

Mr. Coberly

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October 14, 1971

Xylene (mixture of 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene)

Mr. Greg S. Baker, Chief  
Petitions Control Branch  
Pesticides Tolerances Division

002530

Dow Chemical Company  
P. O. Box 1705  
Midland, Michigan 48640

American Cyanamid Co.  
P. O. Box 409  
Princeton, New Jersey 08540

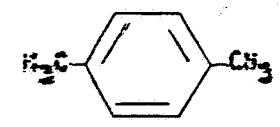
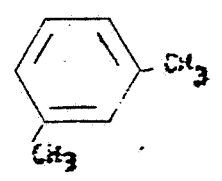
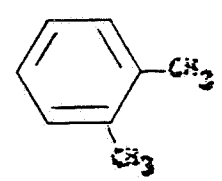
Two chemical companies have submitted requests concerning the inert status of xylene. The Dow Chemical Company requested (letter of Nov. 18, 1970 to Mr. D. M. Baker) xylene be added to the pending subparagraph of 21 CFR 120.1001 which will exempt inert ingredients in pesticide formulations applied to animals from the requirement of tolerance. The American Cyanamid Company made a similar request concerning xylene on stored grains (letter of Dec. 14, 1970) and on food animals (letter Dec. 18, 1970).

Chemical Structure

1,2-dimethylbenzene

1,3-dimethylbenzene

1,4-dimethylbenzene



Function: Solvent

Percentage in Formulations: 3.51 to 612

Vapor Pressure (mm Hg): 11 at 30°C

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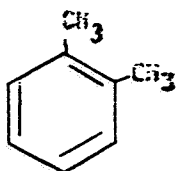
## Xylene

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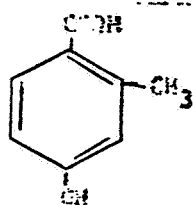
Biochemistry

Xylene is absorbed from the gastrointestinal tract. Because of its fat solubility, it is distributed to the tissues in proportion to their fat content. Part of the xylene absorbed into the blood is exhaled unchanged.

The xylenes are also transformed by the liver into water soluble metabolites which are excreted in the urine as conjugates of glycine, glucuronic acid or sulfuric acid.

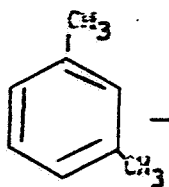
Urinary Metabolites

o-Xylene

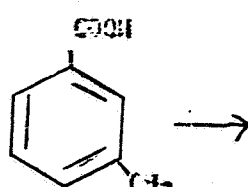


Hydroxy-o-Toluic acid

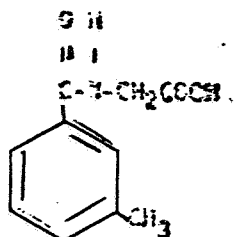
(guinea pig)



m-Xylene



m-Toluic acid

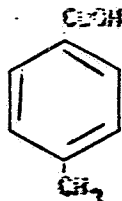


m-Toluric acid

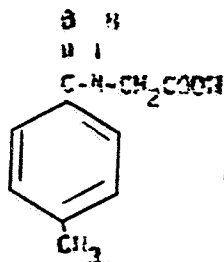
(dog &amp; guinea pig)



p-Xylene



p-Toluic acid



p-Toluric acid

(probable mechanism, Thorne, N.Y., 1950)

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**Xylene**

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Small amounts of phenolic products formed by oxidation of the molecular nucleus have been isolated in the urine of rats, rabbits and guinea pigs (Fabre et. al., 1960). Bray et. al. (1950) considered that only with the ortho-isomer is the production of phenolic products significant from the point of toxicity.

Threshold Limit Values - 1960

The human TLV for xylene is 435  $\text{mg}/\text{m}^3$  or approximately 22  $\text{mg}/\text{kg}/\text{day}$  when calculated as a total body intake using the formula in the back of this report.

Acute Toxicity

Rat Oral - Male  $\text{LD}_{50}$  = ~ 4.3  $\text{gm}/\text{kg}$

Rabbit Dermal - Moderate to marked irritation was noted along with moderate necrosis.

Rabbit Eye Irritation - Slight conjunctival irritation and very slight corneal injury was produced by the undiluted material.

Rat Reproduction (Dermal exposure) - A mixture containing 2,940 ml of distilled water, 30 ml of xylene and 30 ml of alkyl phenoxypoly ethoxyethanol was applied on the backs of each rat at the dosage rates of 5.9, 11.8, and 23.6  $\text{gm}/100$   $\text{gm}$  of body weight. The xylene content of these levels would be 59, 118 and 236  $\text{mg}/100$   $\text{gm}$  of body weight.

A single application was made to 9 or 12 females of each level on the 6th, 9th or 12th day post breeding.

Observations for effects included the examination of newborn, number of newborn, weight of newborn, pup viability index and parent fertility. Pups surviving 21 days were weighed.

Results - The mixture did not have an apparent effect on the parameters measured.

Chronic Toxicity

133 Day Fat Inhalation - Fabre & Truhaut (1954) - Ref., Sevarde, 1960 - In Toxicology and Biochemistry of Aromatic Hydrocarbons, p. 171-180

These data were presented in a very brief literature summary. An unspecified number of rats were exposed to a level of 650 ppm (3.0  $\text{mg}/\text{L}$ ) of mixed

Xylenes

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xylenes for eight hours per day, 6 days per week for 130 days. The only parameter measured appears to be peripheral blood.

Results - No significant deviations were noted in the peripheral blood. No-effect level is 630 ppm (3.9 mg/L) or approximately 529 mg/kg/day when calculated as a total body intake using the formula in the back of this report. CORE - *Supplementary*

130 Day Rabbit Inhalation - Fabre & Truhaut (1954) - Ref., Gerarde, 1960 - In Toxicology and Biochemistry of Aromatic Hydrocarbons, p. 171-180

These data were presented by Gerarde as a very brief literature summary. An unspecified number of rabbits were exposed to a level of 630 ppm (3.0 mg/L) of mixed xylenes for eight hours per day, 6 days per week for 130 days. The only criteria listed was peripheral blood examination.

Results - No significant deviations were noted in the peripheral blood. No-effect level is 630 ppm (3.0 mg/L) or approximately 779 mg/kg/day when calculated as a total body intake using the formula in the back of this report. CORE - *Supplementary*

55 Day Rabbit Inhalation - Fabre & Truhaut (1954) - Ref., Gerarde, 1960 - In Toxicology and Biochemistry of Aromatic Hydrocarbons, p. 171-180

These data were part of a very brief literature summary. An unknown number of rabbits were exposed to a level of 1150 ppm (5 mg/L) for eight hours per day, 6 days per week for 55 days. Parameters measured included RBC, WBC and platelet counts.

Results - The animals exhibited a decrease in the RBC and WBC counts and an increase in the platelet count.

The no-effect level is less than 1150 ppm (5.0 mg/L) or approximately 1284 mg/kg/day when calculated as total body intake using the formula in the back of this report. CORE *Supplementary*

Summary

The data submitted by Dow Chemical Co. is composed of published data. There are in many cases only summaries re-reported once or twice by several reporters often failing to list the test animal, observations, or dose regime. More often than not, xylene was only a constituent of the material tested or reported on. Two areas void of information are residue data and subacute oral ingestion studies.

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## Xylene

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However, the data show xylene to exhibit a low degree of acute oral lethal toxicity, moderate to marked dermal irritation, a chronic rat inhalation no-effect level of greater than 590 ppm (3.0 mg/L) and a chronic rabbit inhalation no-effect level of 690 ppm (3.0 mg/L).

The TLV gives a safe daily intake of approximately 22 mg/kg/day for humans.

This inhalation no-effect level can be converted to an estimated mg/kg/day intake level by the following equation:

$$\frac{A \times B \times C}{D} = \text{mg/kg/day}$$

where: A = Minute volume - (Rat = 0.0735 L/minutes) (Rabbit = 1.07 L/minutes)

B = Exposure rate in mg/L

C = Daily exposure in minutes

D = Average body weight in kg

For the Rat

$$\frac{0.0735 \times 3.0 \times 480}{0.25} = 529.2 \text{ mg/kg/day (10,584 ppm)}$$

For the Rabbit

$$\frac{1.07 \times 3.0 \times 480}{2.5} = 770 \text{ mg/kg/day (25,423 ppm)}$$

### Conclusion

In consideration of the limited toxic effects achieved among laboratory animals during subacute inhalation studies at high dosage levels, the TLV of 435 mg/m<sup>3</sup> in humans, the rate of application, volatility, percentages used in formulations, application percentage and alveolar excretion of the unchanged chemical, it is concluded that the expected xylene residues would be toxicologically insignificant.

The evaluation of PP No. 1E1133 by Dr. Krishna P. Misra, Toxicology Branch, Pesticides Tolerances Division on 12/23/70 also provided guidance in this

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conclusion. Thus, with the Chemistry Branch's considerations permitting, the reviewed toxicological data supports the safety of the requested exemption from the requirement of a tolerance.

Robert D. Coberly  
Toxicology Branch  
Pesticides Tolerances Division

cc:

DE Fitzhugh

JG Cummings

PR/EPA

Ferrine Sr.

Atlanta Sr. (CLewis)

Division Reading File

Branch Reading File

RD Coberly/ccw 10/14/71

Inlt: GC Sizemore

Inlt: CH Williams

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