NVIRONMENTAL PROTECTION
ENCY

[SH-FRL-1973-4; OPTS-42005]

Alkyl Phthalates and Benzyl Butyl Phthalate; Response to the Interagency Testing Committee

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: In the initial report of the Interagency Testing Committee (ITC), transmitted to EPA on October 4, 1977, the ITC recommended to the Administrator of EPA the chemical category "alkyl phthalates" for consideration for testing of environmental effects. On October 24, 1980, the ITC further recommended a related phthalate ester, benzyl butyl, for the development of test rules for environmental effects similar to those proposed for the alkyl phthalates and also for health effects. On October 2, 1981, the Agency received a proposal from the Chemical Manufacturers Association (CMA) on behalf of the Phthalate Esters Program Panel, whereby the phthalate ester industry, through CMA, has agreed to test voluntarily and expeditiously both alkyl alates and benzyl butyl phthalate e environmental and health effects oncern to the Agency and to the ITC. Consequently, the Agency has made a preliminary decision, pending review of public comment received too late for consideration prior to the statutory deadline for this action, not to propose at this time a section 4(a) rule to require environmental or health effects testing of alkyl phthalates or benzyl butyl phthalate.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Jr., Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460. Toll free: (800-424-9065). In Washington: (202-554-1404). 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 gency Testing Committee (ITC) to nend to EPA a list of chemicals to sidered for the promulgation of testing rules under section 4(a) of the Act. The ITC may designate up to 50 of its recommendations at any one time for priority consideration by EPA. The ITC designated alkyl phthalates for environmental effects testing on October 4, 1977, notice of which appears in the Federal Register of October 12, 1977 (42 FR 55026). The alkyl phthalates are a chemical category consisting of alkyl diesters of 1,2-benzene dicarboxylic acid. The ITC's specific recommendations for the category alkyl phthalates were that the high production phthalate esters should be tested for chronic and reproductive effects to aquatic organisms, especially fish. The recommendations were based on (1) the large production volume of the phthalate esters, some over one hundred million pounds per year; (2) the known stability of some of the alkyl phthalates which would cause them to persist in the environment; (3) the reported chronic effects of some of the alkyl phthalates to freshwater species; and (4) the ability of the alkyl phthalates to accumulate in aquatic organisms.

As part of its recommendations to the Agency, the ITC mentioned that the health effects of oncogenicity and mutagenicity were not adequately characterized. However, the ITC reported that tests of mammalian and bird toxicity revealed a low order of toxicity to these organisms, and in its report the ITC recommended no health effects testing for the alkyl phthalates. Since that time, however, a positive bioassay on di-2-ethylhexyl phthalate (DEHP), a high production alkyl phthalate, has indicated oncogenicity may be a concern for this class of compounds. The Agency has taken into consideration these recent test results and does not believe that the current data are adequate to evaluate the human health effects posed by the alkyl phthalates. The Agency's concerns for health effects testing of the alkyl phthalates under section 4(a) of TSCA are therefore also addressed in this notice.

On October 24, 1980, the ITC designated a compound structurally related to the alkyl phthalates, benzyl butyl phthalate (BBP), for testing under TSCA section 4(a), notice of which appears in the Federal Register of November 25, 1980 (45 FR 78432). Like the alkyl phthalates, BBP is a diester of 1,2-benzene dicarboxylic acid. It differs from the alkyl phthalates in that along with the alkyl (butyl) group an aromatic (benzyl) group is attached to the benzene molecule at one of the two ester linkages. The ITC recommended that BBP be tested for environmental effects, based on its high production volume and similar structure to the alkyl phthalates. It also recommended that BBP's oncogenic potential be more thoroughly evaluated based on the results of an NCI (1980) carcinogenicity bioassay on BBP. The Committee further recommended that BBP be tested for potential reproductive effects.

II. CMA's Proposed Testing Program

On October 2, 1981, the Agency received a comprehensive testing proposal for phthalate esters from the Chemical Manufacturers Association on behalf of the Phthalate Esters Program Panel, consisting of manufacturers of phthalate esters and of the raw materials of the phthalate esters, and users of phthalate esters.

A. Environmental Effects

CMA has proposed performing phased testing for environmental effects, encompassing 13 alkyl phthalates identified as being produced in quantities greater than ten million pounds and benzyl butyl phthalate. CMA's proposal will specifically resolve unanswered questions in the areas of aquatic toxicity, potential environmental transport and fate, and biodegradation of the alkyl phthalates and benzyl butyl phthalate. These are the environmental effects of concern to the Agency and to the ITC.

In Phase I of the testing approach, basic tests will be performed to determine acute lethality to fish, aquatic invertebrates, and algae. Tests on reproduction in aquatic invertebrates will also be performed, as will preliminary biodegradation tests and tests to determine vapor pressure, water solubility and log $P_{octanol/water}$. In Phase II of the testing approach more advanced tests, including early life-stage testing on fish, bioconcentration tests in oysters, soil and water biodegradation tests, and tests of soil transport will be performed. The tests and chemicals selected for Phase II testing will be determined primarily by the results of the Phase I tests. As the results of the Phase I tests come in, they will be evaluated by both CMA and EPA scientists.

B. Health Effects

The CMA health effects proposal is directed towards the oncogenic and mutagenic potential of phthalate esters. It includes a multistage test program with two first-stage screening components which is being undertaken in an attempt to establish biological markers to aid in assessing the mutagenic and oncogenic potential of the alkyl phthalate class of compounds.

The first component is a battery of short-term tests, mostly mutagenic in character, used to evaluated mutagenic and oncogenic potential. The second component is a 21-day *in vivo* test with rats that will focus on effects of the phthalate esters to various organs and especially the liver. An initial validation phase using, di-2-ethylhexyl phthalate, mono-2-ethylhexyl phthalate, 2-ethylhexanol and di-2-ethylhexyl adipate will also be conducted to (1) help optimize test selection; (2) confirm past (*in vivo*) test results; and (3) more closely examine the potential utility of mutagenicity screening tests for the alkyl phthalate class of compounds.

Six alkyl phthalates (di-n-butyl, di-n-[hexyl, octyl, decyl], di-[heptyl, nonyl, undecyl], diisonoyl, diisooctyl, and diundecyl phthalate) and benzyl butyl phthalate have been selected for testing in the CMA test battery on the bases of production volume and representative structural characteristics. Dimethyl phthalate has also been selected, on the basis of past test data, for testing in the short-term test battery only.

The CMA's short-term test battery will include an Ames assay with *Salmonella typhimurium*, a mouse lymphoma test, a cell transformation test, an *in vitro* chromosomal aberration test and an unscheduled DNA synthesis test. Positive results in a well-designed battery of short-term mutagenicity tests can often be useful indicators for potential oncogenic as well as mutagenic effects in higher animals (Bartsch 1976, Brusick 1979). The results of past mutagenicity tests on alkyl phthalates have, however, been negative or, in a few cases, only weakly positive. Based on these past tests, the alkyl phthalates do not appear to be strong mutagens. The short-term tests, therefore, may not be sufficient to indicate the potential oncogenicity for the phthalate ester class of compounds. Therefore, in conjunction with the short-term tests, *in vivo* tests on rats will be performed with all of the compounds selected for the mutagenicity tests. The *in vivo* screening tests are based on the property of certain compounds, including DEHP and di-2-ethylhexyl adipate, to show effects on the livers of test animals, especially the effect of hepatic peroxisome proliferation. Hepatic peroxisome proliferation combined with hypolipidemia and hepatomegaly are apparently common characteristics of a divese group of chemicals, including DEHP, that give rise to hepatic cancer in rodents (Moody and Reddy, 1978, Reddy 1980).

Concurrent with the above testing, CMA will be examining the metabolism of DEHP in the rat at various dose levels in the diet and conducting a comparative study of the metabolism of DEHP in the mouse, the rat and a non-human primate.

CMA's testing proposal, then, is an attempt initially to establish valid biological markers that will indicate the mutagenic and oncogenic potential for the alkyl phthalate class of compounds. Depending on the nature of the results from this first phase of testing, CMA will undertake such additional testing as it considers necessary to determine whether the compounds are mutagenic or carcinogenic and, if so, what degree of hazard they present. Because of the experimental nature of the CMA testing program, and the broad range of possible outcomes of the initial testing, CMA has not specified the exact content of these further phases of testing. However, for substances which have not demonstrated a low potential for oncogenicity, they may include subchronic testing, metabolism testing, a two-year bioassay, or other appropriate tests. Additional compounds in the various structural subcategories (e.g., symmetrical, long-chain, branched, even-numbered isomers) may also be examined in the short-term screening tests. Positive results in the mutagenicity screens may, similarly, also be followed up with more advanced mutagenicity testing. CMA will consult with EPA prior to making these decisions on the content of the later testing phases.

CMA is expected to begin testing of the phthalates esters as described in its voluntary proposal shortly after the publication of this Federal Register notice.

C. Good Laboratory Practices

The Agency has reviewed the protocols of both the health and environmental tests that CMA has proposed and finds them acceptable. The described laboratory practices and quality control methods that will be carried out during the testing have also been reviewed and these are also acceptable to the Agency. For the Phase I environmental toxicity tests and the *in vivo* tests on rats for the oncogenicity screen, adherence to the Food and Drug Administration's "Good Laboratory Practices," published in the Federal Register of December 22, 1978 (43 FR 59986), will provide the necessary quality assurances. Similarly, the chemical fate tests, the mutagenicity screening tests and the Phase II environmental tests are expected to be performed using good laboratory practices. CMA has further agreed to arrange for EPA's auditing of the various laboratory facilities where the tests will be performed during the testing period.

III. Other Phthalate Testing

The National Toxicology Program (NTP) is performing and currently has plans to perform fairly extensive toxicological testing on various alkyl phthalate esters. NTP's testing initiative includes mutagenicity screening studies including (1) mutagenicity screening assays (Ames Tests) on 22 alkyl phthalates and related compounds; (2) tests of di-2-ethylhexyl phthalate and di-2-ethylhexyl adipate in *Drosophila melanogaster*; (3) tests of di-2-ethylhexyl phthalate, di-2-ethylhexyl adipate, benzyl butyl phthalate, diethyl phthalate and phthalic anhydride in *in vivo* cytogenetics assays; and (4) a study examining the propensity of di-2-ethylhexyl phthalate to incorporate into cellular macromolecules (i.e. rat hepatic RNA, DNA and protein). NTP will also be performing a two-year oncogenicity study on diethyl phthalate. Some special toxicity studies on diethyl phthalate will also be done, including an examination of hematopoietic effects in both male and female rats and mice and an examination in male rodents of hormonal and sperm effects. Di-2-ethylhexyl phthalate will also undergo reproductive effects testing and is under consideration for teratology and fetotoxicity studies. NTP is also studying the effects of several phthalate esters on mitochondrial function in whole animals to determine sites of action of phthalate mitochondrial toxicity. Depending on the outcome of these various tests, NTP may further broaden its testing initiative to include additional toxicity testing. Other researchers in the United States and Europe are also doing various other phthalate testing.

In regard to the ITC's recommendation that benzyl butyl phthalate be tested for reproductive effects, the EPA has nominated BBP for reproductive effects testing under the NTP's testing program.

IV. Public Comment

On August 27, 1981, EPA published a notice in the Federal Register indicating that EPA was considering a CMA voluntary testing proposal on alkyl phthalates, and providing for a public meeting and a deadline for submittal of written comments (46 FR 43298). The notice also indicated that various materials relevant to the testing proposal were available on the public record.

Pursuant to the notice, a public meeting was held on September 15, 198

to brief the public on the CMA voluntary testing proposal as an alternative to a test rule under TSCA section 4. The briefing was followed by an opportunity for discussion and comment.

At the conclusion of the meeting, and by letter of September 21, 1981, the Natural Resources Defense Council (NRDC) requested additional time to review and comment on the proposed testing scheme for the phthalates. Although EPA believes that it had provided adequate opportunity for the public to examine the proposed test scheme and comment upon it, because this is the first time the Agency has considered deferring testing because of a voluntary test scheme, EPA agreed to accept NRDC comments up to October 21, 1981. However, because section 4(e) of TSCA requires EPA to publish a response to the ITC within one year from the date a chemical is designated by the committee, EPA has not had an opportunity to consider these comments so as to issue a final decision not to test at this time. Instead, EPA elected in this instance to issue this notice in the form of a preliminary decision not to proceed with development of a test rule; the Agency will consider NRDC's comments before issuing a final decision, no later than November 30, 1981.

It is EPA's intention in the future to publish decisions not to test, where appropriate, in final form no later than the date of when a response to the ITC is due. EPA requests comments on how it can effectively provide for public input while assuring that statutory deadlines are met.

V. Decision Not To Require Testing

EPA feels that CMA's environmental effects testing proposal will meet the testing concerns of the Agency and the ITC for the alkyl phthalates and for benzyl butyl phthalate. For this reason, EPA has decided not to require environmental testing of the alkyl phthalates or benzyl butyl phthalate at this time.

EPA also believes that CMA's multiphase testing proposal for health effects will lead to the timely development of data relevant to determination of future regulatory needs for this class of compounds. Both EPA and CMA recognize the experimental nature of CMA's initial testing effort which is intended to indicate the carcinogenic potential of major compounds in this class. However, the Agency feels this approach is reasonable and has sufficient scientific rationale to recommend its use. NTP's testing initiative will also contribute a substantial amount of knowledge on the potential toxicity of the phthalate esters to human health. CMA's testing, in combination with NTP's initiative, is expected at the very least to clarify future testing needs for the alkyl phthalates.

As discussed above, it is likely that some additional testing will be necessary to develop information sufficient to determine if regulatory action is appropriate. Because these testing needs cannot be specified at this time, it is impossible for EPA to state that the later testing phases CMA will undertake are completely adequate for the Agency's purposes. However, there are several reasons why EPA believes that it should accept the CMA offer in lieu of proposing a test rule under section 4(a) of TSCA. First, EPA believes it would be difficult or impossible to specify at this time a reasonable, complete phthalate health effects testing scheme that would assure the development of all the data ultimately necessary for regulatory decisionmaking on the various phthalates. Second, CMA's consultations with EPA at decision points following the initial phase of tests will give the Agency an opportunity to provide scientific and regulatory guidance to CMA. Third, EPA believes that CMA has made a good faith commitment to develop data reasonably necessary to perform health effects assessments on the phthalates, although this does not preclude future disagreements on precisely what testing should be performed. Fourth, should CMA's initial testing indicate to EPA the need for testing beyond that which CMA is willing to conduct, the Agency reserves its right to pursue the issuance of a section 4 test rule at that time. Finally, acceptance of CMA's voluntary test program will result in a substantial savings in time and Agency resources over pursuing this matter through the full regulatory process.

Therefore, on the basis of the information available to the Agency, and public comments received by the Agency prior to October 1, 1981, EPA is not proceeding with the development of test rules on the health effects of the alkyl phthalates or butyl benzyl phthalate. However, since October 1, 1981, EPA has received additional comment from NRDC and will consider such information before making a final decision on the acceptance of the CMA testing proposal no later than November 30, 1981.

VI. References

1. Bartsch, EH. 1976. Predictive value of mutagenicity test in chemical carcinogenesis mutation. Mutation Res. 38:177–190.

2. Brusick, D. 1979. Bacterial mutagenesis and its role in the identification of potential animal carcinogens. In: Griffin C, Shaw CR, ed. Carcinogens: Identification and Mechanisms of Action. New York: Raven Press. pp. 93–105.

3. Moody DE, Reddy JK. 1978. Hepatic peroxisome (microbody) proliferation in rats fed plasticizers and related compounds. Toxicol. Appl. Pharmacol. 45:497–504.

4. NCI. 1980a. National Cancer Institute. Carcinogenesis bioassay of di-2-ethylhexyl phthalate (draft report). Washington, DC: Department of Health and Human Services NIH 81–1773.

5. NCI. 1980b. National Cancer Institute. Bioassay of butyl benzyl phthalate for possible carcinogenicity (draft report). Washington, DC: Department of Health and Human Services. DHHS Pub. NIH 80–1769.

6. Reddy JK. 1980. Hepatic peroxisome proliferative and carcinogenic effects of hypolipidemic drugs. In: Fumagalli R, Kritchevsky D, and Paoletti R, eds. Drugs affecting lipid metabolism. Elsevier/North Holland Biomedial Press. pp. 301–309.

VII. Public Record

EPA has established a public record for this decision not to pursue testing under section 4, docket number OPTS-42005, which is available for inspection in the OPTS reading room from 8:00 a.m. to 4:00 p.m. on working days in Rm. E-106, 401 M St., S.W. Washington, DC 20460. This record includes basic information considered by the Agency in developing this decision. The Agency will supplement the record with additional relevant information as it is received. The record includes the following information:

(1) Federal Register notices containing the designation of alkyl phthalates and benzyl butyl phthalate to the Priority List.

(2) Communications before proposal:

(a) Public and Intra-agency or Interagency Memoranda, Comments and Proposals.

(b) Contact reports of telephone conservations.

(c) Meetings.

(3) Public comments on the ITC reports.

(4) Reports—published and unpublished data.

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

Dated: October 23, 1981.

Anne M. Gorsuch,

Administrator.

[FR Doc. 81-31552 Filed 10-29-81; 8:45 am]

BILLING CODE 6560-31-M