UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: December 14, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment - Xylene

FROM: Pauline Wagner, Chief Pauline Wagner 12/15/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Lois A. Rossi, Director
Registration Division (7505C)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of three inert exemption(s) from the requirement of a tolerance. The reassessment decision is to maintain each of the three inert tolerance exemptions "as-is."

Chemical: Xylene

CFR and CAS Registry Number and Name:

Citation as it Appears in the CFR				CAS Registry Numbers and Names
40 CFR	Tolerance Exemption Expression	Limits	Uses	
180.910	Xylene meeting the specifications listed in 21 CFR 172.884(b)(4)	In pesticide formulations for grain storage only.	Solvent, cosolvent	1330-20-7 Benzene, dimethyl- (9CI) 95-47-6 Benzene, 1,2-dimethyl- (9CI) 108-38-3 Benzene, 1,3-dimethyl- (9CI) 106-42-3 Benzene, 1,4-dimethyl- (9CI)
180.920	Xylene	-----		
180.930	Xylene	-----		

Use Summary: Xylene is used as a solvent in a wide variety of consumer products. It is used an inert ingredient in agricultural crop products, post-harvest grain storage products, and residential pesticide products used in and around the home.

List Reclassification Determination: The current List Classification for xylene is 2. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to xylene when used as inert ingredients in pesticide formulations, the List Classification for xylene will change from List 2 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the three exemptions from the requirement of a tolerance for the inert ingredient xylene (CAS Reg. No. 1330-20-7, 108-38-3, 95-47-6, and 106-42-3), and with the List reclassification determination, as described above. I consider the three exemptions established in 40 CFR part 180.910, 920, and 930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

December 23, 2005

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

December 14, 2005

MEMORANDUM

SUBJECT: Reassessment of Three Exemptions from the Requirement of a Tolerance for Xylene

FROM: Karen Angulo
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

BACKGROUND

Attached is the science assessment for xylene. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure, environmental fate, and ecotoxicity of xylene. The purpose of this document is to reassess the three existing exemptions from the requirement of a tolerance for residues of xylene as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

Xylene is used as an inert ingredient in a wide variety of agricultural and residential pesticide products used in and around the home. Xylene's three exemptions from the requirement of a tolerance are for grain storage, growing crops, and animal uses under 40 CFR 180.910, 920, and 930, respectively. Xylene has been well studied and a significant amount of information, studies, and assessments are available to the public, including the U.S. Agency for Toxic Substances and Disease Registry (ATSDR). In addition, EPA recently completed a Regregistration Eligibility Decision (RED) (09/2005) on the use of xylene as an active ingredient (A.I.) aquatic herbicide.

Xylene is rapidly absorbed by all routes of exposure, rapidly distributed throughout the body, and, if not metabolized, quickly eliminated in exhaled air. Animal studies show xylene has low acute toxicity for effects of concern, with oral NOAELs from 500 to 1,000 mg/kg/day and LOAELs from 1,000 to 2,000 mg/kg/day, and an inhalation NOAEL of 460 ppm and a LOAEL of 1,300 ppm. Developmental/reproductive

toxicity effects from inhalation exposures occurred at lower doses than those from oral exposure. The inhalation NOAELs for developmental/reproductive effects ranged from 250 to 1,000 ppm and the LOAELs ranged from 500 to 775 ppm. According to the ATSDR, "In general, developmental studies in animals reported adverse fetal effects only at concentrations that caused maternal toxicity."

Dietary and residential exposures are possible from inert ingredient uses of xylene, but the chemical's volatility and ready biodegradation reduce the potential for exposures of concern. In evaluating the A.I. use of the chemical in a ready-to-use aquatic weed herbicide containing 98% xylene, EPA's RED concluded "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", and "Thus, the Agency has no risk concerns for dietary exposure from use of xylene in irrigation water." This conclusion also applies to the inert ingredient food use of xylene because the amount per acre of xylene that is applied to crops as an A.I. (98% of the pesticide formulation) exceeds the amount applied as an inert ingredient (typical range is between 5 and 15% of the pesticide formulation). Contributions to drinking water are not anticipated because of the chemical's volatility and ready biodegradation. Therefore, dietary (food and drinking water) risks of concern are not expected from the use of xylene as an inert ingredient in pesticide formulations.

Inhalation and dermal exposures from outdoor residential uses are expected to be small because of xylene's volatile properties. The amount of xylene that can be used in indoor pesticide products is limited by the chemical's flammability potential. Product labels typically warn of fire hazard and instruct users to provide adequate ventilation or work outdoors, and doing so has the added benefit of limiting inhalation exposure potential. To gain some understanding of the magnitude of an individual's worst-case exposure in a residential setting, EPA modeled indoor inhalation exposure using E-FAST (U.S. EPA). The conservative exposure scenario that was selected assumed a person would be spraying aerosol paint in an enclosed room for 20 minutes. Considering the conservative nature of E-FAST, the modeled estimate is not a substantial exposure and does not indicate a duration of exposure capable of producing the effects observed in animal species.

Exposures of concern for aquatic and terrestrial ecosystems are not expected considering xylene's volatile nature and ready biodegradation.

Taking into consideration all available information on xylene, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to xylene when considering exposure through dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of xylene when used under 40 CFR 180.910 in pesticide formulations for grain storage only, under 40 CFR 180.920 on growing crops only, and under 40 CFR 180.930 for use on animals can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for xylene, a pesticide inert ingredient with three tolerance exemptions under 40 CFR 180.910, 920, and 930. There is sufficient information to conduct this assessment.

Xylene has three isomers: ortho-xylene, meta-xylene, and para-xylene. "Mixed xylene" is a mixture of the three isomers. The toxicity findings for mixed xylene are similar to those of the three isomers, therefore, only data for mixed xylene will be presented and discussed here. The three tolerance exemptions include the three isomers. For ease of reading, mixed xylene will be called xylene.

II. Use Information

A. Pesticides

Xylene is used as an inert ingredient in a wide variety of agricultural and residential pesticide products used in and around the home. The tolerance exemptions for xylene are provided in Table 1 below.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Numbers and Names
40 CFR	Tolerance Exemption Expression	Limits	Uses	
180.910 [a]	Xylene meeting the specifications listed in 21 CFR 172.884(b)(4)	In pesticide formulations for grain storage only.	Solvent, cosolvent	1330-20-7 Benzene, dimethyl- (9CI) 95-47-6 Benzene, 1,2-dimethyl- (9CI) 108-38-3 Benzene, 1,3-dimethyl- (9CI) 106-42-3 Benzene, 1,4-dimethyl- (9CI)
180.920 [b]	Xylene	-----		
180.930 [c]	Xylene	-----		

a. Residues listed in 40 CFR 180.910 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities (RACs) after harvest.

b. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

c. Residues listed in 40 CFR 180.930 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

B. Other Uses

In their toxicological profile for xylene, the ATSDR described uses of xylene as follows: "Xylene is one of the top 30 chemicals produced in the United States in terms of volume. It is primarily used as a solvent (a liquid that can dissolve other substances) in the printing, rubber, and leather industries. Along with other solvents, xylene is also widely used as a cleaning agent, a thinner for paint, and in varnishes. Xylene is used, to a lesser extent, as a material in the chemical, plastics, and synthetic fiber industries and as an ingredient in the coating of fabrics and papers. Isomers of xylene are used in the manufacture of certain polymers (chemical compounds), such as plastics." "Xylene also occurs naturally in petroleum and coal tar and is formed during forest fires, to a small extent. It is a colorless, flammable liquid with a sweet odor."

The U.S. Food and Drug Administration (FDA) permits certain food additive uses of xylene. The tolerance exemption under 40 CFR 180.910, which is limited to pesticide formulations for grain storage only, requires that xylene meet the specifications listed in 21 CFR 172.884(b)(4). This part in the 21 CFR pertains to multipurpose food additives that are permitted for direct addition to food for human consumption. Xylene is considered under Sec. 172.884 "Odorless light petroleum hydrocarbons".

Table 2. FDA Direct Food Additive Uses: Odorless Light Petroleum Hydrocarbons

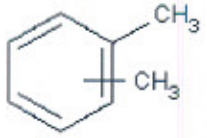
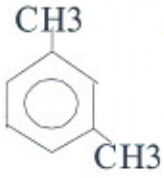
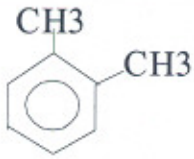
Name	21 CFR	Use Pattern
Odorless light petroleum hydrocarbons	172.884(b)(4)	Summary: Odorless light petroleum hydrocarbons may be safely used in food in accordance within the prescribed ultraviolet absorbance limits under 21 CFR 178.3620(b)(1)(ii).

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of xylene and its isomers are found in Table 3 (ATSDR; Hazardous Substances Data Base [HSDB]).

Table 3. Physical and Chemical Properties of Xylene (ATSDR and HSDB)

Property	Mixed Xylene	Meta-Xylene	Ortho-Xylene	Para-Xylene
CAS Reg. No.	1330-20-7	108-38-3	95-47-6	106-42-3
CAS name (9CI)	Benzene, dimethyl-	Benzene, 1,3-dimethyl-	Benzene, 1,2-dimethyl-	Benzene, 1,4-dimethyl-
Molecular formula	C_8H_{10}	C_8H_{10}	C_8H_{10}	C_8H_{10}

Table 3.	Physical and Chemical Properties of Xylene (ATSDR and HSDB)			
Property	**Mixed Xylene**	**Meta-Xylene**	**Ortho-Xylene**	**Para-Xylene**
Structural formula				
Molecular weight	106.16	106.17	106.16	106.17
Physical state	Liquid	Liquid	Liquid	Liquid
Vapor Pressure	7.9 mm Hg at 25^{0}C	8.9 mm Hg at 25^{0}C	6.6 mm Hg at 25^{0}C	8.8 mm Hg at 25^{0}C
Flash Point	25^0 C (77^{0}F)	25^{0}C (77^{0}F)	17^0 C (62^{0}F)	25^0 C (77^0 F)
Water Solubility	Practically insoluble, 130 mg/L (130 ppm) @ 25^{0}C	Insoluble, 146 mg/L (146 ppm) @ 25^{0}C	Insoluble, 178 mg/L (178 ppm) @ 25^{0}C	Insoluble, 198 mg/L (198 ppm) @ 25^{0}C
Henry's Law constant	6.4 x 10^{-3} atm-m^3/mol	7.66 x 10^{-3} atm-m^3/mol	5.19 x 10^{-3} atm-m^3/mol	7.66 x 10^{-3} atm-m^3/mol
Log K_{OW}	3.12 – 3.20	3.20	3.12	3.15

IV. Hazard Assessment

Xylene is sponsored under EPA's High Production Volume (HPV) Challenge Program (http://www.epa.gov/chemrtk/volchall.htm). The goal of the HPV program is to collect and make publicly available a complete set of baseline health and environmental effects data on those chemicals that are manufactured in, or imported into, the U.S. in amounts equal to or exceeding one million pounds per year. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsor's robust summary report. The industry sponsor has not yet submitted a robust summary for xylene.

A. Hazard Profile

EPA's recent RED (9/26/05) presents its assessment of potential human health effects of dietary (food and drinking water) and occupational exposures, as well as possible ecological risks, from the A.I. use of xylene as an aquatic herbicide. In addition, xylene has been well studied and a significant amount of information and studies are available to the public on the internet, such as in the Hazardous Substances Data Base (HSDB). Substantial assessments of xylene also are available on the internet, including those from the World Health Organization (WHO), EPA's Integrated Risk Information System (IRIS), and the ATSDR. EPA has no additional data that would alter the findings in these assessments. Therefore, considering that there are robust assessments of xylene that have been conducted by reputable organizations as well as a recent RED, this document provides only a brief summary of the conclusions of these assessments that are relevant for the evaluation of the inert ingredient use of xylene. The reader is referred to these sources for the full discussion and conclusions.

B. Toxicological Data

Acute Toxicity

Table 4. Summary of Acute Toxicity Data for Xylene (ATSDR)

Parameter	Toxicity Value
Inhalation	LD_{50} male rat = 6,350 - 6,700 ppm
	Mouse, male, 1-minute exposure: NOAEL = 460 ppm. LOAEL = 1,300 ppm, 50 % decrease in respiratory rate.
Oral	LD_{50} rat = 3,523 mg/kg/day
	Rat, 14-day exposure: NOAEL = 500 mg/kg/day. LOAEL = 1,000 mg/kg/day, decrease in body weight gain in males (18%).
	Mouse, 14-day exposure: NOAEL = 1,000 mg/kg/day. LOAEL = 2,000 mg/kg/day, decrease in body weight gain (89%).
Eye irritation	Rabbit, one exposure, LOAEL for slight-to-moderate eye irritation 0.1 mL (23 mg/kg/day).

Table 4. Summary of Acute Toxicity Data for Xylene (ATSDR)	
Parameter	**Toxicity Value**
Skin irritation	LOAELs for mild-to-severe skin irritation were 2.3 mg/kg/day in the guinea pig, 57 mg/kg/day in the mouse, and 114 mg/kg/day in the rabbit.

In the mouse, adverse effects for acute inhalation (I minute exposure) of xylene were observed at 1,300 ppm (LOAEL), and no effects were observed at 460 ppm (NOAEL). For oral administration, after 14 days of dosing the NOAELs ranged from 500 (rat) to 1,000 (mouse) mg/kg/day, and the LOAELs ranged from 1,000 (rat) to 2,000 (mouse) mg/kg/day (ATSDR). Instillation of 0.1 mL (23 mg/kg/day) of xylene into the eyes of rabbits resulted in slight-to-moderate eye irritation.

Neurotoxicity

According to ATSDR, "Studies in animals have shown that mixed xylene and individual isomers are neurotoxic at airborne concentrations ranging from 50 to 2,000 ppm." "Decreased motor performance and impaired learning have been reported in rats exposed to concentrations between 100 and 3,000 ppm" (ATSDR).

Reproductive and Developmental

Table 6. Summary of Reproductive and Developmental Toxicity Data for Xylene (ATSDR).	
Parameter	**Toxicity Value**
Inhalation (Strain differences may account for the differential response reported in these studies.)	Reproductive, female rat, 8-day exposure, LOAEL = 775 ppm, 8% decrease in fertility, increase resorptions.
	Reproductive, male rat, 61-day exposure, NOAEL = 1,000 ppm.
	Developmental, male and female rat, 166-day exposure: * NOAEL = 250 ppm. * LOAEL = 500 ppm, 7% decrease in fetal weight.
Oral acute	Developmental, female mouse, 10-day exposure: * NOAEL = 1,030 mg/kg/day. * LOAEL = 2,060 mg/kg/day, cleft palate.

Table 6. Summary of Reproductive and Developmental Toxicity Data for Xylene (ATSDR).	
Parameter	**Toxicity Value**
Oral subchronic	NOAELs for reproductive, 13-week exposure: * Rat = 1,000 mg/kg/day. * Mouse = 2,000 mg/kg/day. No LOAELs were reported.
Oral chronic	NOAELs for both systemic and reproductive, 103-week exposure: * Rat = 500 mg/kg/day. * Mouse = 1,000 mg/kg/day. No LOAELs were reported.

According to the ATSDR, "In general, developmental studies in animals reported adverse fetal effects only at concentrations that caused maternal toxicity. Developmental effects in laboratory animals exposed by inhalation include delayed ossification of the skeleton at maternally toxic concentrations and reduced fetal body weight, which is also influenced by maternal body weight effects".

For developmental/reproductive effects in the rat from inhalation administration, the NOAELs ranged from 250 ppm (166-day exposure) to1,000 ppm (61-day exposure). The LOAELs ranged from 500 (166-day exposure; 7% decrease in fetal weight) to 775 ppm (8-day exposure, 8% decrease in fertility, increase resorptions). ATSDR summarized these studies as follows:

> "Continuous exposure of CFY rats for 8 days on days 7-14 during pregnancy to 775 ppm mixed xylene produced an increased number of resorptions without any maternal toxicity; reduced fertility was also observed (Balogh et al. 1982). However, no adverse reproductive effects were noted following inhalation exposure of male and female CD rats to mixed xylene at concentrations as high as 500 ppm during premating, mating, pregnancy, and lactation (Bio/dynamics 1983). Inhalation exposure of male Sprague-Dawley rats to 1,000 ppm mixed xylene for 61 days produced no alterations in testes, accessory glands or circulating male hormone levels (Nylen et al. 1989). Strain differences may account for the differential response to mixed xylene in these studies." (ATSDR)

For oral acute toxicity, an adverse developmental effect (cleft palate) was seen in the mouse at 2,060 mg/kg/day (LOAEL); the NOAEL was 1,030 mg/kg/day. "Significantly increased incidences of cleft palate and decreased fetal body weight were reported following maternal oral exposure during gestation days 6-15 to doses of 2,060 mg/kg/day mixed xylene in mice. Mixed xylene was also toxic to the dams, producing 31.5% mortality at 3,100

mg/kg/day. It is unclear whether the observation of cleft palate in this study is associated with maternal toxicity or a predisposition of mice under stress to give birth to offspring with this birth defect." (ATSDR)

In a 13-week exposure subchronic oral administration study, the reproductive NOAELs were 1,000 mg/kg/day for the rat and 2,000 mg/kg/day and for the mouse. NOAELs in a 103-week exposure chronic oral study for the rat and mouse were 500 and 1,000 mg/kg/day, respectively. No LOAELs were reported for either the subchronic or chronic study (ATSDR).

Carcinogenicity

ATSDR and IRIS report that evaluations of genotoxic effects of xylene have consistently given negative results. A study on the rat and mouse concluded that xylene was not carcinogenic to either rats or mice at the highest doses administered (NTP).

C. Metabolism and Pharmacokinetics

Studies in animals have shown that xylene is well absorbed by the inhalation and oral routes. Approximately 60% of inspired xylene is retained and approximately 90% of ingested xylene is absorbed. Absorption of xylene also occurs by the dermal route, but to a much lesser extent than by the inhalation and oral routes especially following exposure to xylene vapor. Following absorption, xylene is rapidly distributed throughout the body by way of the systemic circulation and accumulates primarily in adipose tissue. In the blood, xylene is primarily bound to serum proteins (ATSDR).

Xylene and its three isomers are primarily metabolized by oxidation of a methyl group and conjugation with glycine to yield methylhippuric acid. Approximately 95% of the absorbed xylene is excreted in the urine with about 5% excreted unchanged in the exhaled air. Elimination from most tissue compartments is rapid, with slower elimination from muscle and adipose tissue. Greater than 90% of xylene is excreted in the urine as methylhippuric acid and less than 2% as xylenol. Aromatic hydroxylation of xylene to xylenol occurs only to a limited extent. Other minor metabolites found in urine include methylbenzyl alcohol and glucuronic acid conjugates of the oxidized xylene (ATSDR).

D. Special Considerations for Infants and Children

According to the ATSDR for xylene, "In general, developmental studies in animals reported adverse fetal effects only at concentrations that caused maternal toxicity." Developmental and reproductive effects from inhalation exposures were observed at lower doses than from oral exposures, and inhalation is the most likely route of exposure to xylene when it is used as an inert ingredient in pesticide products. The lowest inhalation

developmental/reproductive NOAEL was 250 ppm and the lowest LOAEL was 500 ppm (7% decrease in fetal weight) (both in the rat and 166-day exposures). The potential for exposure to xylene from its use as an inert ingredient is expected to be similar to acute, sporadic exposure. For inhalation acute exposures, the lowest NOAEL was 460 ppm and the LOAEL was 1,300 ppm (50% decrease in respiratory rate) (both in the mouse, 1-minute exposure) (ATSDR). As discussed later in this document, exposure to xylene when used as an inert ingredient is expected to be below the levels where effects of concern could be seen.

Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to xylene when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

EPA's RED evaluated the A.I. use of xylene. It is sold in one product as a ready-to-use aquatic weed herbicide containing 98% xylene. The 98% xylene product is added to irrigation ditches, and then the xylene-treated irrigation waters are applied to fields or sprayed onto plants by overhead irrigation. The RED's environmental fate characterization is applicable to inert ingredient uses of xylene (typical range is between 5 and 15 % of the pesticide formulation) because the A.I. is used at a much higher concentration (98% of the pesticide formulation). The following are excerpts from the RED that describe the environmental fate of xylene:

"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."

"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."

Considering xylene's volatile nature (7.9 mm Hg at 25°C) and ready biodegradation in soils, run-off into surface/drinking water is not expected from its use as an inert ingredient in pesticide products.

VI. Exposure Assessment

Xylene is used as an inert ingredient in a wide variety of agricultural and residential pesticide products used in and around the home and home garden. Residential exposure is expected to be primarily through the inhalation route because of xylene's volatility. Additional exposure may occur via consumption of agricultural crops to which this inert ingredient has been applied as a solvent or cosolvent.

Dietary

In evaluating whether there was a potential for dietary exposure from the A.I. use of the chemical in a ready-to-use aquatic weed herbicide containing 98% xylene, EPA's RED concluded the following:

> "At present, xylene is exempt from requirement for a tolerance (40 CFR 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 x 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."

The conclusions of the RED's dietary assessment apply to the inert ingredient food use of xylene (including use in home vegetable gardens) because the amount per acre of xylene that is applied to crops as an A.I. (98% of the pesticide formulation) exceeds the amount applied as an inert ingredient. Inert ingredient use of xylene typically ranges between 5 and 15% in pesticide products. In addition, considering xylene's highly volatile nature (5 to 9 mm Hg at 25°C) and ready biodegradation in soils, exposure through surface/drinking water is not expected from its use as an inert ingredient in pesticide products.

Residential

Xylene is used in many residential use pesticide products, including those used for home gardens, lawns, ornamental plants, flea and roach foggers, crack and crevice

treatment, etc. Many of the residential pesticide products that contain xylene are used outdoors, which limits inhalation exposure. Dermal exposure is also not expected to be of concern because of the chemical's volatile properties. Therefore, inhalation and dermal exposures from outdoor residential uses are expected to be small.

The amount of xylene that is used in indoor pesticides products is limited by the chemical's flammability potential. Product labels typically warn of fire hazard and instruct users to provide adequate ventilation or work outdoors, which will limit inhalation exposure potential. To estimate worst-case residential indoor inhalation exposure, EPA used E-FAST[1] (U.S. EPA) to model conservative exposure scenarios in which aerosol paint products containing 5, 10, or 15% xylene were sprayed for 20 minutes in an enclosed utility room (with little air exchange). Using E-FAST's standard model assumptions, EPA determined that for 15% xylene the Peak Concentration (an exposure metric for inhalation acute exposure) would be 299.24 ppm (1,290.00 mg/m^3) and the Average Daily Concentration (inhalation chronic exposure) would be 0.08ppm (0.36 mg/m^3) (TABLE 7) (Appendix A).

Table 7. E-FAST Modeling Results: Representative Residential-Use Product Containing 5, 10, and 15 Percent Xylene.

Percent Xylene	Inhalation Exposure
5	Acute: Peak Concentration = 98.85 ppm (429.00 mg/m^3) Chronic: Average Daily Concentration = 0.01ppm (0.12 mg/m^3)
10	Acute: Peak Concentration = 199.77 ppm (867.00 mg/m^3) Chronic: Average Daily Concentration = 0.06ppm (0.24 mg/m^3)
15	Acute: Peak Concentration = 299.24 ppm (1,290.00 mg/m^3) Chronic: Average Daily Concentration = 0.08ppm (0.36 mg/m^3)

The E-FAST estimates are considered worst-case for several reasons: (1) it is unlikely that all indoor residential-use products use high concentrations of xylene considering the chemical's flammability, (2) E-FAST is designed as a screening tool and modeled estimates of concentrations and doses are specifically designed to reasonably overestimate exposures, and (3) it is anticipated that the E-FAST scenario selected here for xylene (spraying for 20 minutes in an enclosed utility room with little air exchange) will yield exposure estimates that are not likely to be encountered in residential use. For outdoor-use products, EPA believes that exposure would be no greater than for indoor use and, in fact, is expected to be much less due to the dissipation of xylene into the air.

[1] The E-FAST model, which stands for "Exposure and Fate Assessment Screening Tool" is used by EPA's Office of Pollution, Prevention and Toxics to conduct New Chemicals exposure assessment. It was developed to provide screening-level estimates of the concentrations of chemicals released from consumer products. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening level assessment.

VII. Aggregate Exposures

In examining aggregate exposure, the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For xylene, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to xylene as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to xylene and any other substances and this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that xylene has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Human Health Risk Characterization

Xylene is used as an inert ingredient in a wide variety of agricultural and residential pesticide products used in and around the home. Xylene has been well studied and a significant amount of information, studies, and assessments are available to the public, including the ATSDR and IRIS. In addition, EPA recently completed a RED on the use of xylene as an A.I. aquatic herbicide.

Animal studies show xylene has a low level of acute toxicity. For acute oral toxicity, NOAELs ranged from 500 to 1,000 mg/kg/day and LOAELs ranged from 1,000 to 2,000 mg/kg/day. For acute inhalation toxicity, the NOAEL was 460 ppm and the LOAEL was 1,300 ppm. The body of experimental animal data show evidence of neurotoxicity typically associated with prolonged exposures to solvents, including liver effects. No dermal chronic studies were reported. Evaluations of the genotoxic effects of xylene have consistently given negative results.

According to the ATDSR, "In general, developmental studies in animals reported adverse fetal effects only at concentrations that caused maternal toxicity." Developmental and reproductive effects from inhalation exposures were observed at lower doses than from oral exposures. For developmental/reproductive effects in the rat from inhalation exposure, the NOAELs ranged from 250 ppm (166-day exposure) to 1,000 ppm (61-day exposure). The LOAELs ranged from 500 (166-day exposure; 7% decrease in fetal weight) to 775 ppm (8-day exposure, 8% decrease in fertility, increase resorptions). Animal strain differences may account for the differential response reported in these studies.

Xylene is rapidly absorbed by all routes of exposure, rapidly distributed throughout the body, and, if not metabolized, quickly eliminated in exhaled air.

In evaluating the A.I. use of the chemical in a ready-to-use aquatic weed herbicide containing 98% xylene, EPA's RED concluded "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", and "Thus, the Agency has no risk concerns for dietary exposure from use of xylene in irrigation water." This conclusion also applies to inert ingredient food uses (including home vegetable gardens) of xylene because the amount per acre of xylene applied to crops as an A.I. (98% pesticide formulation) exceeds the amount applied as an inert ingredient (typical range is between 5 and 15% of the pesticide product). Contributions to drinking water are not anticipated because of the chemical's volatility and ready biodegradation. Therefore, dietary (food and drinking water) risks of concern are not expected from the use of xylene as an inert ingredient in pesticide formulations.

Exposure to xylene from residential pesticide products is expected to be similar to a series of acute, sporadic exposures (rather than chronic) considering the chemical's volatile nature and rapid dissipation. Inhalation and dermal exposures from outdoor residential uses are expected to be small because of xylene's volatile properties. Indoor uses, such as insect sprays and foggers, can result in inhalation exposure. The amount of xylene that can be used in indoor pesticide products is limited by the chemical's flammability potential. Product labels typically warn of fire hazard and instruct users to provide adequate ventilation or work outdoors, and doing so has the added benefit of limiting inhalation exposure potential.

To gain some understanding of the magnitude of an individual's worst-case exposure in a residential setting, EPA used E-FAST to model indoor inhalation exposure. The conservative exposure scenario that was selected assumed a person would be spraying aerosol paint in an enclosed room for 20 minutes with little air exchange. For 15% xylene, the Peak Concentration (an exposure metric for inhalation acute exposure) was estimated to 299.24 ppm (1,290.00 mg/m^3) and the Average Daily Concentration (inhalation chronic exposure) would be 0.08ppm (0.36 mg/m^3). Considering the conservative nature of E-FAST, this modeled estimate is not a substantial exposure and does not indicate a duration of exposure capable of producing the effects observed in animal species.

Taking into consideration all available information on xylene, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to xylene when considering dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of xylene when used under 40 CFR 180.910 in pesticide formulations for grain storage only, under 40 CFR 180.920 on growing crops only, and under 40 CFR 180.930 for use on animals can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

The following excerpts are from EPA's RED: "In general, results of acute toxicity studies indicate that xylenes and xylene isomers are moderately to highly toxic to aquatic species. " and "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."

Exposures of concern for aquatic and terrestrial ecosystems are not expected from the use of xylene as an inert ingredient in pesticide products considering the chemical's volatile nature and ready biodegradation.

REFERENCES:

Carcinogenesis of Xylenes (mixed) (60% m-xylene, 14% p-xylene, 9% o-xylene, and 17% ethylbenzene) (CAS No. 1330-20-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). 1986. National Toxicology Program (NTP), U.S. Department of Health and Human Services, Publication No. 87-2583.

E-FAST, Exposure, Fate Assessment Screening Tool. U.S. Environmental Protection Agency. Office of Prevention, Pesticides & Toxic Substances. Office of Pollution Prevention and Toxics. Last website update: May 25, 2004. http://www.epa.gov/opptintr/exposure/docs/efast.htm

Toxicological Profile for Xylene, September 2005, U.S. Agency for Toxic Substances and Disease Registry (ATSDR). http://www.atsdr.cdc.gov/toxprofiles/tp71.html

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APPENDIX A: E-FAST Results for Xylene 5, 10, and 15 % Latex Paint (Inhalation)

Inputs for 5% xylene content

Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	106.2	Vapor Pressure (torr):	7.9
Weight Fraction - Median (unitless):	0.05	Weight Fraction - 90% (unitless):	0.05
Inhalation Inputs			
Frequency of Use (events/yr):	6	Years of Use:	11
Mass of Product Used per Event - Median (g)	227	Mass of Product Used per Event -90% (g):	738
Inhalation Rate During Use (m^3/hr):	0.55	Duration of Use - Median (hours/event):	0.333
Inhalation Rate After Use (m^3/hr):	0.55	Duration of Use - 90% (hours/event):	1
Zone 1 Volume (m^3):	20	Whole House Volume (m^3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Portion of Aerosol in Air (unitless):	0.01		
Activity Patterns			
User:	1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1	Start Time: 9	
Non-User:	1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1	Room of Use: 5. Utility Room	
Hour:	0 6 12 18		
Avg. Time, ADD_{pot}, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	4.02e+03
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

Outputs for 5% xylene content

Inhalation Rate (m^3/day): 0.55			Years of Use (years): 11	
Body Weight (kg): 71.8			Frequency of Use (events/year): 6	
Exposure Units			**Result**	**AT (days)**
Chronic Cancer	$LADD_{pot}$ (mg/kg-day)		3.24e-03	2.74e+04
	$LADC_{pot}$ (mg/m^3)		1.76e-02	2.74e+04
Chronic Non-Cancer	ADD_{pot} (mg/kg-day)		2.21e-02	4.02e+03
	ADC_{pot} (mg/m^3)		1.20e-01	4.02e+03
Acute	ADR_{pot} (mg/kg-day)		4.34e+00	1.00e+00
	Cp_{pot} (mg/m^3)		4.29e+02	1.00e+00
LADD - Lifetime Average Daily Dose (mg/kg-day) ADD - Average Daily Dose (mg/kg-day) ADR - Acute Dose Rate (mg/kg-day)			LADC - Lifetime Average Daily Concentration (mg/m^3) ADC - Average Daily Concentration (mg/m^3) Cp - Peak Concentration (mg/m^3)	

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051.4/1998

Inputs for 10% xylene content

Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	106.2	Vapor Pressure (torr):	7.9
Weight Fraction - Median (unitless):	0.1	Weight Fraction - 90% (unitless):	0.1
Inhalation Inputs			
Frequency of Use (events/yr):	6	Years of Use:	11
Mass of Product Used per Event - Median (g)	227	Mass of Product Used per Event -90% (g):	738
Inhalation Rate During Use (m^3/hr):	0.55	Duration of Use - Median (hours/event):	0.333
Inhalation Rate After Use (m^3/hr):	0.55	Duration of Use - 90% (hours/event):	1
Zone 1 Volume (m^3):	20	Whole House Volume (m^3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Portion of Aerosol in Air (unitless):	0.01		

Activity Patterns

User:	1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1	Start Time: 9	
Non-User:	1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1	Room of Use: 5. Utility Room	
Hour:	0 6 12 18		
Avg. Time, ADD_{pot}, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	4.02e+03
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

Outputs for 10% xylene content

Inhalation Rate (m^3/day): 0.55			Years of Use (years): 11	
Body Weight (kg): 71.8			Frequency of Use (events/year): 6	
Exposure Units			**Result**	**AT (days)**
Chronic Cancer	$LADD_{pot}$ (mg/kg-day)		6.48e-03	2.74e+04
	$LADC_{pot}$ (mg/m^3)		3.53e-02	2.74e+04
Chronic Non-Cancer	ADD_{pot} (mg/kg-day)		4.42e-02	4.02e+03
	ADC_{pot} (mg/m^3)		2.40e-01	4.02e+03
Acute	ADR_{pot} (mg/kg-day)		8.69e+00	1.00e+00
	Cp_{pot} (mg/m^3)		8.67e+02	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day)
ADD - Average Daily Dose (mg/kg-day)
ADR - Acute Dose Rate (mg/kg-day)

LADC - Lifetime Average Daily Concentration (mg/m^3)
ADC - Average Daily Concentration (mg/m^3)
Cp - Peak Concentration (mg/m^3)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051.4/1998

Inputs for 15% xylene content

Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	106.2	Vapor Pressure (torr):	7.9
Weight Fraction - Median (unitless):	0.15	Weight Fraction - 90% (unitless):	0.15
Inhalation Inputs			
Frequency of Use (events/yr):	6	Years of Use:	11
Mass of Product Used per Event - Median (g)	227	Mass of Product Used per Event -90% (g):	738
Inhalation Rate During Use (m^3/hr):	0.55	Duration of Use - Median (hours/event):	0.333
Inhalation Rate After Use (m^3/hr):	0.55	Duration of Use - 90% (hours/event):	1
Zone 1 Volume (m^3):	20	Whole House Volume (m^3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Portion of Aerosol in Air (unitless):	0.01		

Activity Patterns

User: 1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1 Start Time: 9

Non-User: 1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1 Room of Use: 5. Utility Room

Hour: 0 6 12 18

Avg. Time, ADD_{pot}, $LADC_{pot}$ (days): 2.74e+04 Avg. Time, ADD_{pot}, ADC_{pot} (days): 4.02e+03

Avg. Time, ADR_{pot}, Cp_{pot} (days): 1.00e+00

Outputs for 15% xylene content

Inhalation Rate (m^3/day): 0.55		Years of Use (years): 11	
Body Weight (kg): 71.8		Frequency of Use (events/year): 6	
Exposure Units		**Result**	**AT (days)**
Chronic Cancer	$LADD_{pot}$ (mg/kg-day)	9.72e-03	2.74e+04
	$LADC_{pot}$ (mg/m^3)	5.29e-02	2.74e+04
Chronic Non-Cancer	ADD_{pot} (mg/kg-day)	6.63e-02	4.02e+03
	ADC_{pot} (mg/m^3)	3.60e-01	4.02e+03
Acute	ADR_{pot} (mg/kg-day)	1.30e+00	1.00e+00
	Cp_{pot} (mg/m^3)	1.29e+03	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day)
ADD - Average Daily Dose (mg/kg-day)
ADR - Acute Dose Rate (mg/kg-day)

LADC - Lifetime Average Daily Concentration (mg/m^3)
ADC - Average Daily Concentration (mg/m^3)
Cp - Peak Concentration (mg/m^3)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051.4/1998