

[OPTS-42025; FRL 2224-4]

Toxic Substances; Xylenes; Response to the Interagency Testing Committee**AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Notice.

SUMMARY: This notice constitutes EPA's response to the Interagency Testing Committee's designation of xylenes for priority consideration for mutagenicity and teratogenicity testing and for an epidemiological study under section 4(a) of the Toxic Substances Control Act. With respect to mutagenicity and teratogenicity, EPA does not plan to initiate rulemaking under section 4(a) to require health effects testing of xylenes at this time because the Agency finds that there are sufficient data now available to reasonably predict any potential effects of this nature from xylenes. Although epidemiological data are highly desirable, a study is not now being required because the mixed exposure pattern associated with these chemicals makes conducting such a study infeasible.

FOR FURTHER INFORMATION CONTACT: Douglas G. Bannerman, Acting Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-511, 401 M St., SW., Washington, D.C. 20460, toll free: (800-554-1404), in Washington, D.C.: (554-1404), outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION:**I. Background**

Section 4(a) of the Toxic Substances Control Act (TSCA) authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances and mixtures in order to develop data relevant to determining the risks that such chemicals may present to health and the environment.

Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for the promulgation of testing rules under section 4(a) of the Act.

In October, 1977, the ITC designated xylenes for mutagenic and teratogenic effects testing and an epidemiological study (42 FR 55026). Xylenes are a category consisting of the three isomers of dimethyl benzene: *ortho*-xylene, *meta*-xylene and *para*-xylene. The composition of commercial "mixed xylenes" varies depending on feedstock source and refinery conditions. However, the main components are

ortho-, *meta*- and *para*-xylene and ethylbenzene.

The individual isomers are used primarily as feedstocks for various chemical processes in the plasticizer, fiber, and resin industries. Mixed xylenes are used primarily in blending gasoline and as solvents.

The ITC's recommendations were based on annual xylenes production of 8 billion pounds, annual release to the environment of 900 million pounds. National Occupational Hazard Survey rank of 13 out of approximately 7,000 agents ranked in terms of number of workers exposed, and a wide variety of consumer uses resulting in general population exposure. The ITC found that mutagenicity tests had not been reported for any of the xylenes. The ITC believed that mutagenicity testing should be conducted because of widespread exposure to xylenes and the evidence of toxic effects to several organ systems. The ITC also found information suggesting that xylenes cross the placenta and were embryotoxic. For these reasons, the ITC believed xylenes should be tested for teratogenic effects. Because of their long-term use, the large number of people exposed and demonstrated effects in animals, the ITC felt an epidemiological study would be particularly important in assessing the human health effects of xylenes and should be conducted.

This notice provides EPA's response to the ITC's designation of xylenes for testing.

II. Decision Not To Initiate Rulemaking

EPA has decided that a section 4 rule requiring testing of xylenes for mutagenic and teratogenic effects is not warranted because sufficient data have been identified to characterize those effects adequately.

In evaluating the health effects of xylenes, the EPA has accepted as sufficient the results of adequately performed tests on commercial mixed xylenes, as well as tests on the individual isomers. The opportunity for exposure occurs predominantly with mixed xylenes rather than with the pure isomers (Ref. 15). It has been shown that toxicological testing under standardized conditions on mixed xylenes and the individual isomers of xylene showed no major differences in biological activity (Refs. 2, 4, 5, 6, 10, 11, 14). The National Toxicology Program (NTP) is currently conducting cancer bioassay in rats and mice using a xylene mixture containing 9.1 percent *o*-xylene, 60.2 percent *m*-xylene, 13.6 percent *p*-xylene 17.0 percent ethylbenzene and 0.1 percent water. (Ref. 7).

There is reason to believe that ethylbenzene has biological activity similar to the isomers of xylene based on acute toxicity, mutagenicity (Ames) and teratogenicity tests (Refs. 8, 16, 17). In addition to other testing already completed, ethylbenzene has been selected for an NTP bioassay (Ref. 7).

Xylenes have been assayed for mutagenic activity by several methods: *Salmonella* assays on the individual isomers and the mixture (Refs. 2, 11, 12, 13), a yeast assay (Ref. 2), a mouse lymphoma cell assay (Ref. 2), an assay on human cells in culture (Ref. 9), and a dominant lethal assay on the mixture (Ref. 1). None of these assays detected any mutagenic activity associated with xylenes.

Teratogenic activity has been demonstrated in several studies on xylenes. An NTP teratogenicity study on mixed xylenes (same mixture as listed above for cancer bioassay) administered by gavage to mice produced malformed fetuses, with cleft palate being the major malformation at doses of 2.4 and 3.0 ml/kg (Ref. 10). This study confirms the positive indications found with the individual isomers in another gavage study in mice (Ref. 14).

A teratogenicity study by inhalation exposure to individual isomers in the rat yielded at the highest dose (3000 mg/m³) fetal growth retardations, skeletal retardation, increases in fetal loss pre- and post-implantation, and a decrease in the activity of several kidney enzymes which are characteristic of functional maturity of the nephron (Ref. 18). These adverse biological effects were identified for all three isomers while the intensity of the biological responses varied with the different isomers of xylene (Ref. 18). EPA believes that these studies are adequate to reasonably predict the teratogenic potential of xylenes and will use them to evaluate the need for and priority of any EPA actions to further control exposure to xylenes.

Although reproductive effects testing was not recommended by the ITC, the American Petroleum Institute is performing a one-generation reproductive effects study on rats exposed to mixed xylenes by inhalation in order to assist in characterizing any potential reproductive effects hazard that might be associated with xylenes (Ref. 3).

The Agency knows of no epidemiological studies that were specific for xylenes. The EPA has decided not to require an epidemiological study at this time, as occupational and consumer exposure to xylenes occur in combination with many other chemicals. The Agency has

reviewed the criteria for conducting a valid epidemiological study and has determined that it would be extremely difficult to conduct such a study because the effects of xylenes could not be isolated from the effects of other chemicals to which concurrent exposure occurs.

III. References

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- (3) American Petroleum Institute. 1982. Parental and fetal reproduction and inhalation toxicity study in rats—draft report. Submitted to API by Bio/dynamics Inc. Project No. 80-2520. Unpublished.
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(17) Price B. 1982 (June 10). American Petroleum Institute, Washington, DC 20037. Letter and attachments to S. Newburg-Rinn, Assessment Div., Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460.

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IV. Public Record

EPA has established a public record for this testing decision (docket number OPTS-42025). The record includes:

1. Federal Register notice containing the designation of xylenes to the Priority List.
2. Letters.
3. Contact reports of telephone conversations and meeting summaries.
4. Published and unpublished data.

The record, which includes basic information considered by the Agency in developing this decision, is available for inspection in the OTS Reading Room from 8 a.m. to 4 p.m. on working days in Rm. E-107, 401 M St., SW., Washington, D.C., 20460. The Agency will supplement the record with additional relevant information as it is received.

(Sec. 4, 90 Stat. 2003 (15 U.S.C. 2601))

Dated: December 3, 1982.

Anne M. Gorsuch,
Administrator.

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