene

List C

Case No. 3020

Approved by: _____ **Date:**_____

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Director
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Reregistration Eligibility Decision

Xylene

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Background:

EPA has completed its Registration Eligibility Decision (RED) document for xylene. In this document, EPA presents the results of its review of the potential human health effects of dietary, drinking water, and occupational exposure to xylene, as well as ecological risks. Currently, there are no homeowner products, so there are no use patterns that are likely to result in residential handler or postapplication exposures. The only use is as an aquatic herbicide in programs of the Bureau of Reclamation, U.S. Department of Interior, and for its cooperating water user organizations. There are also inert ingredient uses for xylene which the Agency will be assessing, but these uses are considerably different from these aquatic herbicide uses of the active ingredient, so another document is being written by the Agency's Lower Risk Pesticide Chemical Focus Group to reassess the exemption from the requirement for tolerances for the inert ingredient uses of xylene.

I. Executive Summary:

Xylene is used as an aquatic herbicide. There is only one registered pesticide product containing xylene as the active ingredient. The current label for this end use product clearly indicates that it is only for use in programs of the Bureau of Reclamation, U.S. Department of Interior, and for its cooperating water user organizations. For this assessment of xylene, occupational handler inhalation and dermal exposures were examined. An oral NOAEL of 150 mg/kg/day was used to assess short-term risks from dermal exposures. The oral dose was converted to an equivalent dermal dose using a 100% dermal absorption factor (a conservative assumption). An inhalation NOAEL of 57.6 mg/kg/day was used to assess short-term risks from inhalation exposures. This endpoint was based on behavioral effects, and is more health protective than some other studies which could have been selected such as those showing reduced body weight gain, developmental effects, or mortality, all of which were seen at higher exposure doses. Available data indicate that xylene is not a carcinogen.

Due principally to its high vapor pressure, no residues of xylene are expected to occur on harvested crops as a result of irrigation with xylene-treated waters. Thus, the Agency plans to propose revocation of the tolerance exemption for this use at 40CFR 180.1025. Further, based on current and future label restrictions, residues in drinking water are expected to be well below the Maximum Contaminant Level (MCL) established by the Agency under the Safe Drinking Water Act.

For occupational applications of liquid formulations to water, the current label indicates that xylene is directly metered into the suction side of a pump, and injected below the surface of the water to treat aquatic plants. This technique is the only method of application to flowing waters, but is also used for applications to quiescent waters. It has been determined that there is a potential for exposure to xylene in occupational scenarios from handling the xylene product during the mixing/loading and the application process (i.e., mixers/loaders/applicators) and a potential for postapplication worker exposure. Postapplication occupational exposures following application to aquatic areas is likely limited to persons who contact the treated water to perform tests, such as testing the levels of xylene, or persons such as agricultural workers or irrigation water suppliers who contact treated water in irrigation canals. The exposure scenarios and application rates chosen for this risk assessment were based on the anticipated use patterns and the current label for the xylene product.

For the handler assessment, combined dermal plus inhalation risks for all of the handler scenarios (which included only engineering controls for a closed system) are below EPA's level of concern. The dermal margin of exposure (MOE) was calculated to be 840, and the inhalation MOE was calculated to be 39,000. The combined dermal plus inhalation MOE was calculated to be 820. The target MOE is 100. Thus, these occupational exposures do not pose a risk of concern to the Agency.

The most important environmental fate property for xylenes applied to a drainage ditch is volatilization. Xylenes are also susceptible to biodegradation under aerobic conditions, but the rate of volatilization (with a vapor pressure between 5 and 9 mm Hg) is significantly greater than the rate of degradation (half-life on the order of 20 days). Abiotic degradation mechanisms, such as hydrolysis and photolysis, are not important. Although xylenes have high to moderate mobility in soils when applied directly to water, leaching to groundwater is considered unlikely. The Agency evaluated risks to both aquatic and terrestrial organisms. The assessment does show risk to certain aquatic species, however a reduction in allowable discharge concentrations of xylene-treated water and a restriction on the states in which xylene may be used addresses this risk concern.

II. Use Information:

Xylene (dimethyl-benzene) is composed of three isomers: o-, m-, and p-xylene. The CAS Number of the mixed isomers is 1330-20-7, and the CAS Nos. of the individual isomers are 95-47-6 for o-, 108-38-3 for m-, and 106-42-3 for p-xylene. This active ingredient is used in an end-use product which is an aquatic herbicide; there is only one registered pesticide product containing xylene as the active ingredient (EPA Reg. No: 9768-18).

According to information in the Agency REFS database, there had been as many as 1391 products registered with Xylene (OPP Chemical Code 086802) as the active ingredient, and 982 products registered with Xylene Range Aromatic Solvents (OPP Chemical Code 086803); however, except for the one registered product all these other products have been cancelled, the registrants have modified the formulation or, conversely, have not modified the formulation, but have made requests to the Registration Division that the "xylene" or "xylene range aromatic solvent" be considered an inert ingredient (for example, listed on the CSF as an inert ingredient, with declared use as a solvent).

The current label for the one remaining active product lists "Xylene Range Aromatic Solvents" as the active ingredient. According to the Confidential Statement of Formulation on file from the Registrant, the current active ingredient is xylene (mixed isomers). Thus, the revised label, required to be submitted as part of the Product Reregistration process, will correct this active ingredient name, and the product will now be placed into OPP Chemical Code 086802, rather than OPP Chemical Code 086803.

The product is an aquatic weed ready-to-use herbicide produced by the Thatcher Company, containing 98% xylene. This product was first registered in February, 1968, so its original registration was with the U.S. Department of Agriculture, and predates the Environmental Protection Agency.

The tolerance exemption being reassessed in this document, the respective citation in the Code of Federal Regulations (CFR), and the use pattern as an active ingredient are listed in Table 1.

Table 1. Tolerance Exemptions Being Reassessed for Xylene, for both Inert Ingredient and Active Ingredient Uses Listed [1].				
Tolerance Exemption Expression	CAS No.	40 CFR	PC Code	Use Pattern (& Limits)
Xylene	1330-20-7	180.910 [2, 3]	Inert: 886802 [1]	Solvent or co-solvent (in pesticide formulations for grain storage only)
		180.920 [4]		solvent, co-solvent
		180.930 [5]		solvent, co-solvent
		180.1025	Active: 086802 [6]	aquatic herbicide applied to irrigation conveyance systems

1. Xylene used as an inert ingredient has various use patterns, all very different from the use patterns of the aquatic herbicide which is the subject of this RED; therefore, another document is being written to address the inert ingredient tolerances.
2. Expressed in 40 CRF 180.910 as "Xylene meeting the specifications listed in 21 CFR 172.884(b)(4)."
3. Residues listed in 40 CFR §180.910 [formerly 40 CFR§ 180.1001(c)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops or to raw agricultural commodities after harvest.
4. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.1001(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.
5. Residues listed in 40 CFR §180.930 [formerly 40 CFR§ 180.1001(e)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to animals only.
6. The active ingredient PC Code for this end-use product had formerly been considered to be 086803, Xylenes Range Aromatic Solvents; however, the registrant has provided clarification regarding the actual chemical composition of the active ingredient which is being utilized; therefore, 086802, Xylene, is now deemed to be the correct PC Code for this end-use product.

III. Physical/Chemical Properties:

The key physical/chemical properties for xylene are listed in Table 2.

Table 2. Physical/Chemical Properties of the Mixed Isomers of Xylene (CAS No. 1330-20-7)	
Molecular formula	C_8H_{10}
Molecular weight	106.16
Boiling Point	138.5°C
Vapor Pressure	5-9 mm Hg at 25°C
Density	0.864 gm/cm^3
Water Solubility	130 - 190 mg/L
Henry's Law Constant	6.4 x 10^{-3} atm/m^3 • mole
Soil sorption (K_{OC})	2.2
Log K_{ow}	3.12-3.20
Odor Threshold	Air: 0.2 - 3.7 ppm (0.0045 - 0.016 mg/L)
	Water: 0.5 - 2 mg/l

Reference: ATSDR ToxProfile (1995) and HSDB (2005)

IV. Hazard Characterization:

The acute data in Table 3 are from ATSDR (1995), WHO (1991), and ChemIDplus (TOXNET).

Table 3. Acute Toxicity Profile - Mixed Isomers of Xylene and Each Individual Isomer.

Study Type (endpoint)	Species	Isomer	Results	Toxicity Category
Acute oral (LD_{50})	Rat	mixed	3523 - 8700 mg/kg	III - IV
		o -	3608 - 4400 mg/kg	III
		m -	4320 -6661 mg/kg	III - IV
		p -	4029 - 5000 mg/kg	III - IV
Acute dermal (LD_{50})	Rabbit	mixed	1700 mg/kg	III
		o -	no data found	III-IV
		m -	3228 - 14,100 mg/kg	
		p -	no data found	
Acute inhalation (LC_{50})	Rat	mixed	5000 - 10950 ppm (mg/L)	IV
		o -	4330 - 4595 ppm	
		m -	5267 - 5984 ppm	
		p -	4550 - 4740 ppm (mg/l)	
Eye irritation	Rabbit		moderate	III
Dermal irritation	Rabbit		mild to severe	II - IV
Skin sensitization	Guinea Pig		no data	

The toxicity endpoint data in Table 4 were chosen based on a review of toxicological data provided in the IRIS and ATSDR assessments, with a full summary of these data provided in Appendix B.

Table 4. Subchronic, Chronic and Other Toxicity Profile - Xylene

Study Type	Classification/Doses	Results
Oral: 90-day study: male and female Sprague-Dawley rats (Condie 1988, as cited in IRIS (EPA 2003))	0, 150, 750, or 1500 mg/kg-day mixed xylenes (17.6% o-xylene, 62.3% m-xylene and p-xylene [which coeluted], and 20% ethyl benzene)	NOAEL: 150 mg/kg-day LOAEL: 750 mg/kg-day (based on increased kidney weights and early appearance of mild nephropathy in female rats)

Table 4. Subchronic, Chronic and Other Toxicity Profile - Xylene		
Inhalation: 3-month study: male Wistar rats (Korsak et al. 1994, as cited in IRIS (EPA 2003))	0, 50, or 100 ppm m-xylene	**Behavioral** NOAEL: 50 ppm (217 mg/m^3 or 57.6 mg/kg/day) [a] **Behavioral** LOAEL: 100 ppm (based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test)
Carcinogenicity: gavage study in male and female rats and mice, 5 days per week for 103 weeks	rats: 0, 250, or 500 mg/kg/day mice: 0, 500, or 1000 mg/kg/day mixed xylenes (60% m-xylene, 13.6% p-xylene, 9.1% o-xylene, and 17.0% ethylbenzene)	not carcinogenic to either rats or mice at highest doses administered (NTP 1986); Evaluations of genotoxic effects have consistently given negative results (IRIS, 2005)

a mg/m^3 value provided in IRIS documents. Conversion to mg/kg/day = NOAEL (217 mg/m^3) * default respiratory volume for Wistar rat (0.0096 m^3/hr) * exposure time (6 hr/day, from IRIS website) / default body weight for Wistar rat (0.217 kg) = 57.6 mg/kg/day.

Toxicological Endpoint Selection:
For this assessment of xylene, occupational handler inhalation and dermal exposures were examined. An oral NOAEL was used to assess short-term risks from dermal exposures. The dermal dose was converted to an equivalent oral dose using a default/conservative 100% dermal absorption factor. The oral toxicological endpoint of 150 mg/kg-day was used. This NOAEL was based on an increase in kidney weights and an early appearance of mild nephropathy observed in female rats from a 90-day oral toxicity study (Condie, 1988).

An inhalation NOAEL was used to assess short-term risks from inhalation exposures. The inhalation toxicological endpoint of 57.6 mg/kg/day was used. This NOAEL was based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test from a 3-month inhalation study on rats. This endpoint is somewhat "conservative" (i.e., health protective), since it is based on a neurologic or behavioral effect; if another endpoint had been selected based on a frank toxicological effect (i.e., reduced body weight and/or developmental effects), the NOAEL would probably have been 3 to 5 times higher than that in Table 4.

V. Exposure Assessment:

Xylene is formulated as a liquid concentrate for use as an aquatic weed herbicide. For occupational applications of liquid formulations to water, xylene may be directly metered into the suction side of a pump and injected below the surface of the water. This technique is the only method of application to flowing waters, but is also used for applications to quiescent waters. Table 5 provides the maximum application rates. The daily areas treated were defined for each handler scenario (in appropriate units) by determining the amount that can be reasonably treated in a single day. It was assumed that the average occupational workday is 8 hours. It was also assumed that dermal absorption was 100%. The target MOE for this assessment is 100, considering a 10x uncertainty factor for intraspecies variation and a 10x uncertainty factor for interspecies extrapolation.

Table 5: Summary of Maximum Application Rates for Xylene			
Crop Type/ Use Site	**Maximum Application Rate**	**Application Equipment**	**Amount Treated Per Day**
aquatic weeds	2.61 lb ai/min	Direct metering	30 minute treatments over an 8-hour workday (480 minutes/day)

It has been determined that there is a potential for exposure to xylene in occupational scenarios from handling xylene products during the mixing, loading and application process (i.e., mixers/loaders/ applicators) and a potential for postapplication worker exposure. Postapplication occupational exposures following application to aquatic areas is likely limited to persons who contact the treated water to perform tests, such as testing the levels of xylene, or persons such as agricultural workers or irrigation water suppliers who contact treated water in irrigation canals.

The exposure scenarios and application rates chosen for this risk assessment were based on the anticipated use patterns and the current label for the xylene product (see Table 5). The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenario:

Mixer/Loader/Applicators Applying to Water:

(1) Liquid: Direct Metering (using data for mixing/loading liquid formulations in a closed system)

Exposure and Risk Summary

Handler Assessment

A summary of the occupational handler risks for each exposure scenario is presented in Table 6. For the handler assessment, the dermal risk for the handler scenario (which included only engineering controls for a closed system) is well below EPA's level of concern. The target MOE is 100, and the dermal MOE was calculated to be 840. For inhalation exposures, the MOE was calculated to be 39,000, based on the behavioral effects endpoint of 50 ppm (57.6 mg/kg/day) identified in Table 4 (there would be much higher MOEs were this assessment have utilized frank toxicological effects, such as reduced body weight and/or developmental effects, endpoints only observed at much higher inhalation exposures). The combined dermal and inhalation MOE was calculated to be 820. Thus, the Agency does not have worker risk concerns.

Table 6. Summary of Occupational Handler Exposures and Risks from Xylenes									
Exposure Scenario	Crop or Target	App Rate [a]	Time Handled Daily	Engineering Control Unit Exposures		Engineering Controls Dermal [b]		Engineering Controls Inhalation [d]	
				Dermal (mg/lb ai)	Inhalation (µg/lb ai)	Dose (mg/kg/ day)	MOE [c]	Dose (mg/kg/ day)	MOE [e]
Mixer/Loader/Applicator									
Mixing/Loading/ Applying Emulsifiable Concentrate with Direct Metering [f]	aquatic weed	2.61 lb ai/min	480 min/day	0.0086	0.083	0.18	840	0.0015	39,000

a Application rates are the maximum application rates determined from the EPA registered label for xylenes
b Eng Controls Dermal: Closed mixing/loading system, enclosed cab, or enclosed cockpit.
c Dermal MOE = NOAEL (150mg/kg/day) / dermal daily dose (mg/kg/day), where dermal dose = daily unit exposure (mg/lb ai) x application rate x amount handled per day / body weight (60 kg adult).
d Eng Controls Inhalation: Closed mixing/loading system, enclosed cab, or enclosed cockpit.
e Inhalation MOE = NOAEL (57.6 mg/kg/day) / inhalation daily dose (mg/kg/day), where inhalation dose = daily unit exposure (mg/lb ai) x application rate x amount handled per day / body weight (70 kg adult).
f Using PHED: mixing/loading liquid - closed system (engineering controls)

Postapplication Assessment

Postapplication exposure would be limited to persons testing the water in canals/irrigation ditches and also to persons exposed to irrigation water that is applied to crops. At this time there is no known method to assess these type of exposures. However, the Agency assumes that the level of exposure from these scenarios would not exceed that obtained from handling and applying the product. In addition, xylenes are highly volatile and would not be expected to remain in solution for very long, decreasing the potential for postapplication exposure.

VI. Risk Characterization:

Occupational exposure to xylenes through the application of an aquatic herbicide was evaluated in this assessment. Anticipated occupational exposures (dermal and inhalation) were not found to pose a risk (i.e., the calculated MOE was above the target MOE).

VII. Dietary (Food) Exposure:

At present, xylene is exempt from requirement for a tolerance (40CFR 180.1025) based on its use in irrigation water. The Agency expects that when xylene-treated waters are used as irrigation waters applied to fields or sprayed onto plants by overhead irrigation, the xylene will readily volatilize; the xylene isomers have vapor pressures of 5-9 mm Hg at 25° C, and Henry's Law Constants of about 6.4×10^{-3} atm/m^3 • mole, suggesting that xylene will readily partition into the atmosphere from water, soil, and the exposed surfaces of plants. Moreover, the mobility of xylene in soils is predicted to be moderate to high, based on the Koc values ranging from 39-365, suggesting that sorption to soil will also not be likely to add to any amounts of xylene available for incorporation into plant tissues. Therefore, on the basis of this information, it is expected that crops will not bear residues of xylene as a result of their receiving any applications of xylene-treated irrigation waters. Thus, the Agency has no risk concerns for dietary exposure from use of xylene in irrigation water. As a follow-up action to this RED, the Agency intends to propose revocation of the existing tolerance exemption at 40CFR 180.1025.

VIII. Drinking Water Exposure:

To minimize the risks of effects to human health, the current label indicates that water discharged from the treated drainage ditch should not flow into receiving waters if the concentration of xylene exceeds 10 ppm, and also states "Do not allow the treated water to enter any domestic system." The Agency does not have any human health risk concerns, based on the current label because 10 ppm is equivalent to the Maximum Contaminant Level (MCL) established by EPA under the Safe Drinking Water Act. However, additional label refinement will be implemented on the revised label to further clarify the description of "any domestic system," and a lower discharge level (1 ppm) will be specified for discharges of treated water into receiving rivers, streams, or lakes to accommodate the Agency concerns regarding ecological risks to aquatic organisms.

IX. Environmental Fate and Ecotoxicity Considerations:

Environmental Fate and Transport:

Xylene isomers are highly volatile and have been found to disappear rapidly from solution (WHO, 1997); for example, the half-life of o-xylene has been estimated to be 39 minutes in agitated water, 1 meter deep and with a 1 m^2 surface for evaporation. Both m-xylene and p-xylene are readily biodegradable; however, in soil and water, o-xylene has been observed to be more persistent. Bioaccumulation of all three xylene isomers has been reported to be low. Based on experimental K_{oc} values, xylene is expected to have moderate to high mobility in soils, and based on measured K_{oc} values, xylene is expected to adsorb somewhat to sediment or particulate matter in water (HSBD, 2005).

The EFED Science Chapter reports the following: "The most important fate property for xylenes applied to a drainage ditch is volatilization. Xylenes are also susceptible to biodegradation under aerobic conditions, but the rate of volatilization (half-life of about 2 days in a shallow water body; 1.2 days in typical river and 6.0 days in a pond http://www.epa.gov/OGWDW/dwh/t-voc/xylenes.html) is significantly greater than the rate of degradation (half-life on the order of 20 days) (API 1994). Abiotic degradation mechanisms, such as hydrolysis and photolysis, are not important for aromatic petroleum solvents. Although xylenes have high to moderate mobility in soils when applied directly to water, leaching to groundwater is considered unlikely." In addition, additional information is presented indicating that photolysis and hydrolysis are not important environmental fate pathways because the xylene isomers do not absorb photons of light with a wavelength greater than 290 nm, nor do they possess functional groups that are susceptible to hydrolysis under environmental conditions.

Mean background levels of the xylene isomers are around 1 $\mu g/m^3$ and 0.1 $\mu g/L$ in ambient air and in surface waters, respectively (WHO, 1997). Higher values have been measured in industrial areas, particularly around oil industries associated with discharge pipes. High levels of xylenes have been reported in groundwater associated with underground tanks and pipes.

Estimated Environmental Concentrations:

There is some uncertainty regarding the maximum exposure concentrations for aquatic organisms in both the irrigation canals and receiving waters. The solubility limits for xylene isomers are approximately 160-180 mg/L; however, within the irrigation canals, the xylene product is applied with an emulsifier which results in a greater apparent solubility, approaching the initial 740 ppm concentration level. It is known that turbulent mixing with the irrigation waters will immediately result in a lowering of this concentration, probably rapidly approaching the solubility limits of the isomers; in addition, it is known that xylene will readily dissipate from water (by degradation, volatilization, and sorption), further reducing the water concentrations as the treated water moves down-gradient in the irrigation systems.

In addition, there is also uncertainty in assuming the xylene concentrations in water bodies receiving effluents (i.e., unused irrigation water) from those irrigation districts which are discharging xylene-treated waters. The current label permits up to 10 ppm; however, it is assumed that typically very little water would be released, that the concentrations actually present in the discharge water are going to be significantly lower, and that dilution will occur in the receiving waters, as well as continued volatilization, sorption, and degradation, further reducing the actual water concentrations to which aquatic organisms would be exposed downstream in the receiving waters. In summary, the xylene dissipation from the return flows into the receiving water body depends on the amount, rate, and length of the irrigation system, the amount and rate of xylene used to treat the irrigation canals, the length of time it takes for the treated water to reach the receiving body, the volume of any irrigation water which finally enters the receiving body, the degree of turbulent mixing within the receiving water body, and the rate of flow and volume within receiving water body. Some irrigation districts discharge their released water into lakes, while some discharge into small streams, but it is not uncommon for discharges to be into large rivers, such as the Snake River or the Columbia River. Discussions with stakeholders have indicated that of these various types of receiving waters, essentially none are estuarine or marine waters.

Ecotoxicity:

WHO (1997) has described xylene as having moderate to low acute toxicity for aquatic organisms. The variation between each isomer with regard to aquatic toxicity is small. The lowest LC_{50} value, 1 mg/L, is based on a 24-hour exposure with *Daphnia magna*. This value is much higher (close to 10,000 times higher) than the mean background concentrations in surface water, as reported in the WHO (0.1 µg/L). In the WHO (1997) review, the lowest 96-hour LC_{50} value for any fish species was 1.7 mg/L, to the striped bass, a marine species, and the lowest 96-hour LC_{50} value to a freshwater species was 2.6 mg/L to the rainbow trout. Studies on terrestrial organisms (e.g., Japanese quail) have reported no overt toxicity at concentrations as high as 5000 mg/kg and LC_{50}'s of greater than 20,000 mg/kg. No studies on terrestrial plants invertebrates or field effects have been reported. Limited information is available on the chronic exposure of aquatic organisms and none of the effect levels were lower than those observed in the acute studies. The overall risk to the aquatic environment has been determined to be low, considering the rapid volatilization and degradation of xylenes and their low to moderate toxicity to organisms (WHO, 1997).

The EFED Science Chapter characterizes the ecotoxicity data as follows: "In general, results of acute toxicity studies indicate that mixed xylenes and xylene isomers are moderately to highly toxic to aquatic species. The acute toxicity values used to estimate risks to aquatic organisms are as follows:

- freshwater fish: 96-hour LC_{50} value of 2.6 mg/L for p-xylene in rainbow trout (*Salmo gairdneri*);
- freshwater invertebrates: 24-hour LC_{50} value of 1.0 mg/L for m-xylene in water flea (*Daphnia magna*);
- estuarine/marine fish: 24-hour LC_{50} value of 2.0 mg/L for p-xylene in striped bass *(Morone saxatilis)*;
- estuarine/marine invertebrates: 96-hour LC_{50} value of 1.3 mg/L for o-xylene in bay shrimp *(Crago francisocrum)*;
- algae: 72-hour LC_{50} value of 3.2 mg/L for p-xylene in green algae (*Selenastrum capricornutum*)."

In addition, due to the rapid volatilization of xylenes from water (half-lives range from less than 2 days in a shallow flowing water body to 6 days in a pond), chronic exposure of aquatic and terrestrial ecosystems is not expected. Thus, chronic toxicity studies were not assessed, and there are no requirements for additional chronic toxicity testing.

Environmental Risk Assessment:

Xylene is used as an aquatic weed control herbicide in irrigation ditches in the Western United States. This use pattern means xylene will be present in irrigation waters after treatment, and sets up several ecological risk exposure scenarios. The Agency is evaluating risks to both terrestrial and aquatic organisms. For terrestrial organisms, risk scenarios include

both drinking treated water and inhalation resulting from off-gassing from treated irrigation ditches. Risk to aquatic organisms is possible both in the irrigation canals and in the receiving waters.

Terrestrial Organisms

Considering risk to terrestrial animals, birds and mammals were assessed for oral ingestion of xylene-treated water in irrigation canals. In addition, mammals were assessed for potential inhalation risk and for combined inhalation/ingestion risk from xylene-treated irrigation canal water. Due to lack of inhalation toxicity data in birds, acute risks of exposure to birds via inhalation of volatilized xylene and combined exposure via contaminated water and inhalation could not be assessed.

The oral ingestion assessment shows that all acute RQs for mammals and birds for exposure from drinking contaminated water are below acute endangered species LOCs (LOC = 0.1). For birds, acute RQs range from <0.01 (for all three weight classes for water concentrations of 10 and 178 mg/L) to <0.027 (20 g birds for a water concentration of 740 mg/L). For mammals, acute RQs range from 0.0003 (1000 g mammals consuming water at a concentration of 10 mg/L) to 0.032 (15 g mammals consuming water at a concentration of 740 mg/L). Additionally, mammals do not appear to be at acute risk from inhalation exposure or from combined exposure via ingestion of contaminated water and inhalation. Acute RQs for mammals exposed to xylene via inhalation are below the acute endangered species LOCs (LOC = 0.1). The acute inhalation RQ based on the maximum inhalation EEC for the exposure scenario is 0.019 and the acute inhalation RQ based on the minimum inhalation EEC for the exposure scenario is several orders of magnitude below all acute LOCs. Oral ingestion/inhalation acute composite RQs for mammals range from 0.040 (1000 g mammals) to 0.051 (15 g mammals). As a result of this terrestrial risk assessment, risk management is not warranted at this time for terrestrial organism risk.

Aquatic Organisms

Aquatic organisms can be potentially exposed to xylene from both the irrigation canal where the product is used, as well as any naturally occurring water body where treated water is discharged. The Agency's ecological risk assessment does show potential risks to aquatic organisms in the treated canals. However, since these canals are part of highly managed agricultural systems, and are dry much of the year, the agency has decided that risk management is not warranted at this time for aquatic organisms in canals.

The Agency also evaluated potential exposure to aquatic organisms resulting from the discharge of xylene treated irrigation water into natural water bodies and has established a "safe" concentration of 0.04 ppm in receiving water based on the freshwater invertebrate 24-hour LC_{50} value of 1.0 mg/L, and the target RQ for endangered species of 0.05. The current label has the following statement: "Do not allow return flows of treated irrigation water into receiving rivers, streams, or lakes if xylene residues are in excess of 10 parts per million (ppm)." Using 10 ppm as a concentration starting point, the Agency's ecological risk assessment shows potential risks to aquatic organisms. Several scenarios were developed using a steady-state plug flow model. It is not possible to evaluate every discharge location and their varying flow conditions; however the model results consistently showed potential concerns when using a discharge concentration of 10 ppm. At a 1.0 ppm discharge concentration however, only a 1:25 dilution is needed to reach the 0.04 ppm level. When considering that the RQ estimates are based on aquatic toxicity tests of 24-hours or 96-hours duration (for some groups, concentrations are continuously renewed by use of a continuous-flow dilutor), and that once in receiving waters xylene is constantly dissipating due to volatilization and mixing, a 1.0 ppm discharge concentration is considered appropriate. Therefore, the Agency is requiring the following label adjustments:

- Treated irrigation water must be used to irrigate fields. Since xylene is highly volatile (vapor pressure 5-9 mm HG at 25C) this common cultural practice will greatly reduce the amount of xylene in the canal outflows that

ultimately may discharge into natural water bodies.

- If treating the fields is not feasible, the treated water must be held until measurable levels are 1 ppm or less.
- The use of xylene will be restricted to the following four States: Idaho, Montana, Oregon, and Washington.

X. Labeling for End-Use Products:

The following label changes are intended to address the potential ecological risk concerns by minimizing the amount of xylene which reaches natural receiving waters. Table 7 describes how language on the labels should be revised.

Table 7. Label Revisions

Label change	Rationale
Treated water must be either: (1) used to irrigate fields; or, (2) held in an irrigation ditch/canal until the xylene concentration has dropped to 1 ppm or below, as determined by an EPA approved method, before released from the irrigation network.	Xylene is highly volatile (vapor pressure of 5-9 mm Hg at 25C). By ensuring the treated water gets used to irrigate fields, or held until xylene has had enough time to volatilize to a target concentration of 1 ppm prior to release from the irrigation network.
Restricting the use to four States.	Currently xylene is only used in four Western States, Washington, Oregon, Idaho, and Montana. By modifying the label to reflect the actual use pattern, the Agency will have a better understanding of the possible impact of xylene on endangered species.

XI. Tolerance Reassessment:

Based on this scientific assessment, the Agency concludes that crops irrigated with xylene will bear no residues as a result of treatment of irrigation waters. Thus the tolerance exemption is not needed. As a follow-up action to this decision, the Agency will propose revocation of the exemption at 40CFR 180.1025.

XII. References:

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Ungváry, G; Varga, B; Horváth, E; Tátrai, E; Folly, G. 1981. Study on the role of maternal sex steroid production and metabolism in the embryotoxicity of para-xylene. Toxicology. 19:263–268.

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World Health Organization. 1997. United Nations Environment Programme, International Labour Organization, World Health Organization. International Programme on Chemical Safety. Environmental Health Criteria 190: Xylenes.
(Available on-line as http://www.inchem.org/documents/ehc/ehc/ehc190.htm)

Appendix A - Xylene Label Table

Summary of Labeling Changes for Xylene		
Description	Amended Labeling Language	Placement on Label
Environmental Hazards Statements Required by the RED and Agency Label Policies	"This pesticide is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. Do not contaminate water when disposing of equipment washwaters."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals
End Use Products Intended for Occupational Use		
PPE Requirements Established by the RED for Liquid Formulations[1]	"Personal Protective Equipment (PPE)" "Some materials that are chemical-resistant to this product are" *(registrant inserts correct chemical-resistant material)*. "If you want more options, follow the instructions for category" *[registrant inserts A,B,C,D,E,F,G, or H]* "on an EPA chemical-resistant category selection chart." "All handlers and applicatiors and other handlers must wear long sleeved shirt, long pants, shoes and socks, and chemical resistant gloves."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals

User Safety Recommendations	"User Safety Recommendations Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet. Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)
Environmental Hazards	"Irrigated water treated with this product may be hazardous to aquatic organisms." "Runoff may be hazardous to aquatic organisms in water adjacent to treated areas."	Precautionary Statements immediately following the User Safety Recommendations
General Application Restrictions	"Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."	Place in the Direction for Use directly above the Agricultural Use Box.
Other Application Restrictions (Risk Mitigation)	"For use only in Washington, Oregon, Idaho, and Montana." "Treated water must be either held on the irrigated field until absorbed by the soil or held in an irrigation ditch/canal until the xylene concentration has dropped to 1 ppm or below, as determined by an EPA approved method, before being released from the irrigation network."	Directions for Use

[1] PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

Appendix B - Data Supporting Guidelines for the Reregistration of Xylene

Appendix B. Data Supporting Guideline Requirements* for the Reregistration of Xylene (086802)

REQUIREMENT			CITATION(S)
PRODUCT CHEMISTRY			
New Guideline Number	Old Guideline Number	** Guidelines in bold and italicized are those listed as required in GDCI dated January 2004.*	
830.6304	63-4	Odor	ATSDR ToxProfile 1995; HSDB 2005
830.7050	*none*	UV/Visible Absorption	Gab et al, 1977
830.7220	63-6	Boiling Point	ATSDR ToxProfile 1995; HSDB 2005
830.7300	63-7	Density	ATSDR ToxProfile 1995; HSDB 2005
830.7550 830.7560 830.7570	63-11	Octanol/Water Partition Coefficient	ATSDR ToxProfile 1995; HSDB 2005
830.7840 830.7860	63-8	Solubility	ATSDR ToxProfile 1995; HSDB 2005
830.7950	63-9	Vapor Pressure	ATSDR ToxProfile 1995; HSDB 2005
ECOLOGICAL EFFECTS (Terrestrial and Aquatic Nontarget Organisms)			
850.1010	***72-2B***	Aquatic invertebrate acute toxicity, test, freshwater daphnid	Abernathy et al. 1986 (supplemental); Galassi et al, 1988 (supplemental); Holcombe et al. 1987 (supplemental)
850.1025	***72-3B***	Oyster acute toxicity test (shell deposition)	Reserved; exposure to estuarine/marine invertebrates not expected, based on current use pattern.
850.1035	***72-3C***	Mysid acute toxicity test	Abernathy et al. 1986 (supplemental);
850.1045		Penaeid acute toxicity test	Tatem et al (supplemental) 1978
850.1055	***72-3***	Bivalve acute toxicity test, estuarine/marine	Reserved; exposure to estuarine/marine invertebrates not expected, based on current use pattern.
850.1075	***72-1C***	Fish acute toxicity, freshwater	Folmar 1976; Galassi et al, 1988 (supplemental); Holcombe et al. 1987 (supplemental)
850.1075	***72-3A***	Fish acute toxicity, estuarine/marine	Reserved; exposure to estuarine/marine fish not expected, based on current use pattern.
850.1300	***72-4B***	Daphnid chronic toxicity test	Reserved; chronic exposures to freshwater and estuarine/marine invertebrates not expected, based on current use pattern.
850.1350		Mysid chronic toxicity test	
850.1400	***72-4***	Fish- Early Life Stage	Galassi et al, 1988
850.1950	***72-7***	Field Testing for aquatic organisms	Ogata and Miyaka 1978; Ogata et al. 1984

Appendix B. Data Supporting Guideline Requirements* for the Reregistration of Xylene (086802)

REQUIREMENT			CITATION(S)
850.2100	***71-1***	Avian Acute Oral Toxicity	Hill and Carmardese, 1986 (supplemental, adjusted values based on data in this study)
850.2200	***71-2A***	Avian Dietary Toxicity - Quail	Hill and Carmardese, 1986 (supplemental)
850.2300	***71-4A***	Avian Reproduction - Quail	Reserved; repeated-dose exposure to birds during breeding is not expected, based on current use pattern.
850.2300	***71-4B***	Avian Reproduction - Duck	
Nontarget Plant Protection			
850.4025	***121-1***	Target area phytotoxicity	Reserved; exposure is not expected, based on current use pattern.
850.4100	***122-1***	Terrestrial Plant Toxicity, Tier 1 (seedling emergence)	
850.4150	***122-1***	Terrestrial Plant Toxicity, Tier 1 (vegetative vigor)	
850.4200	***122-1***	Seedling Germination/Root Elongation	Reserved; no additional data is needed beyond Tier 1 screening levels, based on current use pattern.
850.4225	***123-1A***	Seedling Emergence, Tier 2	
850.4250	***123-1B***	Vegetative Vigor, Tier 2	
850.4300	***124-1***	Terrestrial plants field study, Tier 3	
850.4400	***123-2***	Aquatic plant toxicity test using Lemna spp. Tiers I and II	
850.4450	***124-2***	Aquatic plants field study, Tier 3	
TOXICOLOGY			
870.1100	***81-1***	Acute Oral Toxicity	Wolf et al. 1956; Smyth et al. 1962; Hine and Zuidema 1970; NTP 1986
870.1200	***81-2***	Acute Dermal Toxicity	Smyth et al. 1962
870.1300	***81-3***	Acute Inhalation Toxicity	Bonnet et al. 1979; Bonnet et al. 1982; Carpenter et al. 1975
870.2400	***81-4***	Acute Eye Irritation	Smyth et al. 1962
870.2500	***81-5***	Acute Dermal Irritation	Smyth et al. 1962
870.2600	***81-6***	Skin Sensitization	*Data gap, will be required in PDCI*
870.3100	***82-1A***	90-Day Oral Toxicity - Rodent	Condie et al. 1988; NTP 1986; Wolfe et al. 1988
870.3150	***82-1B***	90-Day Oral Toxicity - Non-rodent	Reserved; long-term oral exposure is not expected, based on current use pattern.
870.3200	***82-2***	21/28-Day Dermal Toxicity	Reserved; long-term dermal exposure not expected, based on current use pattern.
870.3465	82-4	90-Day Inhalation-Rat	Korsak et al. 1994; Korsak et al. 1992; Gralewicz et al. 1995; Gralewicz and Wiaderma 2001

Appendix B. Data Supporting Guideline Requirements* for the Reregistration of Xylene (086802)

REQUIREMENT			CITATION(S)
870.3700	***83-3A***	Prenatal Developmental Toxicity – Rat	Ungvary et al. 1980; Ungvary et al.1981; Ungvary and Trarai 1985
870.3700	***83-3B***	Prenatal Developmental Toxicity - Rabbit	Ungvary and Trarai 1985
870.3800	***83-4***	Reproduction and Fertility Effects	Reserved; data not needed at this time, because chronic exposures are not expected, based on current use pattern.
870.4100	***83-1A***	Chronic Toxicity	NTP 1986
870.4200	***83-2A, B***	Carcinogenicity	NTP 1986
870.4300	83-5	Combined Chronic Toxicity/ Carcinogenicity	NTP 1986
870.5100	84-2A	Bacterial Reverse Mutation Test (Ames Test)	Lebowitz et al. 1979; Bos et al. 1981; Haworth et al. 1983; Connor et al. 1985; Shimizu et al. 1985; Zeiger et al. 1987
870.5300	***84-2A***	*In vitro* Mammalian Cell Gene Mutation Test	Lebowitz et al. 1979
870.5375	***84-2B***	*In vitro* Mammalian Chromosomal Aberration Test	Gerner-Smidt and Freidrich 1978; Anderson et al. 1990
870.6200	81-8	Acute Neurotoxicity Screen	NTP 1986
870.7485	***85-1***	Metabolism and Pharmacokinetics	Dutkiewicz and Tyras 1968; Engstrom et al. 1977; Riihimaki et al. 1979a, b; Ogata et al. 1980; Wallen et al. 1985; Kawai et al. 1991; Huang et al. 1994
ENVIRONMENTAL FATE			
835.1230	***163-1***	Sediment and soil absorption/desorption for parent and degradates	API, 1994
835.1240	163-1	Leaching/Adsorption/Desorption	Pavlostathis and Mathavan 1992; Vowles and Mantoura 1987; Lindhart et al. 1994
835.2120	***161-1***	Hydrolysis	HSDB 2005; ATSDR 1995
835.2240	***161-2***	Photodegradation - Water	HSDB 2005; ATSDR 1995
835.2370	161-4	Photodegradation - Air	HSDB 2005; ATSDR 1995
835.2410	161-3	Photodegradation - Soil	HSDB 2005; ATSDR 1995
835.4100	***162-1***	Aerobic Soil Metabolism	Tsao et al. 1998
835.4200	162-2	Anaerobic Soil Metabolism	API, 1994
835.4300	***162-4***	Aerobic Aquatic Metabolism	API, 1994
835.4400	***162-3***	Anaerobic Aquatic Metabolism	API, 1994
835.6100	164-1	Terrestrial Field Dissipation	Aurelius and Brown 1987
835.6200	164-2	Aquatic Field Dissipation	Walsh et al., 1977
835.8100	163-3	Field Volatility	Smith and Harper 1980

Appendix B. Data Supporting Guideline Requirements* for the Reregistration of Xylene (086802)

REQUIREMENT			CITATION(S)
850.1730	165-4	Accumulation in Fish	Ogata and Miyaka 1978; Ogata et al. 1984
RESIDUE CHEMISTRY			
860.1300	***171-4A***	Nature of Residue - Plants	Not applicable
860.1300	***171-4B***	Nature of Residue - Livestock	
860.1340	***171-4C***	Residue Analytical Method - Plants	
860.1340	***171-4D***	Residue Analytical Method - Animals	
860.1380	***171-4E***	Storage Stability	
860.1400	***171-4F, 171-4G, 171-4H, 165-5***	Water, fish and irrigated crops	
860.1480	***171-4J***	Magnitude of Residues - Meat/Milk/Poultry/Egg	
860.1520	***171-4L***	Processed food/feed (ABIU)	
OTHER			
850.3020	141-1	Honey Bee Acute Contact	Reserved; exposure to nontarget terrestrial insects is not expected, based on current use pattern.

Appendix C – Occupational Handler Calculations

Handler Calculations:

(1) Daily Exposure:

E = UE * AR * AT

Where:

E	=	amount (mg or µg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
UE	=	unit exposure value (mg or µg ai/lb ai) derived from August 1998 PHED data, from ORETF data, from CMA data, and from Proprietary data;
AR	=	normalized application rate based on a logical unit treatment, such as acres, square feet, gallons, or cubic feet. Maximum values are generally used (lb ai/A, lb ai/sq ft, lb ai/gal, lb ai/cu ft); and
AT	=	normalized application area based on a logical unit treatment such as acres (A/day), square feet (sq ft/day), gallons per day (gal/day), or cubic feet (cu ft/day).

(2) Daily Dose:

ADD = E * (ABS / BW)

Where:

ADD	=	absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day);
E	=	amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
ABS	=	a measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed); and
BW	=	body weight determined to represent the population of interest in a risk assessment (kg).

(3) Margins of Exposure:

MOE = (NOAEL or LOAEL) / ADD

Where:

MOE	=	margin of Exposure, value used to represent risk or how close a chemical exposure is to being a concern (unitless);
NOAEL or LOAEL	=	dose level in a toxicity study, where no observed adverse effects (NOAEL) or where the lowest observed adverse effects (LOAEL) occurred in the study; and
ADD	=	average Daily Dose or the absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day).

Appendix D - Toxicological Data Summary from review of IRIS (EPA, 2003)

Route:	Oral (gavage)			
Study	**Organism**	**Doses**	**Chemical**	**Results**
NTP Chronic 2-year study (1986)	Rats	0, 250, or 500 mg/kg-day	Mixed xylenes (60% m-xylene, 13.6% p-xylene, 9.1% o-xylene, 17.0% ethylbenzene)	NOAEL: 250 mg/kg-day LOAEL: 500 mg/kg-day (based on decreased body weight and decreased survival)
NTP Chronic 2-year study (1986)	Mice	0, 500, or 1000 mg/kg-day		NOAEL: 500 mg/kg-day LOAEL: 1000 mg/kg-day (based on hyperactivity)
NTP 13-week study (1986)	Rats	0, 62.5, 125, 250, 500, or 1000 mg/kg-day	Mixed xylenes (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, 9.1% o-xylene)	NOAEL: 500 mg/kg-day LOAEL: 1000 mg/kg-day (based on decreased body weight in male rats without tissue lesions)
NTP 13-week study (1986)	Mice	0, 125, 250, 500, 1000, and 2000 mg/kg-day		NOAEL: 1000 mg/kg-day LOAEL: 2000 mg/kg-day (based on transient signs of nervous system depression in mice without tissue lesions)
Wolfe (1988a) 90-day study	Rats	0, 100, 200, or 800 mg/kg-day	*m-xylene (99% purity)*	NOAEL: 200 mg/kg-day LOAEL: 800 mg/kg-day (based on decreased body weight)
Wolfe (1988b) 90-day study	Rats	0, 100, 200, or 800 mg/kg-day	*p-xylene (99% purity)*	NOAEL: 200 mg/kg-day LOAEL: 800 mg/kg-day (based on early mortality in male rats that showed signs of test material aspiration into the lungs)
Condie (1988) 90-day study	Rats	0, 150, 750, or 1500 mg/kg-day	Mixed xylenes (17.6% o-xylene, 62.3% m-xylene and p-xylene [which coeluted], 20% ethyl benzene)	**NOAEL: 150 mg/kg-day** LOAEL: 750 mg/kg-day (based on increased kidney weights and early appearance of mild nephropathy in female rats)

NTP (1986) study:

Chronic 2-year study

- Target organisms:
  - 50 male and 50 female Fischer 344 rats
  - 50 male and 50 female B6C3F1 mice
- Doses/Length of study:
  - Mixed xylenes (60% m-xylene, 13.6% p-xylene, 9.1% o-xylene, 17.0% ethylbenzene)
  - Administered by gavage in corn oil
  - Rats: 0, 250, or 500 mg/kg-day
  - Mice: 0, 500, or 1000 mg/kg-day
  - 5 days/week for 103 weeks
- Results:
  - Rats: LOAEL is 500 mg/kg-day and the NOAEL is 250 mg/kg-day for decreased body weight and decreased survival
  - Mice: The LOAEL is 1000 mg/kg-day and the NOAEL is 500 mg/kg-day for hyperactivity

Subchronic 13-week study

- Target organisms:
  - 10 male and 10 female Fischer 344 rats
  - 10 male and female $B6C3F_1$ mice
- Doses/Length of study:
  - Mixed xylenes (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, 9.1% o-xylene)
  - Administered by gavage in corn oil
  - Rats: 0, 62.5, 125, 250, 500, or 1000 mg/kg-day
  - Mice: 0, 125, 250, 500, 1000, and 2000 mg/kg-day
  - 5 days/week for 13 weeks
- Results:
  - Rats: The LOAEL is 1000 mg/kg-day and the NOAEL is 500 mg/kg-day based on decreased body weight in male rats without tissue lesions.
  - Mice: The NOAEL is 1000 mg/kg-day and the LOAEL is 2000 mg/kg-day for transient signs of nervous system depression in mice without tissue lesions.

Wolfe (1988a):

- Target organisms:
  - 20 male and 20 female Sprague-Dawley rats
- Doses/Length of study:
  - m-xylene (99% purity)
  - Administered by gavage in corn oil
  - 0, 100, 200, or 800 mg/kg-day
  - 90 consecutive days
- The NOAEL and LOAEL are identified as 200 and 800 mg/kg-day, respectively, based on decreased body weight

Wolfe (1988b):

- Target organisms:
  - 20 male and 20 female Sprague-Dawley rats
- Doses/Length of study:
  - p-xylene (99% purity)
  - Administered by gavage in corn oil
  - 0, 100, 200, or 800 mg/kg-day
  - 90 consecutive days
- The NOAEL and LOAEL are identified as 200 and 800 mg/kg-day, respectively, based on early mortality in male rats that showed signs of test material aspiration into the lungs

Condie (1988):

- Target organisms:
  - 10 male and 10 female Sprague-Dawley rats
- Doses/Length of study:
  - Mixed xylenes (17.6% o-xylene, 62.3% m-xylene and p-xylene [which coeluted], 20% ethyl benzene)
  - Administered by gavage in corn oil
  - 90 consecutive days
  - 0, 150, 750, or 1500 mg/kg-day
- The LOAEL is 750 mg/kg-day, based on increased kidney weights and early appearance of mild nephropathy in female rats, and the NOAEL is 150 mg/kg-day.

Route:	Inhalation			
Study	**Organism**	**Doses**	**Chemical**	**Results**
Korsak et al. (1992) 6-month study	Rats	0 or 100 ppm for 6 months or 1000 ppm for 3 months	toluene, m-xylene, or a 1:1 mixture	NOAEL: not identified LOAEL: 100 ppm (based on decreased rotarod performance and decreased spontaneous motor activity)
Korsak et al. (1994) 3-month study	Rats	0, 50, or 100 ppm	m-xylene or n-butyl alcohol or a 1:1 mixture	**NOAEL: 50 ppm** LOAEL: 100 ppm (based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test)
Gralewicz et al. (1995) 3-month study	Rats	0, 100, or 1000 ppm	"pure" m-xylene (exact purity not provided)	NOAEL: Not identified LOAEL: 100 ppm (based on deficits in radial maze performance)
Gralewicz and Wiaderna (2001) 4-week study	Rats	0 or 100 ppm	m-xylene	NOAEL: Not identified LOAEL: 100 ppm (based on neurobehavioral effects)

Korsak et al. (1992):

- Target organisms:
  - 12 male Wistar rats
- Doses/Length of study:
  - toluene, m-xylene, or a 1:1 mixture
  - 6 hours per day, 5 days per week
  - Concentration of 0 or 100 ppm for 6 months or 1000 ppm for 3 months
- Results:
  - The LOAEL is 100 ppm, based on decreased rotarod performance and decreased spontaneous motor activity. No NOAEL was identified.

Korsak et al. (1994):

- Target organisms:
  - 12 male Wistar rats
- Doses/Length of study:
  - 0, 50, or 100 ppm
  - m-xylene or n-butyl alcohol or a 1:1 mixture (purity of chemicals not provided)
  - 6 hours per day, 5 days per week, for 3 months
- Results:
  - The LOAEL is 100 ppm, based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test, and the NOAEL is 50 ppm.

Gralewicz et al. (1995):

- Target organisms:
  - 8-month-old, male LOD-Wistar rats
- Doses/Length of study:
  - 0, 100, or 1000 ppm
  - "pure" m-xylene (exact purity not provided)
  - 6 hours per day, 5 days per week, for 3 months
- Results:
  - The lowest exposure level in this study, 100 ppm, is designated as a LOAEL for deficits in radial maze performance.

Gralewicz and Wiaderna (2001):

- Target organisms:
  - Male Wistar rats
- Doses/Length of study:
  - 0 or 100 ppm
  - m-xylene
  - 6 hours per day, 5 days per week for 4 weeks
- Results:
  - Identified 100 ppm as a LOAEL for neurobehavioral effects