

**ENVIRONMENTAL PROTECTION
AGENCY****40 CFR Parts 795 and 799****[OPTS-42100; FRL-3289-6]****Tributyl Phosphate: Proposed Test
Rule****AGENCY:** Environmental Protection
Agency (EPA).**ACTION:** Proposed rule.

SUMMARY: EPA is proposing that manufacturers and processors of tributyl phosphate (TBP, CAS No. 126-73-8) be required, under section 4 of the Toxic Substances Control Act (TSCA), to perform testing for neurotoxicity, developmental toxicity, reproductive toxicity, mutagenicity, oncogenicity, dermal sensitization, oral/dermal pharmacokinetics, environmental effects, and chemical fate. This rule is proposed in response to the Interagency Testing Committee's (ITC's) designation of TBP for priority consideration for chemical fate, health effects, and environmental effects testing.

DATES: Submit written comments on or before January 11, 1988. If persons request an opportunity to submit oral comment by December 28, 1987, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting see Unit VII of this preamble.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42100), in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Room NE-C004, 401 M St., SW., Washington, DC 20460.

A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 a.m. to 4 p.m..

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Monday through Friday except legal holidays.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-700), Office of Toxic Substances, Room E-543, 401 M St., SW., Washington, DC 20460, (202) 554-1404.

SUPPLEMENTARY INFORMATION: EPA is issuing a proposed test rule under section 4(a) of TSCA in response to the ITC's designation of TBP for chemical fate, health effects, and environmental effects testing consideration.

I. Introduction

A. ITC Recommendation

TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*) established the ITC under section 4(e) to recommend to EPA a list of chemical substances and mixtures (chemicals) to be considered for testing under TSCA section 4(a).

The ITC recommended TBP (CAS No. 126-73-8) with intent to designate for chemical fate, health effects, and environmental effects testing in its 18th Report, published in the Federal Register of May 19, 1986 (51 FR 18368). The ITC designated TBP for priority consideration in its 19th Report, published in the Federal Register of November 14, 1986 (51 FR 41417). The ITC recommended that TBP be considered for health effects testing, consisting of chronic toxicity including oncogenic, neurotoxic, renal, reproductive, and developmental effects; chemical fate testing, including persistence in anaerobic soils and sediments; and environmental effects testing, including chronic effects on aquatic and terrestrial plants, daphnids and/or other aquatic invertebrates, and acute and chronic effects on benthic organisms and soil invertebrates, if found persistent under anaerobic conditions.

The ITC's rationale for health effects testing was based on: (1) A large production volume; (2) a high number of workers occupationally exposed; and (3) the lack of data on health effects.

The ITC's rationale for chemical fate testing was based on: (1) The large production volume; (2) detection of TBP in municipal and industrial effluents, sediments, and in river, estuarine, ground, and drinking waters; and (3) detection of TBP in human and fish lipid tissue.

The ITC's rationale for environmental effects testing was based on: (1) TBP's presence in various surface and groundwaters; (2) available information showing that TBP has acute effects on a variety of aquatic organisms at moderately low concentrations and on

terrestrial plants; and (3) the appearance of continual exposure of nearly all types of biota to low concentrations of TBP.

B. Opportunity for Negotiating A Consent Order

EPA has issued an Interim Final Rule that amends EPA's procedural regulations in 40 CFR Part 790 for the development and implementation of testing requirements under section 4 of TSCA. The amendments established procedures for using enforceable consent orders to require testing under section 4 of the Act. EPA intends to use such consent orders where a consensus exists among the Agency, affected manufacturers and/or processors, and interested members of the public about the need for and scope of testing requirements. The consent order provides an alternative to the test rule development process, facilitating the rapid development of test data without the necessity of EPA using the lengthy rulemaking process.

Where EPA concludes that the Agency, the affected industry and interested parties cannot reach a consensus on the testing requirements or other provisions to be included in the consent order, the Agency will proceed with rulemaking under section 4(a) of TSCA. A description of the procedures governing consent orders and test rules appears in detail in the Federal Register of June 30, 1986 (51 FR 23766).

The first step in determining the feasibility of developing a consent order for a specific compound is the identification of interested parties who may wish to participate in negotiations with EPA. In the Federal Register of July 2, 1986 (51 FR 24222), EPA announced that the Agency was considering developing a testing consent order for TBP. This notice requested interested parties to identify themselves. FMC Corporation, Mobay Chemical Corporation, and Stauffer Chemical Company requested participation in negotiating a consent order; however, a final agreement was not obtained. Consequently, the Agency is proceeding with rulemaking under section 4(a) of TSCA.

C. Test Rule Development Under TSCA

This document is part of the overall implementation of section 4 of TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*), which contains authority for EPA to require development of data relevant to assessing the risks to health and the environment posed by exposure to a particular chemical.

Under section 4 of TSCA, EPA must require testing of a chemical to develop

health or environmental data if the Administrator makes certain findings as described in TSCA under section 4(a)(1) (A) or (B). Detailed discussions of the statutory section 4 findings are provided in the Agency's first and second proposed test rules which were published in the Federal Register of July 18, 1986 (51 FR 46524) and June 5, 1981 (46 FR 30300).

In evaluating the ITC's testing recommendations for TBP, EPA considered all available relevant information including the following: Information presented in the ITC's report recommending testing consideration and public comments on the ITC's recommendations; production volume, use, exposure, and release information reported by manufacturers of TBP under the TSCA section 4(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 4(d) Health and Safety Data Reporting Rule (40 CFR Part 716); and published and unpublished data available to the Agency. From its evaluation, as described in this proposed rule, EPA is proposing health effects testing under section 4(a)(1) (A) and (B) and environmental effects testing under section 4(a)(1)(B). By this action, EPA is responding to the ITC's designation of TBP for priority testing consideration.

II. Review of Available Data

A. Profile

TBP is a colorless, odorless liquid (Ref. 1). It has a molecular weight of 266.32 daltons (Ref. 7), measured water solubility of 280 ± 36 mg/L at 25 °C, a measured vapor pressure of 127 mm Hg at 177 °C, a measured boiling point of 289 °C at 760 mm Hg, and a measured $\log K_{ow}$ of 4.0 (Ref. 8). Muir (1984) estimated a Henry's law constant (Hc) for TBP to be 2.48×10^{-2} atm m³/mol (Ref. 54). The Agency believes this estimate of Hc is 2 to 3 orders of magnitude too high.

B. Production

TBP is produced in the United States (U.S.) by two manufacturers: FMC Corporation and Stauffer Chemical Company. Monsanto Company, a former manufacturer, discontinued TBP production at the end of 1985. The estimated 1985 combined production capacity of TBP is 6 to 9 million pounds per year (Ref. 45). The actual production and import volumes for 1985 have been submitted as confidential business information.

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Acyclic triphosphates such as TBP are commercially prepared from phosphorus oxychloride and the appropriate alcohols (Ref. 1). Phosphorus oxychloride reacts violently with water or moisture in the air, and consequently the reaction is usually contained in a closed process and is run under a dry nitrogen blanket. When the reaction is completed, the triester may be washed with a mild basic solution and then with water which is subsequently removed by decanting and vacuum distillation. Depending on the amount produced, the triester is then pumped into tank cars, tank wagons, 55-gallon drums, or smaller containers for shipment to customers (Ref. 1).

C. Uses

Some 40 to 60 percent of all TBP consumed is used as a base stock in the formulation of fire-resistant aircraft hydraulic fluids. Formulation concentrations are typically 50 to 60 percent of the hydraulic fluid. These hydraulic fluids are usually prepared by metering and pumping the individual components into a mixing tank where the components are blended. The fluids are then pumped into 55-gallon drums or tank trucks which are shipped to distributors/customers. When used, the fire-retardant hydraulic fluids are pumped into the system, which is bled to ensure that no air remains in the system. The bleeding of the system may result in small amounts of overflow (Ref. 1).

Some 10 to 20 percent of the production volume of TBP is used for extraction and separation processes in the PUREX (Plutonium Uranium Reduction Extraction) process for the separation of plutonium and uranium from spent nuclear fuel elements. It is also used to purify ^{235}U produced from the bombardment of protactinium-231. Many other metals can be extracted using TBP as the solvent. For example, cerium(IV) is separated from trivalent lanthanides; polonium can be separated from lead, bismuth, and niobium, from tantalum, or from impurities in niobium ore. TBP is also used to extract indium, thorium, uranyl nitrate, and, in an analytical procedure, strontium-90. It is used as an ion-association reagent (acid media) for metals, and also used in liquid-liquid extraction as a modifier in a mixture with an extractant and a diluent (Ref. 1), and in equipment cleaning (Ref. 2).

Approximately 5 to 10 percent of TBP is used as a defoamer in the paper industry and in textile sizings, inks, lacquers, and as a plasticizer (Ref. 1).

Minor uses of TBP as a chemical reagent include the following: Use in

combination with other chemicals to split viruses for the preparation of subvirion vaccines; for impregnation into resins that remove trace metal impurities from acid solutions; as a coating on high-performance liquid chromatographic columns that are used to quantify urinary porphyrins; for extraction of oxalic acid in a high-performance liquid chromatographic method to determine oxalic acid in urine; and as a pigment-grinding assistant, a very minor use (Ref. 1).

D. Environmental Release

TBP is expected to enter the environment as a result of wastewater releases from sites where it is made or used and from leachate releases from landfills.

During production, TBP may be released to surface waters in the wastewater used in washing procedures. Small amounts of TBP could also occur in distillation bottoms and would subsequently be incinerated or landfilled (Ref. 2).

During processing and use of TBP, release to water may result from such activities as the cleaning of equipment used in formulating aqueous-based polishes and from spillage during the draining and/or refilling of airplane hydraulic systems (Ref. 2). Some release could occur during ore extraction. The reported presence of TBP in industrial effluents, as discussed in the following paragraph, suggests that many uses of the compound result in eventual release into the aquatic environment. There are usually no direct releases of phosphate esters from the solid materials into which they are incorporated (Ref. 2).

TBP was found in municipal and industrial effluents at concentrations ranging from 6.9 $\mu\text{g/L}$ to 13,517 $\mu\text{g/L}$ (Ref. 1). Although the names and locations of the plants are confidential, the industries represented include paint and ink, printing and publishing, organics and plastics, pulp and paper, pharmaceuticals, explosives, foundries, aluminum, electronics, organic chemicals, transportation equipment, and publicly owned treatment works. Dunlap et al. (Ref. 4) identified 1.7 mg/L of TBP in groundwater underlying a landfill in Norman, Oklahoma and Hutchins et al. (Ref. 5) identified traces of TBP in groundwater in Fort Polk, Louisiana. TBP (concentration not given) was also found in Philadelphia drinking water (Ref. 6).

In a study by Williams et al. (Ref. 40), TBP was found in drinking water derived from the Great Lakes or adjacent water bodies in 12 Canadian communities at concentrations ranging from 0.8 ng/L to 29.5 ng/L. About half

the locations are near U.S. communities such as Buffalo, NY and Niagara Falls, NY that may draw water from the same sources.

EPA conducted a study for the purpose of compiling a list of all organic compounds that have been found in water (Ref. 41). TPB was also found in water (Cincinnati, OH and Miami, FL), effluent from a chemical plant, effluent from two landfill leachates, a well, and a river. The report gave only the locations mentioned and no TBP concentrations (Ref. 57).

E. Human Exposure

1. Occupational

EPA believes that there are numerous possibilities for occupational exposure to TBP. However, the extent to which such exposures actually occur in TBP's production, distribution, and use is unclear because of a lack of detailed information about many of the specific industries involved. According to the National Occupational Hazard Survey (NOHS, 1972-1974) by the National Institute for Occupational Safety and Health (NIOSH), 30,555 workers in 15 industries and 30 occupations were potentially exposed to TBP. Approximately $\frac{1}{2}$ of these workers fall into the Standard Industrial Classification (SIC) for "Transportation by Air" (Ref. 53). This probability sample was based upon a 1970 list of businesses covered under the Occupational Safety and Health Act. Potential exposure estimates thus refer to the year 1970. Estimates are derived from surveyor observations of three basic types.

- Actual.* The surveyor observed the use of the specific agent.
- Tradename.* The surveyor observed the use of a tradename product known to contain the specific agent.
- Generic.* The surveyor observed a product in some type of general use which leads NIOSH to suspect that the specific agent may be contained in that product.

According to the National Occupational Exposure Survey (NOES, 1981-1983) by NIOSH, 12,111 workers in 6 industries and 13 occupations were potentially exposed to TBP (Ref. 3). However, this survey does not include workers in the SIC category, "Transportation by Air", which includes the aircraft mechanic occupation that EPA considers an important area of potential exposure to TBP. Also, the NOES, using probability sampling techniques, selected approximately 4,500 workplaces in the U.S. for walk-through surveys. It is a broad-scope survey, not

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designed to stand as a definitive study or provide precise information for any one particular hazard. The NOES data used are preliminary. The NOES includes only a few of the SIC codes and consists solely of actually observed uses of TBP in the work place.

EPA estimates 12 to 15 workers to be potentially exposed to TBP at each of its two manufacturing sites for 25 days per year (Ref. 2). Because of the corrosive nature of TBP and its phosphorus oxychloride precursor (see Unit II.B.1.), workers manufacturing TBP operate processes which are closed and usually conducted under a blanket of nitrogen. Further, because of the hazardous character of phosphorus oxychloride, workers normally are protected through the use of local ventilation, appropriate respiratory equipment, and suitable protective clothing. Thus, little or no routine exposure of workers is expected during the synthesis of TBP (Ref. 2).

On completion of the manufacturing operation, the finished materials are drummed or packaged for shipment. Incidental dermal contact may be encountered during routine connection of transfer lines between reactor and drumming station and during drumming. If no gloves were worn, this contact could amount to some 1,300 to 3,900 mg/contact if both hands were exposed and from 1 to 3 mg of material/cm² adhered to the skin. Similar dermal contact would occur when equipment is cleaned and maintained (Ref. 2).

The processing of TBP primarily involves mechanical transfer of pure material as it is received for a blending operation. In the processing of TBP for aircraft hydraulic fluid, EPA estimates the involvement of less than 70 site-days per year and 2 to 4 workers per site with a dermal contact potential of 650 to 1950 mg/day (Ref. 2).

An industrial hygiene report from Los Alamos Scientific Laboratory indicated that irritating fumes may form when TBP is heated, necessitating ventilation of the work area (Ref. 1). However, the heating of TBP during industrial production, processing, or use would be very unusual because it breaks down at high temperatures. For this reason it is generally used at ambient temperature (Ref. 27 and 33). This would reduce the possibility of inhalation contact except, for example, here aerosol formation may occur as a result of spraying operations.

The largest potentially exposed worker population is in aircraft maintenance because manual operations could result in exposure to TBP-containing hydraulic fluid (Unit II.C.). The Bureau of Labor Statistics (BLS) of the U.S. Department of Labor reported 99,000 aircraft engine mechanics and 15,000 aircraft nonengine mechanics in 1986 (Ref. 42); the latter

figure is consistent with the roughly 10,000 aircraft workers estimated to be exposed in the NOHS. Preliminary information indicates that mechanics involved in large aircraft repair at one site are, on the average, potentially exposed to hydraulic fluid approximately once per week for 30 minutes to 2 hours (Ref. 43); however, EPA is uncertain whether that exposure scenario is typical for the industry and what the range of actual individual exposures might be. A potential for hand exposure to hydraulic fluid (1,300 to 3,900 mg, both hands) applies to aircraft mechanics in the same manner as that described earlier in this Unit for the transfer and packaging phase of manufacturing operation and the cleaning and maintenance of equipment.

In the case of ore extraction (primarily uranium ore beneficiation), EPA estimates that there are up to 25 plant sites and 2 to 8 workers per site. Mechanical transfers and automated processes are typical (Ref. 2). However, possibilities of exposure exist which are similar to those found in TBP's manufacture and the processing of other products as described earlier in this Unit: transfer of stock material, drumming or packaging, and cleaning and maintenance of equipment.

Exposure in plastics production is assumed to be limited because of the frequent use of mechanical transfers and automated processes (Ref. 2). However, possibilities of exposure exist which are similar to those found in TBP's manufacture and the processing of other products as described earlier in this Unit: transfer of stock material, drumming or packaging, and cleaning and maintenance of equipment.

The identification of TBP in releases from the spectrum of industries cited in Unit II.D suggests a potential for worker exposures in those industries, particularly in smaller operations where procedures are less likely to be automated and isolated from potential worker contact. The Agency encourages the submission of relevant data, especially on exposure potential and work practices in the paper, textile, inks, and coatings industries (see Unit II.C.).

2. General Population

A potential route of general population exposure is through contact with contaminated environmental media, including drinking water (see Unit II.D.). TBP has been found in numerous industrial effluents, groundwater in Oklahoma and Louisiana, in drinking water in Philadelphia, PA; Cincinnati, OH; and Miami, FL; and in river water. TBP has also been found in the drinking water of several Canadian municipalities that obtain their water from the Great Lakes

(see Unit II.D.). Tens of thousands of people draw their water from these sources. Although the concentrations of TBP found so far in drinking water are extremely low, EPA will examine closely any additional evidence of such exposure.

EPA conducted an analysis of human adipose tissue samples for the detection of chemical substances. The primary focus was to document trends in human exposures to environmentally persistent contaminants. Forty-six composite samples (20 adipose tissue samples per composite sample) were analyzed. A trace of TBP was found in one composite sample of a 0 to 14 year old group from the East North Central area (Ohio, Indiana, Illinois, Michigan, and Wisconsin) (Ref. 20). The significance of this evidence of TBP exposure is difficult to evaluate.

F. Health Effects

1. Acute Toxicity

LD50 or LC50 values for TBP in rats ranged from 1,300 to 3,200 mg/kg with oral administration (Refs. 9 through 12), 500 to 1,800 mg/kg with intraperitoneal administration (Refs. 13 and 51), and less than 2,000 mg/L of air via inhalation administration (Ref. 14). In another rat inhalation study, one third of the animals died after a 6-hour exposure at 3,800 ppm of TBP (Ref. 11). Two dermal toxicity studies with rabbits produced LD50 values ranging from equal to or greater than 3.1 g/kg to equal to or greater than 10.0 g/kg (Refs. 10 and 15), and two dermal irritation studies with rabbits showed TBP to be a mild to severe irritant (Refs. 14 and 53).

These studies are sufficient to reasonably determine or predict the acute toxicity of TBP.

2. Dermal Sensitization

Skydrol® 500B-4, an aircraft hydraulic fluid containing less than 25 percent TBP (Ref. 28), was patch-tested for dermal irritation and sensitization in 53 men and women; all completed the test (Ref. 24). Approximately 0.2 mL of test material was placed on each patch, and a series of 15 alternate-day applications (weeks 1 to 5) was carried out during the induction phase. Each patch was removed and the dermal area examined after 24 hours for three successive days. None of the 53 participants were sensitized. Photosensitization was not evaluated, and the exact TBP concentration tested is unknown but may have been too low to have elicited a reaction. For this reason, EPA concludes that these data are not sufficient to reasonably determine or predict the sensitization effects of TBP.

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Fourteen guinea pigs were tested for dermal sensitization to TBP by the "drop on" method. Six of the 14 were sensitized (Ref. 32). The test method, including the control procedures and the grading system, was not described. No photosensitization test was conducted. Although this study suggests a skin sensitization hazard due to TBP exposure, it does not supply sufficient data to fully determine or predict the dermal sensitization potential of TBP.

3. Subchronic Toxicity

Groups of Sprague-Dawley rats consisting of 12 males and 12 females per group were given 0.20 or 0.30 g/kg of TBP by gavage 5 days/week for 18 weeks in the low-dose group and for 6 weeks in the high-dose group (Ref. 22). A control group was given water by gavage. Because no change was seen after 6 weeks in the high-dose group, their dosage was increased to 0.35 g/kg for the remaining 12 weeks. Although no overt signs of toxicity were observed, rats in both dose groups showed diffuse hyperplasia of the urinary bladder epithelium on histopathological examination (see Unit II.F.8. for discussion). Numerous other organs were examined histopathologically but showed no pathological changes. The investigators also reported decreased body weight in high-dose males and decreased red blood cell count in high-dose females.

In another study (Ref. 23), TBP (over 99 percent purity) was administered continuously in the diet of Sprague-Dawley rats for at least 90 days at concentrations of 0, 8, 40, 200, 1,000, and 5,000 ppm. Fifteen male and fifteen female rats were randomly assigned to each dose group. No mortality occurred during this study. Histopathologic examinations were conducted on selected tissues from all control and high-dose animals and on livers and urinary bladders from all animals. The no-effect dose level of TBP was 200 ppm.

Treatment-related histopathological effects included generalized transitional-cell hyperplasia in the urinary bladders of the males receiving 1,000 ppm and 5,000 ppm of TBP and the females receiving 5,000 ppm (see Unit II.F.8. for discussion). Clinical signs that may have been treatment-related were sporadic abdominal staining on several males and females receiving 1,000 ppm and 5,000 ppm TBP doses during the first 19 days of the study, a significant decrease in platelets in the males receiving 1,000 ppm, and a significant elevation of the mean activated partial thromboplastin time in the males receiving 5,000 ppm. These studies are sufficient to reasonably

determine or predict the subchronic effects of TBP.

4. Neurotoxicity

TBP (80 mg/kg) was one of several organic phosphates tested by injection into the tail vein of rats (number in test groups not given and no mention of controls) (Ref. 16). Uncoordination and mild anesthesia occurred in about 1 hour and pronounced weakness in about 4 hours. With a dose of 100 mg/kg, anesthesia and pronounced dyspnea occurred in 8 to 10 minutes followed by respiratory failure. There were no cholinergic symptoms. The paper states that artificial respiration had to be given in some cases, but does not specify for which chemicals. Also, chemical purity is not stated; no-effect levels were not determined. Apparently TPB administered intravenously is much more toxic to rats than administered by other routes (I.L.C.).

Two dose groups of ten male and ten female Sprague-Dawley rats per group were given 0.28 and 0.42 ml/kg/day of a mixture of 98.4 percent TBP and 1.3 percent tributoxethyl phosphate (an occasional contaminant of TBP, Ref. 44) by gavage for 14 days (Ref. 17). A control group was force-fed tap water. A significant reduction in conduction velocity of the caudal nerve was observed in high dose male rats (four rats/group) 24 hours after administration of the last dose. Electron microscope examination of the sciatic nerve showed morphological changes such as retraction of Schwann cell processes surrounding fibers in both sexes of the high dose group.

A study was performed to test TBP (purity not given) for delayed neurotoxicity in 16-month old leghorn hens (Ref. 18). The oral LD50 for TBP in hens without atropine protection against acute cholinergic effects was determined to be 1,500 mg/kg. A group of 20 hens received a single oral dose of 1,500 mg/kg of TBP, in gelatin capsules, on day 0. Hens that survived were dosed again on day 21 with atropine sulfate protection. Another group of 10 hens were given two dermal doses of 1,500 mg/kg of TBP on day 0 and day 21. On both days atropine sulfate was administered. Controls consisted of a positive control group for delayed neurotoxicity treated with a single oral dose of 750 mg/kg of tri-o-cresyl phosphate; another group was given gelatin capsules. Although a total of six hens died following the oral administration of TBP, none of the surviving hens developed delayed neurotoxicity throughout the 42-day experiment. All of the hens treated with dermal doses of TBP survived the 42-day

experiment and none of them developed signs of toxicity. These results indicate that delayed neurotoxicity is not a concern with TBP.

Although the first two studies cited suggest that TBP may cause neurotoxic effects, they are inadequate to determine or predict the acute and chronic neurotoxic potential of TBP.

5. Developmental Toxicity

No developmental toxicity data for TBP have been found in the literature or have been reported under the TSCA section 8(d) rule (51 FR 18323; May 19, 1986).

6. Reproductive Toxicity

In a 1984 study by Laham et al. (Ref. 19) two groups of ten male and two groups of ten female Sprague-Dawley rats were given 0.14 and 0.42 ml/kg of TBP (98.4 percent) by gavage daily for 14 days. A control group was force-fed tap water. One out of four of the male rats in the high-dose group showed microscopic degenerative changes in approximately 50 percent of the seminiferous tubules.

A follow-up 18-week study which was conducted by the same investigators failed to identify any testicular changes in rats of the same strain exposed by gavage to TBP (98.4 percent) levels up to 0.35 gm/kg/day 5 days/week (Ref. 22).

The negative results of the follow-up study contradict the previous study. However, the high TBP dosage in the follow-up study was less than in the previous study. Tubular degeneration is said to have occurred in 50 percent of tubules examined rather than in one out of four of the rats examined in the high dose group. In addition to the contradictions in these two studies, there are no available reproductive studies designed to provide general information about the effects of TBP on gonadal function, conception, parturition, and the growth and development of the offspring. Therefore, EPA concludes that existing data are not sufficient to reasonably determine or predict the reproductive effects of TBP.

7. Mutagenicity

An Ames test was conducted by the FMC Corporation with TBP (100 percent) using five strains of test bacteria (strains TA 1535, TA 1538, TA 1537, TA 98, TA 100) both with and without the addition of an exogenous source of liver enzyme for metabolic activation of the test agent. No evidence of mutagenic activity was found by this method (Ref. 29). EPA concludes that this is a valid negative test.

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A test using the Cy/Bly method was conducted with *Drosophila* to measure the accumulation of recessive lethals on the second chromosome of flies exposed over a number of generations for 18 months to increasing levels of TBP (Ref. 46). TBP was not found to be mutagenic in *Drosophila*. The frequencies of accumulated lethal mutations in the TBP-treated flies and the controls were 11.1 and 9.3 percent. Only one population cage was used per chemical and control, and the number of flies sampled was low. Because of the lack of historical data and the unusual nature of the experiment it is impossible to calculate the power of the test. In addition, this test has not been validated in terms of test repeatability, and sensitivity. Given these uncertainties, the study is not sufficient to reasonably determine or predict the mutagenic effects of TBP on *Drosophila*.

Although there are valid negative data for the Ames test, no further data are available to reasonably determine or predict gene mutation or chromosomal aberration effects of TBP.

8. Oncogenicity

Urinary bladder hyperplasia was reported in both of the subchronic studies discussed earlier (Unit II.F.3.). In an 18-week, two-dose gavage study with Sprague-Dawley rats (Ref. 22), animals in both dose groups (0.20 and 0.30-0.35 g/kg) showed diffuse hyperplasia of the bladder epithelium. In a 90-day dietary feeding study with Sprague-Dawley-derived rats at TBP concentrations 0, 8, 40, 200, 1,000, and 5,000 ppm (Ref. 23), the only treatment-related histopathological finding was generalized transitional-cell hyperplasia in the urinary bladders of the 1,000 ppm and 5,000 ppm males and the 5,000 ppm females.

Although all hyperplasia does not necessarily lead to neoplasia, hyperplasia has been shown to be associated with tumor development with many chemicals. The development of hyperplasia and of neoplasia is both time and dose dependent. In a 2-year study, it could be expected that bladder

hyperplasia would be observed at dose levels well below those used in the subject studies. Furthermore, in EPA's judgement, the degree of hyperplasia induced in the TBP subchronic studies strongly suggests a potential for progression to tumor formation.

The available data suggest that TBP may have oncogenic potential, but are not sufficient to fully determine or predict the oncogenic effects of TBP.

9. Pharmacokinetics (Oral/Dermal Absorption, Distribution, Metabolism, and Excretion)

Jones (Ref. 35) concluded that TBP is metabolized to the corresponding dialkyl phosphate and S-alkyl cysteine. Jones further concluded that monodealkylation appears to be a common route of metabolism for trialkyl phosphates, most likely occurring through enzymatic hydrolysis (P-O cleavage) and de-O-alkylation (C-O cleavage, with reduced glutathione acting as an alkyl receptor). Test species were male rats and mice.

Marzulli et al. (Ref. 36) demonstrated that ³²P- and ¹⁴C-labeled TBP can penetrate sheets of human stratum corneum conjunctum in diffusion cells. From *in vitro* measurements of steady state rates of penetration, the investigators were able to predict *in vivo* skin penetration rates. This *in vitro* model gave essentially the same results as tests on anterior forearms of three human subjects.

Eleven phosphorus-containing metabolites were identified in a 24-hour urine sample from rats following intraperitoneal injection of 250 mg/kg of TBP (Ref. 37). The major metabolites included dibutyl hydrogen phosphate, butyl dihydrogen phosphate, and butyl bis(3-hydroxybutyl) phosphate. Small amounts of derivatives hydroxylated at other carbons of the butyl groups were also detected. The major metabolic intermediates were considered to be dibutyl 3-hydroxybutyl phosphate and dibutyl 3-oxobutyl phosphate.

In a follow-up study (Ref. 38) to determine whether these metabolites are formed by mixed-function oxidases,

by esterases, or by glutathione S-transferase, investigators identified sulfur-containing metabolites of TBP. In this study, the major urinary metabolites following a single intraperitoneal injection of TBP were (3-oxobutyl)- and (3-hydroxybutyl)mercapturic acid. Traces of 2-oxobutyl- and (2-hydroxybutyl)mercapturic acids were also detected.

Sasaki et al. (Ref. 39) determined the *in vitro* metabolic pathway of TBP using liver homogenate, forming first tributyl hydroxy phosphate and then tributyl dihydroxyphosphate, with dibutyl phosphate being only a minor dead-end point in the *in vitro* pathway.

Following a single oral dose of ¹⁴C-TBP (14 mg/kg) to male rats, 50, 10, and 6 percent of the label was excreted in the urine, exhaled air, and feces, respectively, within 24 hours (Ref. 37). Following a single intraperitoneal injection (14 mg/kg), 70, 7 and 4 percent was excreted in the urine, exhaled air, and feces, respectively, within 24 hours.

Although available data give some information about human *in vitro* and *in vivo* skin penetration, intraperitoneal rat metabolism and excretion of TBP, comparative oral/dermal or intravenous pharmacokinetics studies are not available. None of the studies include comparative guinea pig/rat bioavailability, skin absorption, or tissue distribution of TBP. EPA believes that available data are not sufficient to reasonably determine or predict the comparative oral/dermal pharmacokinetics of TBP.

G. Environmental Effects

1. Acute Toxicity

Several studies were performed to estimate the toxicity and bioconcentration of TBP in aquatic organisms. All these studies used nominal TBP concentrations or static test conditions, except the studies conducted by Geiger et al. and the Analytical Bio Chemistry Laboratories, Inc. (Ref. 26 and 49) which used measured TBP concentrations and flow-through conditions. The following Table 1 is a summary of the studies:

TABLE 1—AQUATIC TOXICITY AND BIOCONCENTRATION OF TBP

Organism	Test days	Test value	(Ref. No.)
<i>Chlorella emersonii</i>	2	EC50 = 5-10 mg/L.....	30
	1	EC50 = 5.8 mg/L.....	
<i>Daphnia magna</i>	2	LC50 = 9.0 mg/L.....	47
	1	LC50 = 12.8 mg/L.....	56
Fathead minnow.....	2	LC50 = 3.7 mg/L.....	56
	3	LC50 = 2.1 mg/L.....	56
	4	LC50 = 8.0 mg/L.....	26

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TABLE 1—AQUATIC TOXICITY AND BIOCONCENTRATION OF TBP—Continued

Organism	Test days	Test value	(Ref. No.)
Killifish.....	4	LC50=11.0 mg/L.....	26
	4	LC50=6.4 mg/L.....	49
	4	LC50=9.6 mg/L.....	50
	4	LC50=8.8 mg/L.....	50
Goldfish.....	4	LC50=11.4 mg/L.....	56
Zebrafish.....	4	LC50=10-14 mg/L.....	47
Rainbow trout.....	4	LC50=5-9 mg/L.....	51
	4	LC50=8.2 mg/L.....	30
	4	LC50=11.0 mg/L.....	52
Zebrafish.....	10	Tox Threshold=13.5 mg/L.....	56
	48	Tox Threshold=8.3 mg/L.....	56
Goldfish.....	4	BCF=7.....	50
Killifish.....	4	BCF=30.....	50
	38	BCF=21-35.....	29

EPA carefully analyzed the available acute toxicity data and concluded the following: (1) *Chlorella* is a relatively insensitive species of alga compared to *Selenastrum* and testing in *Selenastrum* will provide more useful data; (2) available data with *D. magna*, while generated by methods unacceptable for TBP, suggest a time dependent acute toxicity that may indicate cumulative toxicity, toxicity of a byproduct that would not be removed from static test systems, or potential chronic toxicity; (3) while all of the 4-day fish LC50 values, including those conducted under flow-through conditions, are very similar (within a factor of 3), it is reasonable to require a flow-through test with rainbow trout to provide more reliable data to assess the potential hazard of TBP.

The logic for requiring flow-through tests for TBP is based on biodegradation potential and hydrophobicity of TBP. Available data show that after 4 days' incubation in river water containing a relatively low concentration of TBP-acclimated bacteria, at least 10

percent of TBP was biodegraded (Unit I.H.). This susceptibility to biodegradation and TBP's relative hydrophobicity indicate that flow-through testing would better provide for continuous exposure to a relatively constant TBP concentration than static or renewal systems. Static tests on such compounds may underestimate toxicity. EPA concludes that most of the acute toxicity data listed in Table 1 are not sufficient to reasonably determine or predict the acute toxicity of TBP to daphnids, gammarids, rainbow trout, or algae.

TBP's herbicidal properties for terrestrial plants were tested with various seedlings (sweet corn, cucumber, cotton, lima bean, tobacco, and tomato). The seedlings were dipped in 0.5 and 5.0 percent water solutions of TBP (frequency of dipping not given). Within 1 week, all TBP-treated plants were severely injured or dead (Ref. 25).

This study makes no provision for the determination of concentration of free TBP, metabolites, and soluble and

bound residues in pooled plant organs and pooled whole plants. Therefore, EPA concludes that the above data are not sufficient to reasonably determine or predict plant uptake and translocation of TBP.

2. Chronic Toxicity

No information was found on the chronic toxicity of TBP to aquatic or terrestrial organisms.

H. Chemical Fate

TBP is expected to partition to the aquatic and sediment environments. Available data suggest that TBP is substantially biodegraded in aerobic, but not anaerobic environments. EPA considers these data adequate to determine or predict aerobic and anaerobic biodegradation. An adequate measurement of log Kow is also available (Ref. 13). The following Table 2 shows the biodegradability data of TBP.

TABLE 2.—BIODEGRADABILITY OF TRIBUTYL PHOSPHATE

Test	Test days	Test value	(Ref. No.)
OECD 301C (TBP loss).....	28	77%.....	47
OECD 301D (BOD).....	28	92%.....	54
OECD 301E (DOC Loss).....	28	89%.....	54
SCAS ¹	91	96% @ 3 mg/L/day.....	8
SCAS.....	147	56± 21% @ 13 mg/L/day.....	8
River die-away.....	4	10%.....	8
	7	100%.....	8
Ultimate biodegradation.....	7	1% of theoretical CO ₂ at 20 mg/L.....	8
	28	3% of theoretical CO ₂ at 20 mg/L.....	8
	7	30% of theoretical CO ₂ at 19.4 mg/L.....	8
	28	91% of theoretical CO ₂ at 19.4 mg/L.....	8
Anaerobic biodegradation (TBP loss).....	30	0%.....	28

¹ Semi-Continuous Activated Sludge.

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As noted by the ITC, the ubiquitous environmental appearance of TBP at various concentrations (see Unit II.D.) may mean that it is not effectively degraded below some threshold concentration or that the continuous release of TBP into the environment leads to some low-level equilibrium concentration reflecting both input and removal processes (51 FR 18369).

III. Findings

EPA is basing its proposed health effects testing for TBP on the authority of sections 4(a)(1) (A) and (B) and environmental effects testing on the authority of section 4(a)(1)(B) of TSCA.

A. Findings Under TSCA Section 4(a)(1)(A)

1. Health Effects

EPA finds that the manufacture, processing, use, and disposal of TBP may present an unreasonable risk of injury to human health due to potentially significant levels of occupational and general population exposure as discussed in Unit II.E., and to its potential to cause oncogenicity, neurotoxicity, and dermal sensitization based on available animal studies (see Unit II.F.).

The finding of potential oncogenicity risk is based on two reports of hyperplasia of the urinary bladder epithelium in rats after oral administration of TBP (Refs. 22 and 23). Although all hyperplasia does not necessarily lead to neoplasia, hyperplasia has been shown to be associated with tumor development with many chemicals (Unit II.F.8.) (Ref. 34). The data suggest that TBP may be oncogenic, but are derived from studies that are too brief to adequately characterize this effect.

The finding of potential neurotoxicity risk is based on uncoordination, anesthesia, weakness, and respiratory failure in rats after injection of TBP (Ref. 16), and reduction in caudal nerve velocity and retraction of Schwann cell processes surrounding sciatic nerve fibers in rats after the administration of 98.4 percent TBP by gavage (Ref. 17).

The finding of potential dermal sensitization risk is based on the sensitization of 6 out of 14 guinea pigs exposed to TBP (Ref. 32).

For the reasons stated in Unit II., EPA also finds that available data are insufficient to reasonably determine or predict the oncogenicity, neurotoxicity, and dermal sensitization effects from exposure during TBP's manufacture, processing, use, and disposal. The Agency finds that testing is necessary to develop health effects data, and

believes that the data resulting from these test requirements will be relevant to a determination that the manufacturing, processing, use, and disposal of TBP does or does not present an unreasonable risk of injury to human health.

2. Environmental Effects

EPA finds that the manufacturing, processing, use, and disposal of TBP may present an unreasonable risk of injury to the environment because of its release to the environment and its potential to cause lethality in terrestrial plants. The concern for potential plant uptake effects is based on a study in which TBP was lethal to various seedlings for which soluble and bound residues in the plants were not measured (Ref. 25). Available data are insufficient to reasonably determine or predict the plant uptake and translocation of TBP resulting from exposure due to release during its manufacture, processing, use, and disposal. The Agency finds that testing is necessary to develop these data. EPA believes that the data resulting from this test requirement will be relevant to a determination that the manufacturing, processing, use, and disposal of TBP do or do not present an unreasonable risk of injury to the environment.

B. Findings Under TSCA Section 4(a)(1)(B)

1. Health Effects

EPA finds that TBP is produced in substantial quantities, and that there is or may be significant occupational and general population exposure from its manufacture, processing, use, and disposal (see Unit II.E.). From 6 to 9 million pounds of TBP was produced in the U.S. in 1985 (Ref. 45). According to the NOHS, (1972-1974), 33,555 workers are potentially exposed to TBP; according to the NOES (1981-1983), 12,111 nonaircraft workers are potentially exposed; and according to the BLS (1986), there are 15,000 nonengine aircraft mechanics potentially exposed (largest potential exposure group) (Unit II.E.). Although the major exposure route is thought to be dermal, the detection of TBP in drinking water in the U.S. and in Canadian drinking water taken from the Great Lakes indicates the possibility of human exposure by the oral route (Unit II.D.) to substantial numbers of people in the general population.

TBP's major use as an ingredient in aircraft hydraulic fluid creates the possibility of dermal exposure of 15,000 aircraft mechanics (Unit II.E.1.) at significant levels. TBP is also used in

extraction and separation processes for various metals, in textile sizings, inks, and lacquers, and as a plasticizer. It has several minor uses, for example, the splitting of viruses (Unit II.C.). Although some of these uses are highly automated, the other uses may result in exposure of a substantial number of industrial workers.

Available data are insufficient to reasonably determine or predict the neurotoxicity, developmental toxicity, reproductive and fertility effects, mutagenicity, oncogenicity, dermal sensitization, and oral/dermal pharmacokinetics of TBP resulting from exposure during its manufacture, processing, use, and disposal. The Agency finds that testing is necessary to develop health effects data. EPA believes that the data resulting from these test requirements will be relevant to a determination that the manufacturing, processing, use, and disposal of TBP do or do not present an unreasonable risk of injury to human health.

2. Environmental Effects

EPA finds that TBP is produced in substantial quantities (6 to 9 million pounds in 1985 (Ref. 45)). It enters or may reasonably be anticipated to enter the environment in substantial quantities during manufacture, processing, use, and disposal, as evidenced by its detection in surface water, sediment, and groundwater (see Unit II.D.). EPA believes that the low concentration of TBP detected in or released to the environment at numerous, widely-dispersed locations suggest that the total quantity released to the environment is substantial (see Unit II.D.). EPA believes that for chemicals with substantial production and ubiquitous environmental distribution, reliable data should be developed to assess their toxicity and persistence. Available data are insufficient to reasonably determine or predict TBP's acute effects on aquatic algae, fish, and invertebrates, and chronic effects on fish and aquatic invertebrates (free swimming and in sediment). The Agency finds that testing is necessary to develop environmental effects data, and believes that the data resulting from these test requirements will be relevant to a determination that the manufacturing, processing, use, and disposal of TBP does or does not present an unreasonable risk of injury to the environment.

The ITC recommended terrestrial invertebrate testing for TBP. EPA is considering possible test species and methods for such testing but has not yet

TW

determined the best approach to testing for this effect under TSCA section 4. The Agency is soliciting public comments on this issue (see Unit V.) and is not proposing the testing at this time.

3. Chemical Fate

EPA finds that TBP is produced in substantial quantities (6 to 9 million pounds in 1985 (Ref. 45)). It enters or may reasonably be anticipated to enter the environment in substantial quantities during manufacture, processing, use, and disposal, as evidenced by its detection in surface water, sediment, and groundwater (see Unit II.D.). Available data are insufficient to reasonably determine or predict TBP's vapor pressure at 25 °C, log K_{oc}, and hydrolysis rate. Vapor pressure data at 25 °C are needed to estimate a reliable H_c for TBP. Data on log K_{oc} are needed to estimate the sorption of TBP to soil and sediments. Finally, hydrolysis rate data, which complement the biodegradation data, are needed to estimate the persistence of TBP in aquatic systems. EPA believes that the data resulting from these test requirements will be relevant to a determination that the manufacturing, processing, use, and disposal of TBP does or does not present an unreasonable risk of injury to the environment.

IV. Proposed Rule

A. Proposed Testing and Test Standards

On the basis of the information presented in Unit II and the findings set forth in Unit III of this preamble, EPA is proposing health and environmental effects testing for TBP. The tests are proposed to be conducted in accordance with EPA's TSCA Good Laboratory Practice Standards in 40 CFR Part 792 and specific TSCA test guidelines in 40 CFR Parts 795, 796, 797, and 798, and other published test methods as specified in the proposed rule for TBP.

The oral/dermal pharmacokinetic test guideline proposed in § 798.7470 is revised and recodified in Part 795 as section § 795.228 *Oral/dermal pharmacokinetic test*. For the purpose of this test rule, these guidelines are being proposed as the test standards that must be met by the test sponsors. The route of administration of TBP for all tests would be oral unless otherwise specified. Data resulting from these tests will assist the Agency in conducting health and environmental risk assessments for TBP.

Final revisions to the TSCA test guidelines were published in the *Federal Register* of May 20, 1987 (52 FR 19056); the Agency is proposing that these

revised test guidelines be adopted as the test standards for TBP.

The TSCA test guidelines, proposed modifications, and other cited test guidelines discussed below specify generally accepted minimal conditions for determining toxicities and properties of substances such as TBP to which human, aquatic, and terrestrial life are expected to be exposed. Conducting the required studies in accordance with these TSCA guidelines will help ensure that the test results are reliable and adequate.

The Agency's review of the TSCA Test Guidelines, which occurs on a yearly basis according to the process described at 47 FR 41857 (September 22, 1982), has found no reason to conclude that these protocols need to be modified significantly.

1. Health Effects

The acute neurotoxicity testing and neurobehavioral toxicity evaluation would consist of the functional observation battery as specified in 40 CFR 798.6050, modified in proposed § 799.4360(c)(1)(i)(A)(2), and the motor activity test as specified in 40 CFR 798.6200, as modified in proposed § 799.4360(c)(1)(i)(B)(2). To assess the effects of repeated long-term exposures to TBP, the Agency is proposing a subchronic (90-day) neurotoxicity and neurobehavioral toxicity evaluation consisting of a neuropathologic evaluation of tissues perfused *in situ* as specified in 40 CFR 798.6400, as modified in proposed § 799.4360(c)(1)(i)(C)(2).

To assess the developmental effects of TBP, the Agency is proposing that testing be conducted by gavage according to the guidelines at 40 CFR 798.4900, as modified in proposed § 799.4360(c)(2)(i)(B).

To assess the reproductive and fertility effects of TBP, the Agency is proposing that testing be conducted according to the guidelines at 40 CFR 798.4700, as modified in proposed § 799.4360(c)(3)(i)(B)(i)(B).

To assess the mutagenic effects of TBP, the Agency is proposing that testing be conducted in tiers. First-tier testing would consist of the detection of gene mutation in somatic cells in culture using the test guidelines at 40 CFR 798.5300, an *in vitro* mammalian cytogenetics test using the test guidelines at 40 CFR 798.5375, and an *in vivo* mammalian bone marrow cytogenetics chromosomal analysis test using the test guidelines at 40 CFR 798.5385, as modified in proposed § 799.4360(c)(5)(i)(B)(2); second-tier testing would consist of a sex-linked recessive lethal assay in *Drosophila*

melanogaster using the test guidelines at 40 CFR 798.5275, as modified in proposed § 799.4360(c)(4)(i)(B)(2), and a rodent dominant lethal test using the test guidelines at 40 CFR 798.5450; and third-tier testing will consist of a mouse visible specific locus test using the test guidelines at 40 CFR 798.5200 and rodent heritable translocation test using the test guidelines at 40 CFR 798.5460, and as modified in proposed § 799.4360(c)(5)(i)(D)(2).

Unless the results of the gene mutation in somatic cells in culture are negative, a sex-linked recessive lethal test in *Drosophila melanogaster* would be required. Positive results in the sex-linked recessive lethal test would trigger the requirement for conducting a mouse visible specific locus (MVSL) test. EPA believes that the MVSL is necessary, when these lower-tier tests are positive, to establish definitively whether a substance is capable of eliciting heritable gene mutations. Under the approach proposed, EPA would consider the positive results in the lower-tier tests in a public program review, together with other relevant information, during which interested persons would be able to give their views to the Agency. If, after the review, EPA determined that the MVSL was still appropriate, EPA would notify the test sponsors by letter or *Federal Register* notice that they must conduct the test. If EPA determined that the test was no longer necessary, EPA would propose to amend the rule to delete the test requirement.

Other test rules have included the requirement for the MVSL, including those for the C9 aromatic hydrocarbon fraction (50 FR 20662), diethylenetriamine (50 FR 21398), and four fluoroalkenes (52 FR 21516). EPA based the requirement in those rules, in part, on information and assumptions about the cost of conducting the test and the availability of laboratories capable of performing the test. The information and assumptions have since proven to be incorrect. Accordingly, EPA is in the process of reexamining the MVSL requirement for all those chemical substances for which the MVSL has been required or proposed to be required. In particular EPA is reviewing whether any laboratories are available to perform the MVSL for industry in accordance with the TSCA Good Laboratory Practice Standards at 40 CFR part 792 and the cost of such testing. EPA is also reviewing possible alternative tests to the MVSL for which costs may be lower or laboratory availability may be more certain.

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Once EPA completes its evaluation of this additional information, EPA will publish a notice in the *Federal Register* concerning the MVSL for TBP and other substances subject to proposed and final TSCA section 4 test rules. This notice will provide up-to-date information on the cost of MVSL testing, availability of laboratories to perform the MVSL, and possible alternative tests to the MVSL together with their costs and laboratory availability. The notice will also address EPA's intentions about any changes to the MVSL requirements in the various test rules and will provide an opportunity for public comment. If, after this exercise, EPA concludes that the MVSL is appropriate for TBP, EPA will include the MVSL requirements with any appropriate modifications in the final rule.

Should the gene mutation in somatic cells test prove negative, no further gene-mutation tests would be required. If the sex-linked recessive lethal test is negative, no further gene-mutation tests would be required of TBP.

If the results of the *in vitro* mammalian cytogenetics test are negative, an *in vivo* mammalian bone marrow cytogenetics, chromosomal analysis test would be required. Unless the results of this *in vivo* test are negative, a rodent dominant lethal test would be required. A positive result in this rodent dominant lethal test would trigger the requirement that a heritable translocation test be conducted. Should the *in vivo* mammalian cytogenetics test results prove negative, no further chromosomal effects testing would be required. If the dominant lethal test is negative, no further chromosomal effects testing would be required for TBP.

Under this proposed rule, if the result of the second-tier rodent dominant lethal test was positive, EPA would hold a public program review before industry would be required to initiate the third-tier heritable translocation test (see Unit IV.D.). The public would participate in this program review either by submitting written comments or commenting during a public meeting. Request for public comment or notification of a public meeting would be published in the

Federal Register. Should EPA determine, from the available weight of evidence, that proceeding to the heritable translocation test was no longer warranted, the Agency would propose to repeal this testing requirement and, after public comment, issue a final amendment to rescind this requirement. EPA would notify the test sponsors by certified letter or *Federal Register* notice, following the public program review of all the then existing data for TBP, if the heritable translocation test must be performed. EPA would also conduct internal program reviews of the reports of the gene mutations in somatic cells in culture assay, the *in vitro* mammalian bone marrow cytogenetics test, and the *in vivo* mammalian bone marrow cytogenetics test and other available mutagenicity data to evaluate whether the sex-linked recessive lethal and the rodent dominant lethal tests have been triggered.

For a more detailed discussion of mutagenicity tiered testing and public program review procedures, see EPA's final test rule for the C₂ aromatic hydrocarbon fraction published in the *Federal Register* of May 17, 1985 (50 FR 20662).

In order to assess the oncogenic effects of TBP, the Agency is proposing that testing be conducted according to the guidelines at 40 CFR 789.3300 in Sprague-Dawley rats and in mice via the oral route of administration and as modified in 40 CFR (c)(6).

To assess the dermal sensitization effects of TBP, the Agency is proposing that testing be conducted according to the guidelines at 40 CFR 798.4100.

For the Agency to extrapolate the oral route of administration of TBP in the tests described above and the dermal route, which is thought to be a primary route of human exposure, the Agency is proposing an oral/dermal pharmacokinetic test with TBP to examine absorption, distribution, metabolism, and excretion. The Agency is proposing that testing be conducted according to the guidelines being proposed under § 795.228. The decision to require most testing of TBP by the oral route is based on the results of

dermal irritation tests showing TBP effects to range from irritating to corrosive (Unit II.F.1.). Moreover, dermal application of the corrosive TBP could stress the test animals, which may distort test results. TBP is well tolerated by the oral route (Unit II.F.).

EPA is not proposing the renal effects test recommended by the ITC. Acute and subacute oral studies by Mitomo et al (Ref. 9) showed kidney tubule damage in rats and mice. However, two oral subchronic rat studies of 90 days and 126 days showed no kidney damage even at dosages higher than the Mitomo studies (Ref. 22 and 23). EPA believes that there are adequate data available to assess the effects of TBP on kidney tubules.

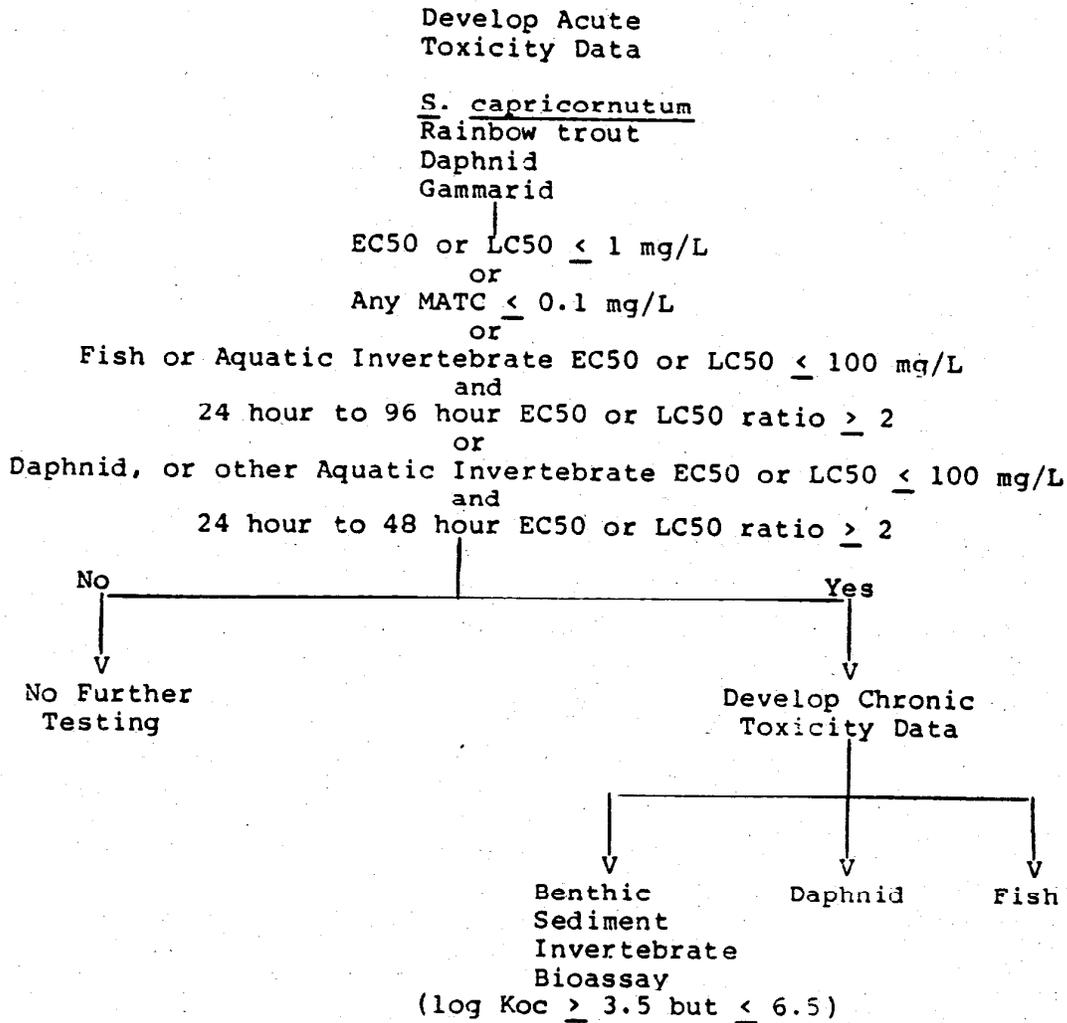
2. Environmental Effects

EPA is proposing environmental effects testing to determine the toxicity of TBP to an alga, a fish, aquatic invertebrates, and terrestrial plants: (1) *Selenastrum capricornutum*, in accordance with the test guidelines at 40 CFR 797.1050 as modified in proposed § 799.4360 (d)(1)(i)(B); (2) rainbow trout in accordance with the guidelines at 40 CFR 797.1400, as modified in proposed § 799.4360(d)(2)(B); (3) daphnids in accordance with the guidelines at 40 CFR 797.1300, and as modified in proposed § 799.4360(d) (3)(B); (4) gammarids in accordance with the guidelines at 40 CFR 797.1310, and as modified in proposed § 799.4360(d) (4)(B); and (5) plant uptake and translocation in accordance with the guidelines at 40 CFR 797.2850. Only one test species, rainbow trout, is proposed for the fish acute toxicity test because an acute test for the fathead minnow is available and adequate in combination with the testing required for the rainbow trout for purposes of assessing the acute toxicity of TBP to fish (see Unit II.G.). All the acute aquatic toxicity data from these tests will be used to determine whether chronic aquatic testing is necessary according to the testing scheme presented in the following figure:

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Figure--PROPOSED DECISION LOGIC FOR DEVELOPING ENVIRONMENTAL EFFECTS DATA



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EPA believes that for chemicals with substantial production and ubiquitous environmental distribution, reliable data should be developed to assess their toxicity and persistence. The Agency also believes that, for widely distributed chemicals such as TBP, hazard-based decision criteria should be applied to the data to determine the need to conduct further testing (see Figure). The Agency believes it is inappropriate to use integrated decision criteria (i.e., criteria based on predicted environmental concentrations) for these chemicals because where their occurrence appears to be widespread it may be very difficult to calculate reliable predicted environmental concentrations.

Therefore, EPA is proposing that if any of the results of acute aquatic toxicity tests satisfy the criteria specified in the Figure, the following chronic tests shall be conducted: (1) The invertebrate *Daphnia* life-cycle test in accordance with the guidelines at 40 CFR 797.1330, as modified in proposed § 799.4360(d)(5)(B); (2) early-life stage toxicity to fish using the fish with the lower LC50 value in accordance with the guidelines at 40 CFR 797.1600, as modified in proposed § 799.4360(d)(6)(B); and (3) a benthic sediment invertebrate bioassay with the midge, *Chironomus tentans* (if TBP's measured log Koc satisfies the log Koc criterion in the Figure), using three different TBP-containing clean, freshwater sediments having low, medium, and high organic carbon content, using the test method by Adams et al. (Ref. 31). This test is modified in proposed § 799.4360(d)(7)(B).

3. Chemical Fate

EPA is proposing measuring the vapor pressure of TBP at 25 °C in accordance with the test guidelines at 40 CFR 796.1950, measuring the sediment and soil adsorption isotherm and calculating log Koc in accordance with the test guidelines at 40 CFR 796.2750 (EPA will provide the soil (2) and sediments (2) samples), and measuring the hydrolysis rate in accordance with the test guidelines at 40 CFR 796.3500.

B. Test Substance

EPA is proposing that TBP of at least 99 percent purity be used as the test substance; TBP of this purity is commercially available. EPA has specified a relatively pure substance for testing because the Agency is interested

in evaluating the effects attributable to TBP itself.

C. Persons Required To Test

Section 4(b)(3)(B) specifies that the activities for which the EPA makes section 4(a) findings (manufacture, processing, distribution, use, and/or disposal) determine who bears the responsibility for testing. Manufacturers and persons who intend to manufacture the chemical are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. Both manufacturers and processors are required to test if the findings are based on distribution, use, or disposal.

Because EPA has found that there are insufficient data and experience to reasonably determine or predict the effects of the manufacture, processing, use, and disposal of TBP on human health and the environment, EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process TBP other than as an impurity, at any time from the effective date of the final test rule to the end of the reimbursement period, be subject to the testing requirements contained in this proposed rule. While EPA has not identified any manufacturers of TBP as a byproduct, such persons would be covered by requirements of this proposed test rule. The end of the reimbursement period will be 5 years after the last final report is submitted or an amount of time after the submission of the last final report required under the test rule equal to that which was required to develop data, if more than 5 years.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to a test rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement. EPA promulgated procedures for applying for TSCA section 4(c) exemptions in 40 CFR Part 790 which would apply to this test rule.

Manufacturers (including importers) subject to a final test rule are required to submit either a letter of intent to perform testing or an exemption application within 30 days after the effective date of the final test rule. The required procedures for submitting such letters and applications are described in 40 CFR Part 790.

Processors subject to a final rule, unless they are also manufacturers, are not to be required to submit letters of intent or exemption applications, or to conduct testing unless manufacturers fail to submit notices of intent to test or later fail to sponsor the required tests. The Agency expects that the manufacturers will pass an appropriate portion of the costs of testing to processors through the pricing of their products or reimbursement mechanisms. If manufacturers perform all the required tests, processors will be granted exemptions automatically. If manufacturers fail to submit notices of intent to test or fail to sponsor all the required tests, the Agency will publish a separate notice in the Federal Register to notify processors to respond; this procedure is described in 40 CFR Part 790.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for TBP. As noted in Unit IV.B, EPA is interested in evaluating the effects attributable to TBP itself and has specified a relatively pure substance for testing.

Manufacturers and processors subject to the final test rule would comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

D. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practice (GLP) standards which appear in 40 CFR Part 792.

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors would submit individual study plans at least 45 days prior to the initiation of each study.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. The Agency is proposing specific reporting requirements for each of the proposed test standards in the following Table 3:

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TABLE 3.—REPORTING REQUIREMENTS FOR TBP

Test	Reporting deadline for final report (months after the effective date of final rule, except as indicated ¹)	Number of interim (6-month) reports required
Functional observational battery (acute and subchronic) (§ 798.6050)	12	1
Motor activity (acute and subchronic) (§ 798.6200)	12	1
Neuropathology (§ 798.6400)	12	1
Developmental toxicity (§ 798.4900)	12	1
Reproduction and fertility (§ 798.4700)	24	3
Detection of gene mutation in somatic cells (§ 798.5300)	6	0
<i>In vitro</i> mammalian cytogenetics (§ 798.5375)	6	0
<i>In vivo</i> mammalian bone marrow cytogenetics (§ 798.5385)	14	0
Sex-linked recessive lethal in <i>Drosophila melaonogaster</i> (§ 798.5275)	18	1
Mouse visible specific locus test (§ 798.5200)	148	7
Rodent dominant lethal (§ 798.5450)	26	1
Rodent heritable translocation (§ 798.5460)	25	3
Oncogenicity (§ 798.3300)	53	8
Dermal sensitization (§ 798.4100)	6	0
Oral/Dermal Pharmacokinetics (§ 795.228)	12	1
Algal acute toxicity (§ 797.1050)	9	0
Fish acute toxicity (§ 797.1400)	9	0
Daphnid acute toxicity (§ 797.1300)	9	0
Gammarid acute toxicity (§ 797.1310)	9	0
Daphnid chronic toxicity (§ 797.1330)	21	1
Fish early life stage toxicity (§ 797.1600)	21	1
Benthic sediment invertebrate bioassay Adams et al. Ref. 31	21	1
Plant uptake and translocation (§ 797.2850)	12	1
Vapor pressure (§ 797.1950)	6	0
Sediment and soil adsorption isotherm (§ 796.2750)	9	0
Hydrolysis rate § 796.3500	6	0

¹ Reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following public program review of all of the then existing data for TBP, the Agency has determined that the required testing must be performed.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by the final rule, the Agency will publish a notice of receipt in the *Federal Register* as required by section 4(d).

Persons who export a chemical substance or mixture which is subject to a final section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) are in 40 CFR Part 707. In brief, as of the effective date of the final test rule, an exporter of TBP must report to EPA the first annual export or intended export of TBP to any one country. EPA will notify the foreign country concerning the test rule for this chemical.

V. Issues for Comment

This proposed rule specifies TSCA test guidelines and published methods as the test standards for health and environmental effects testing. EPA is

soliciting comments as to whether the health and environmental effects test standards are appropriate and applicable for the testing of TBP. Also regarding the testing of TBP, EPA requests comments on:

1. The reporting times for the identified health and ecological effects tests.
2. An appropriate vehicle for TBP in proposed tests which will not interfere with the test chemical or produce toxic effects.
3. The proposed route of administration. Although the major occupational exposure route for TBP is expected to be dermal, EPA is proposing the oral route for TBP health effects testing and a requirement for oral/dermal pharmacokinetics data. The principal reason for this is the irritating effect of TBP on the skin. Such irritation could complicate testing by the dermal route.
4. Appropriateness of production cost information.

5. Human exposure potential. The variety of uses of TBP, the large number of sites where it may be processed and used, and the documented releases to the environment from industrial sources suggest that there may be ample opportunities for worker exposure. However, EPA lacks specific use information about most TBP applications. Because these data gaps introduce considerable uncertainty into the picture of occupational exposure, EPA plans to analyze further the exposure basis for its findings for human health effects testing under sections 4(a)(1) (A) and (B) before promulgating a final rule. To assist in this, EPA is soliciting specific information on: (1) Concentrations of TBP in any TBP-containing products; (2) number of workers potentially exposed and frequency and duration of exposure, both site-specific and industry-wide; (3) measures taken to reduce or eliminate worker exposure to TBP, and whether such measures are recommended or required; (4) any other factors relating to

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worker exposure. EPA also requests information on the presence and concentrations of TBP in consumer products such as paints and coatings.

6. Testing the acute toxicity of chemicals to terrestrial invertebrates. The ITC recommended testing the acute toxicity of TBP to terrestrial invertebrates. Guidelines for developing such data are available, e.g., OECD test guidelines 207, "Earthworm, acute toxicity tests". EPA is soliciting public comments on terrestrial invertebrate toxicity testing including: (1) Data on the relative sensitivity of the earthworm compared to other terrestrial invertebrates, (2) recommendations for terrestrial invertebrate species that could be used to provide terrestrial toxicity data, and (3) guidance on interpretation of acute terrestrial toxicity data as part of an ecological hazard or risk assessment scheme for chemicals in the terrestrial environment.

7. Pharmacokinetic testing. Some pharmacokinetic data for TBP is available. EPA is soliciting public comment as to the usefulness of available data to offset the need for portions of the proposed oral/dermal pharmacokinetics test.

8. Dermal irritation by TBP. To what extent does the irritancy of TBP reduce or preclude the possibility of chronic exposure? Do firms that manufacture, process, and use TBP require workers to wear protective equipment? If so, what equipment is required?

VI. Economic Analysis of Proposed Rule

To assess the potential economic impact of this proposed rule, EPA has prepared an economic analysis that evaluates the potential for significant economic impacts on the industry as a result of the required testing. The economic analysis estimates the costs of conducting the required testing and evaluates the potential costs by examining four market characteristics of tributyl phosphate: (1) Price sensitivity of demand, (2) industry cost characteristics, (3) industry structure, and (4) market expectations. If these indications are negative, no further economic analysis is performed. However, if the first level of analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted which more precisely predicts the magnitude and distribution of the expected impact.

Total testing costs for the proposed testing of tributyl phosphate are estimated to range from \$1.3 to \$1.7 million. To predict the financial decision-making practices of manufacturing firms, these costs have

been annualized. Annualized costs are compared with annual revenue as an indication of potential impact. The annualized costs represent equivalent constant costs which would have to be recouped each year of the payback period to finance the testing expenditure in the first year.

The annualized test costs (using a cost of capital of 7 percent over a period of 15 years) range from \$140,400 to \$186,700. Based on 1986 production of 6 million pounds, the unit test costs range from \$0.02 to \$0.03 per pound. In relation to the selling price of \$1.60 per pound for tributyl phosphate, these costs are equivalent to 1.46 to 1.95 percent of price.

Though the annualized unit costs of the tests relative to the product price of tributyl phosphate appear to be high, EPA believes that the potential for adverse economic impact is low. This conclusion is based on the following observations:

—The demand for tributyl phosphate appears to be inelastic with respect to price in its largest use, primarily because of the current lack of viable substitutes.

—The market for tributyl phosphate appears to be stable.

Refer to the economic analysis which is contained in the public record for this rulemaking for a complete discussion of test cost estimation and potential for economic impact resulting from these costs.

VII. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analysis, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): (202) 554-1404, by December 28, 1987. A meeting will only be held if members of the public indicate that they wish to make an oral presentation. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, the Agency will transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will

become part of EPA's record for this rulemaking.

VIII. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonable foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing" (publication PB 82-140773) can be obtained through the National Technical Information Service, 5285 Port Royal Rd., Springfield, VA. In addition, EPA has recently conducted an analysis of the availability and capability of facilities to conduct neurotoxicity testing (Ref. 58). On the basis of these studies, EPA believes that there will be available test facilities and personnel to perform the testing that would be required under this proposed rule. EPA also believes that existing facilities could readily acquire the equipment and personnel needed to conduct the proposed neurotoxicity testing according to the TSCA GLP standards, given sufficient economic incentive.

IX. Rulemaking Record

EPA has established a record for this rulemaking (docket Number OPTS-42100). This record contains the basic information considered by the Agency in developing this proposal and appropriate Federal Register notices.

This record includes:

A. Supporting Documentation

(1) Federal Register notices pertaining to this rule consisting of: (a) Notice containing the ITC's intent to designate TBP to the Priority List (51 FR 18368; May 19, 1986), and designation of TBP (51 FR 41417; November 14, 1986).

(b) Rules requiring TSCA section 8(a) and 8(d) reporting on TBP (51 FR 18323; May 19, 1986).

(c) TSCA test guidelines cited as test standards for this rule.

(d) Notice containing revision of TSCA test guidelines cited as test standards for this rule.

(2) Economic Impact Analysis of Proposed Test Rule for Tributyl Phosphate.

(3) Communications before proposal consisting of: (a) Written public comments and letters.

(b) Contact reports of telephone conversations.

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- (c) Meeting summaries.
 (4) Reports—published and unpublished factual materials.
 (5) Chemical Testing Industry: Profile of Toxicological Testing, October 1, 1981.

B. References

- (1) U.S. Environmental Protection Agency. "Chemical hazard information profile draft report: tri(alkyl/alkoxy) phosphates. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (1985).
 (2) U.S. Environmental Protection Agency. "Production/exposure profile (PEP) on trialkyl/alkoxy phosphate esters." Washington, DC (1985).
 (3) National Institute for Occupational Safety and Health. "National occupational exposure survey (1981-1983)" (data base). Cincinnati, OH: Department of Health and Human Services, National Institute for Occupational Safety and Health. (1986).
 (4) Dunlap, W.J., Skew, D.C., Scaff, M.R., and Cooby, R.L. "Isolation and identification of organic contaminants in groundwater." In: "Identification and analysis of organic pollutants in water." Keith, L.H., ed. Ann Arbor, MI: Ann Arbor Science, pp. 453-477 (1986).
 (5) Hutchins, S.R., Tomson, M.B., and Ward, C.H. "Trace organic contamination of groundwater from a rapid infiltration site: a laboratory-based coordinated study." *Environmental Toxicology and Chemistry* 2:195-216 (1983).
 (6) Suffet, I.H., Brummer, L., and Redzail, J.V. "CG/MS identification of trace organic compounds in Philadelphia waters." In: "Identification and analysis." Keith, L.H., ed. Ann Arbor, MI, Ann Arbor Science, pp. 375-397 (1978).
 (7) CRCs, Inc. "Information review: tributyl phosphate IR-435." prepared under EPA contract No. 68-01-6690 for TSCA Interagency Testing Committee. (1985).
 (8) Saeger, V.W., Hicks, O., Kalley, R.G., Michael, P.R., Miteure, J.P., and Tucker, E.C. "Environmental fate of selected phosphate esters." *Environmental Science and Technology* 13:340-344 (1979).
 (9) Mitomo, T., Ito, T., Ueno, Y., and Terao, K. "Toxicological studies on tributyl phosphate." (1) "Acute and Subacute Toxicities." *Journal of Toxicological Services* 5:270-271 (1980).
 (10) Johansson, F.R., Wright, P.L., Gordon, D.E., Levinakas, G.J., Radue, R.W., and Graham, P.R. "Evaluation of delayed neurotoxicity and dose-response relationships of phosphate esters in the adult hen." *Toxicology and Applied Pharmacology* 41:291-304 (1977).
 (11) Eastman Kodak Company. TSCA 6(d) submission 062884(2). "Summary of tributyl phosphate testing for acute toxicity, skin irritation, eye irritation, and dermal sensitivity" (1988). Submitted to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC (1988).
 (12) Smyth, H.F. and Carpenter, C.P. "The place of the range finding test in the industrial toxicology laboratory." *Journal of Industrial Hygiene and Toxicology* 28:269-273 (1944).
 (13) Fassett, D.W. "Esters." In: "Industrial Hygiene and Toxicology". 2nd ed. Patsy, F.A., ed. New York John Wiley & Sons, Inc., pp. 1915-1916 (1963).
 (14) FMC Corporation. TSCA 6(d) submission 8686000116. "Acute toxicity screening tests Kronite® TBP: Tributyl phosphate" (1976). Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1986).
 (15) Rohm and Haas Company. FYL-OTS-0385-0380 FLWP, Seq. D. Material safety data sheet and toxicity summary on tributyl phosphate. Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 1985.
 (16) Heath, D.F. and Vandekar, M. "Anesthetic effect produced by organophosphorus compounds". *Nature* 179:154-155 (1957).
 (17) Laham, S., Szabo, J. and Long, G. "Effects of tri-n-butyl phosphate on the peripheral nervous system of the Sprague-Dawley rat." *Drug and Chemical Toxicology* 6:363-377 (1983).
 (18) Monsanto Company. TSCA Sec. (d) submission 86860000103. "Studies on the delayed neurotoxicity of tributyl phosphate." Washington, DC. Office of Toxic Substances, U.S. Environmental Protection Agency (1986).
 (19) Laham, S., Long, G., and Bronup, B. "Subacute oral toxicity of tri-n-butyl phosphate in Sprague-Dawley rat." *Journal of Applied Toxicology* 34:150-154 (1984).
 (20) U.S. Environmental Protection Agency. "Broad scan analysis of the FY 82 national human adipose tissue survey specimens, Vol. III—Semi-Volatile Organic Compounds." U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, Washington, DC, EP-560/5-88-037 (1986).
 (21) FMC Corporation. TSCA 6(d) submission 86860000112. "Kronite TBP (Tributyl phosphate) mutagenicity screening test *Salmonella* microassay (Ames Test)." Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1978).
 (22) Laham, S., Long, G., and Bronup, B. "Induction of urinary bladder hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate." *Archives of Environmental Health* 40:301-308 (1985).
 (23) FMC Corporation. TSCA 6(d) submission 8686000106. "Thirteen week feeding study of tributyl phosphate in rats." Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1986).
 (24) Monsanto Chemical Company. "Evaluation to determine potential hazards of dermal contact with SH-79-007, Skydro® 500B-4." Prepared by Product Investigations Inc., Conshohocken, Pennsylvania (1980). Submitted to U.S. Environmental Protection Agency by J.E. Downes, Monsanto Chemical Company (1987).
 (25) Gast, R. and Early, J. "Phytotoxicity of solvents and emulsifiers used in insecticide formulations." *Agricultural Chemicals* 11:42-45, 136-137 (1956).
 (26) Geiger, D.L., Poirier, S.H., Brooke, L.J., and Call, D.J., eds. "Acute Toxicities of organic chemicals in fathead minnow (*Pimephales promelas*)" Vol. III. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, pp. 277-288 (1976).
 (27) Roseberry, R.B. FMC Corporation, 17745 South Metcalf, Stillwell, KS, 666-85-9104. Summarized telephone conversation with R.B. Sanford, U.S. Environmental Protection Agency, Washington, DC. (May 13, 1987).
 (28) Downs, J.E., Monsanto Chemical Company, 660 N. Lindberg Boulevard, St. Louis, MO 63167. Summarized telephone conversation with R.B. Sanford, U.S. Environmental Protection Agency, Washington, DC. (June 22, 1987).
 (29) Sasaki, K., Suzuki, T., Takeda, M., and Uchiyama, M. "Bioconcentration and excretion of phosphoric acid triesters by killifish (*Oryzias latipes*)." *Bulletin of Environmental Contamination and Toxicology* 28:752-759 (1982).
 (30) Dave, G., Blanck, H., and Gustafsson, K. "Biological effects of solvent extraction chemicals on aquatic organisms." *Journal of Chemical Technology and Biotechnology* 28: 249-257 (1979).
 (31) Adams, W.J., Kimerle, R.A., and Mosher, R.G. "Aquatic Safety Assessment of Chemicals Sorbed to Sediments." *Aquatic Toxicology and Hazard Assessment Seventh Symposium, ASTM STP 854, American Society for Testing and Materials Philadelphia, PA.*, pp. 428-453 (1986).
 (32) Eastman Kodak Company. TSCA 6(d) submission 86860000119. "Sensitization of guinea pigs to tributyl phosphate by drop-on method (1986)." Submitted to Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1986).
 (33) Roseberry, R.B. FMC Corporation, 17745 South Metcalf, Stillwell, KS, 66685-9104. Summarized telephone conversation with R.B. Sanford, U.S. Environmental Protection Agency, Washington, DC. (June 25, 1987).
 (34) Littlefield, N.A., Grammen, D.L., Farmer, J.H., and Sheldon, W.G. "Effects of continuous and discontinuous exposure to 3-AAF on urinary bladder hyperplasia and neoplasia." In: "Innovations in cancer risk assessment (ED₀₁ study)". Staffa, J.A., and Mehlmann, M.A. eds. Pashatox Publishers, Inc. pp. 35-55 (1979).
 (35) Jones, A.R. "The metabolism of tri-alkyl phosphates." *Experientia* 28:492-493 (1970).
 (36) Marzuffi, F.N., Callahan, J.F., and Brown, D.W.C. "Chemical structure and skin penetrating capacity of a short series of organic phosphates and phosphoric acid." *Journal of Investigative Dermatology* 44:339-344 (1964).
 (37) Suzuki, T., Sasaki, K., Takeda, M., and Uchiyama, M. "Metabolism of tributyl phosphate in male rats." *Journal of Agricultural and Food Chemistry* 32:803-810 (1984).
 (38) Suzuki, T., Sasaki, K., Takeda, M., and Uchiyama, M. "Some S-containing metabolites of tributyl phosphate in the rat." *Journal of Agricultural and Food Chemistry* 32:1278-1283 (1984).
 (39) Sasaki, K., Suzuki, T., Takeda, M., and Uchiyama, M. "Metabolism of phosphoric acid triesters by rat liver homogenate."

123

Bulletin of Environmental Contamination and Toxicology 33:281-288 (1984).

(40) Williams, D.T., Nesman, E.R., LeBel, G.L., Benoit, F.M., Olson, R. and Lee, EGH. "Determination of mutagenic potential and organic contamination of Great Lakes drinking water." *Chemosphere* No.3 11:263-276 (1982).

(41) U.S. Environmental Protection Agency. "Alkyl/alkoxy phosphates in plant effluents." Ongoing study prepared for the Office of Water Regulations and Standards by U.S. Environmental Protection Agency Research Laboratory/ORD, Athens, GA (1987).

(42) Bureau of Labor Statistics, U.S. Department of Labor. "U.S. DOL 1986 Annual Survey." Washington, DC. (1987).

(43) Johnson, W., Presidential Airways, Inc., Dulles International Airport, Fairfax County, VA. Summarized telephone conversation with R.B. Sanford, U.S. Environmental Protection Agency, Washington, DC (February 4, 1987).

(44) Roseberry, R.B., FMC Corporation, 17745 South Metcalf, Stilwell, KS 66085-9104. Summarized telephone conversation with R.B. Sanford, U.S. Environmental Protection Agency, Washington, DC. (August 6, 1987).

(45) U.S. Environmental Protection Agency. Aggregated production volume for CASRN 126-73-8, 1985. U.S. Environmental Protection Agency, Confidential Data Branch, Office of Toxic Substances, Washington, DC. (1987).

(46) Hanna, P.J. and Dyer, K.F. "Mutagenicity of organophosphorous compounds in bacteria and *Drosophila*." *Mutation Research* 28:405-420 (1975).

(47) Hamburger, B. Letter to Harriet Corbett, U.S. Environmental Protection Agency, Washington, DC. (November 28, 1986).

(48) Analytical Bio Chemistry Laboratories, Inc. Acute toxicity of TBP (AB-78-7384337-1a) to *Daphnia magna*. P.O. Box 1097, Columbia, Missouri 65205 (1978).

(49) Analytical Bio Chemistry Laboratories, Inc. "Acute toxicity of TBP (AB-78-1384337-1c) to fathead minnows (*Pimphales promelas*)" (1978).

(50) Sasaki, K., Takeda, M., and Uchiyama, M. "Toxicity, absorption and elimination of phosphoric acid triesters by killifish and goldfish." *Toxicology* 27:775-782 (1981).

(51) Dave, G., and Lidman, U. "Biological and toxicological effects of solvent extraction chemicals. Range finding acute toxicity in the rainbow trout and in the rat." *Hydrometallurgy* 3:201-216 (1978).

(52) Analytical Bio Laboratories, Inc. "Acute toxicity of TBP (AB-78-1384337-1d) to rainbow trout (*Salmo gairdneri*)" (1978).

(53) National Institute for Occupational Safety and Health. "National occupational hazard survey (1972-1974)" (data base). Cincinnati, OH, Department of Health and Human Services, National Institute for Occupational Safety and Health (1978).

(54) Muir, D.C.A. Phosphate esters. In: "The handbook of environmental chemistry, Vol. 3 Part C." Hutzinger, O., ed. Springer-Verlag, New York (1984).

(55) FMC Corporation, TSCA 8(d) submission 86860000107. "Rabbit skin irritation", 181-508 TBP E1326-34 (1981). Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1986).

(56) Dave, G., Anderson, K., Berglund, R., and Hasselrot, B. "Toxicity of eight solvent extraction chemicals and of calcium to water fleas, *Daphnia magna*, rainbow trout, *Salmo gairdneri*, and zebrafish, *Brachydanio rerio*". *Comparative Biochemical Physiology*, 69:83-98 (1981).

(57) U.S. Environmental Protection Agency. "Frequency of organic compounds identified in water." USEPA Report Number EPA-600/4-78-062. NTIS PB-285 470. U.S. Environmental Protection Agency, Washington, DC (1978).

(58) U.S. Environmental Protection Agency. "Evaluation of TSCA guidelines for neurotoxicity testing." Office of Pesticides and Toxic Substances, Regulatory Impacts Branch, USEPA, Washington, D.C. (April 14, 1987).

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the OPTS Reading Room G-004, NE Mall, 401 M Street, SW., Washington, DC, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays. The Agency will supplement the record periodically with additional relevant information.

X. Other Regulatory Requirements

A. Classification of Rule

Under Executive Order 12291, EPA must judge whether a rule is "Major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that this proposed test rule would not be major because it would not meet any of the criteria set forth in section 1(b) of the Order, i.e., it would not have any annual effect on the economy of at least \$100 million, will not cause a major increase in prices, and will not have a significant adverse effect on competition or the ability of U.S. enterprise to compete with foreign enterprises.

This proposed rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, would not have a significant impact on a substantial number of small businesses because: (1) There are no known small manufacturers, (2) any small processors are not expected to perform testing themselves or to participate in the organization of the testing effort, (3) they will experience only very minor costs, if

any, in securing exemption from testing requirements, and (4) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The information collection requirements contained in this proposed rule have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and have been assigned OMB number 2070-0033. Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs, OMB, 726 Jackson Place NW., Washington, DC 20503, marked "Attention: Desk Officer for EPA." The final rule will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Parts 795 and 799

Chemicals, Environmental protection, Hazardous substances, Testing, Laboratories, Recordkeeping and reporting requirements, Incorporation by reference.

Dated: October 30, 1987.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that 40 CFR Chapter I be amended as follows:

PART 795—[AMENDED]

1. In Part 795:
a. The authority citation for Part 795 would continue to read as follows:

Authority: 15 U.S.C. 2603.

b. By adding § 795.228 to read as follows:

§ 795.228 Oral/dermal pharmacokinetics.

(a) *Purpose.* The purpose of these studies is to: (1) Ascertain whether the pharmacokinetics and metabolism of a chemical substance or mixture ("test substance") are similar after oral and dermal administration.

(2) Determine bioavailability of a test substance after oral and dermal administration.

(3) Examine the effects of repeated dosing on the pharmacokinetics and metabolism of test substance.

(b) *Definitions.* (1) "Bioavailability" refers to the rate and relative amount of administered test substance which reaches the systemic circulation.

(2) "Metabolism" means the study of the sum of the processes by which a particular substance is handled in the body and includes absorption, tissue

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distribution, biotransformation, and excretion.

(3) "Percent absorption" means 100 times the ratio between total excretion of radioactivity following oral or dermal administration and total excretion following intravenous administration of test substance.

(4) "Pharmacokinetics" means the study of the rates of metabolism, absorption, tissue distribution, biotransformation, and excretion.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species*. The rat shall be used for pharmacokinetics testing because it has been used extensively for metabolic and toxicological studies. For dermal bioavailability studies, the rat and the guinea pig shall be used.

(ii) *Test animals*. For pharmacokinetics testing and dermal studies, adult male and female Fischer 344 rats, 7 to 9 weeks of age, shall be used. For dermal studies, guinea pigs, 5 to 7 weeks old, shall also be used. The animals should be purchased from a reputable dealer and shall be identified upon arrival at the testing laboratory. The animals shall be selected at random for the test groups and any animal showing signs of ill health shall not be used. In all studies, unless otherwise specified, each test group shall contain at least 4 animals of each sex for a total of at least 8 animals.

(iii) *Animal care*. (A) The animals should be housed in environmentally controlled rooms with at least 10 air changes per hour. The rooms shall be maintained at a temperature of 24 ± 2 °C and humidity of 50 ± 10 percent with a 12-hour light/dark cycle per day. The animals shall be kept in a quarantine facility for at least 7 days prior to use and shall be acclimated to the experimental environment for a minimum of 48 hours prior to treatment.

(B) During the acclimatization period, the animals should be housed in suitable cages. All animals shall be provided with certified feed and tap water *ad libitum*. The guinea pig diet shall be supplemented with adequate amounts of ascorbic acid in the drinking water.

(2) *Administration of test substance*—

(i) *Test substance*. The use of radioactive test substance is required for all studies. Ideally, the purity of both radioactive and non-radioactive test substance should be greater than 99 percent. The radioactive and nonradioactive test substances shall be chromatographed separately and together to establish purity and identity. If the purity is less than 99 percent or if the chromatograms differ significantly, EPA should be consulted.

(ii) *Dosage and treatment*—(A) *Intravenous*. The low dose of test

substance, in an appropriate vehicle, shall be administered intravenously to four rats and four guinea pigs of each sex.

(B) *Oral*. Two doses of test substance shall be used in the oral study, a low dose and a high dose. The high dose should ideally induce some overt toxicity, such as weight loss. The low dose level should correspond to a no observed effect level. The oral dosing shall be accomplished by gavage or by administering the encapsulated test substance. If feasible, the same high and low doses should be used for oral and dermal studies.

(C) *Dermal*. (1) For dermal treatment, two doses, comparable to the low and high oral doses, shall be dissolved in a suitable vehicle and applied in volumes adequate to deliver the comparable doses. The backs of the animals should be lightly shaved with an electric clipper 24 hours before treatment. The test substance shall be applied to the intact shaven skin (approximately 2 cm² for rats, 5 cm² for guinea pigs). The dosed areas shall be protected with a suitable porous covering which is secured in place.

(2) *Washing efficiency study*. Before initiation of the dermal absorption studies, an initial washing efficiency experiment shall be conducted to assess the removal of the applied low dose of the test substance by washing the exposed skin area with soap and water and an appropriate organic solvent. The low dose shall be applied to 4 rats and 4 guinea pigs in accordance with paragraph (c)(2)(ii)(C)(1) of this section. After application (5 to 10 minutes), the treated areas of 2 rats and 2 guinea pigs shall be washed with soap and water and the treated areas of the remaining rats and guinea pigs shall be washed with an appropriate solvent. The amount of test substance recovered in the washings shall be determined to assess efficacy of its removal by washing.

(iii) *Dosing and sampling schedule*—

(A) *Rat studies*. After administration of the test substance, each rat shall be placed in a metabolic cage to facilitate collection of excreta. For the dermal studies, excreta from the rats shall also be collected during the 6 hour exposure periods. At the end of each collection period, the metabolic cages shall be cleaned to recover any excreta that might adhere to the cages. All studies, except the repeated dosing study, shall be terminated at 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(1) *Intravenous study*. Group A shall be dosed once intravenously at the low dose of test substance.

(2) *Oral Study*. (1) Group B shall be dosed once *per os* with the low dose of test substance.

(ii) Group C shall be dosed once *per os* with the high dose of test substance.

(3) *Dermal studies*. The test substance shall be applied and kept on the skin for a minimum of 6 hours, or as determined by the absorption properties of the substance. At the time of removal of the porous covering, the treated area shall be washed with an appropriate solvent to remove any test substance that may be on the skin surface. Both the covering and the washing shall be assayed to recover residual radioactivity. At the termination of the studies, each animal shall be sacrificed and the exposed skin area removed. An appropriate section of the skin shall be solubilized and assayed for radioactivity to ascertain if the skin acts as a reservoir for the test substance.

(i) Group D shall be dosed once dermally with the low dose of test compound.

(ii) Group E shall be dosed once dermally with the high dose of the test substance.

(4) *Repeated dosing study*. (1) Group F shall receive a series of single daily oral low doses of nonradioactive test substance over a period of at least 7 days. Twenty-four hours after the last nonradioactive dose, a single oral low dose of radioactive test substance shall be administered. Following dosing with the radioactive substance, the rats shall be placed in individual metabolic cages as described above. The study shall be terminated at 7 days after the last dose, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs.

(ii) *[Reserved]*

(5) *Intravenous study*. (1) Group G is to be dosed once intravenously at the low dose of the test substance.

(ii) *[Reserved]*

(B) *Guinea pig studies*—*Dermal studies*. Using four guinea pigs per group:

(1) Group H shall be dosed once dermally with the low dose of test substance.

(2) Group I shall be dosed once dermally with the high dose of the test substance.

(3) After administration of the test substance, each guinea pig shall be kept in a metabolic cage to facilitate collection of excreta. At the end of each collection period, the metabolic cages are to be cleaned to recover any excreta that might adhere to the cages. All studies shall be terminated at 7 days, or after at least 90 percent of the

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radioactivity has been recovered in the excreta (whichever occurs first).

(3) *Types of Studies*—(i) *Pharmacokinetics studies*—(A) *Rat studies*. Groups A through F shall be used to determine the kinetics of absorption of the test substance. In groups administered the test substance by intravenous or oral routes (i.e., Groups A, B, C, F), the concentration of radioactivity in blood and excreta shall be measured following administration. In groups administered the test substance by the dermal route (i.e., Groups D and E), the concentration of radioactivity in blood and excreta shall be measured at selected time intervals during and following the exposure period.

(B) *Guinea pig studies*. Groups G, H, and I shall be used to determine the extent of dermal absorption of the test substance. The amount of radioactivity in excreta shall be determined at selected time intervals.

(ii) *Metabolism studies: rat studies*. (A) Groups A through F shall be used to determine the metabolism of the test substance. Excreta (urine, feces, and expired air) shall be collected for identification and quantification of the test substance and metabolites.

(B) *Reserved*

(4) *Measurements*—(i)

Pharmacokinetics. Four animals from each group shall be used for these purposes.

(A) *Rat studies*—(1) *Bioavailability*. The levels of radioactivity shall be determined in whole blood, blood plasma or blood serum at 15 minutes, 30 minutes, 1 hour, 2 hours, 8 hours, 24 hours, 48 hours, and 96 hours after initiation of dosing.

(2) *Extent of absorption*. The total quantities of radioactivity shall be determined for excreta collected daily for 7 days.

(3) *Excretion*. The quantities of radioactivity eliminated in the urine, feces, and expired air shall be determined separately at appropriate time intervals. The collection of carbon dioxide may be discontinued when less than one percent of the dose is found to be exhaled as radioactive carbon dioxide in 24 hours.

(4) *Tissue distribution*. At the termination of each study, the quantities of radioactivity in blood and in various tissues, including bone, brain, fat, gonads, heart, kidney, liver, lungs, muscle, skin, and residual carcass of each animal shall be determined by assaying appropriate samples.

(5) *Changes in pharmacokinetics*. Results of pharmacokinetics measurements (i.e., biotransformation, extent of absorption, tissue distribution,

and excretion) obtained in rats receiving the single low oral dose of the test substance (Groups B and C) shall be compared to the corresponding results obtained in rats receiving repeated oral doses of the test substance (Group F).

(B) *Guinea pig studies: extent of absorption*. The total quantities of radioactivity shall be determined for excreta daily for 7 days or until at least 90 percent of the test substance has been excreted.

(ii) *Metabolism*. Four animals from each group shall be used for these purposes.

(A) *Rat studies*—(1) *Biotransformation*. Appropriate qualitative and quantitative methods shall be used to assay urine, feces, and expired air collected from rats. Efforts shall be made to identify any metabolite which comprises 5 percent or more of the dose excreted.

(2) *Changes in biotransformation*. Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of radioactive compounds in excreta from rats receiving a single oral dose (Groups B and C) with those in the excreta from rats receiving repeated oral doses (Group H).

(d) *Data and reporting*. The final test report shall include the following:

(1) *Presentation of results*. Numerical data shall be summarized in tabular form. Pharmacokinetics data shall also be presented in graphical form. Qualitative observations shall also be reported.

(2) *Evaluation of results*. All quantitative results shall be evaluated by an appropriate statistical method.

(3) *Reporting results*. In addition to the reporting requirements as specified in 40 CFR Part 792, the following specific information shall be reported:

(i) Species and strains of laboratory animals.

(ii) Chemical characterization of the test substance, including:

(A) For the radioactive compound, information on the site(s) and degree of radio labeling, including type of label, specific activity, chemical purity, and radiochemical purity.

(B) For the nonradioactive compound, information on chemical purity.

(C) Results of chromatography.

(iii) A full description of the sensitivity, precision, and accuracy of all procedures used to generate the data.

(iv) Percent of absorption of test substance after oral and dermal exposures to rats and dermal exposure to guinea pigs.

(v) Quantity and percent recovery of radioactivity in feces, urine, expired air, and blood. In dermal studies on rats and

guinea pigs, include recovery data for skin, skin washings, and residual radioactivity in the covering as well as results of the washing efficiency study.

(vi) *Tissue distribution* reported as quantity of radioactivity in blood and in various tissues, including bone, brain, fat, gonads, heart, kidney, liver, lung, muscle, skin and in residual carcass of rats.

(vii) *Biotransformation pathways* and quantities of test substance and metabolites in excreta collected after administering single high and low doses to rats.

(viii) *Biotransformation pathways* and quantities of the test substance and metabolites in excreta collected after administering repeated low doses to rats.

(ix) *Pharmacokinetic model(s)* developed from the experimental data.

PART 799—[AMENDED]

2. In Part 799:

a. The authority citation of Part 799 would continue to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. By adding § 799.4360 to read as follows:

§ 799.4360 Tributyl phosphate.

(a) *Identification of test substance*. (1) Tributyl phosphate (TBP, CAS No. 126-73-8) shall be tested in accordance with this section.

(2) TBP of at least 99 percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data*. All persons who manufacture or process, or intend to manufacture or process TBP, other than as an impurity, from the effective date of the final rule to the end of the reimbursement period shall submit letters of intent to conduct testing, submit study plans, conduct tests in accordance with Part 792 of this chapter, and submit data or submit exemption applications as specified in this section, Subpart A of this Part, and Part 790 of this chapter for single-phase rulemaking.

(c) *Health effects testing*—(1)

Acute toxicity—(i) *Required testing*.

(A) A functional observational battery shall be conducted with TBP in accordance with § 798.6050 of this chapter except for the provisions of Paragraphs (d)(1)(i), (5) and (6) of § 798.6050.

(2) For the purpose of this section as it relates to § 798.6050 of this chapter, the following provisions also apply:

(i) *Animal selection*. Testing shall be performed in laboratory rats.

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(ii) *Duration of testing.* For the acute testing, the substance shall be administered over a period not to exceed 24 hours; for the subchronic testing, test species shall be exposed daily for at least 90 days.

(iii) *Route of exposure.* Animals shall be exposed to TBP orally.

(B)(1) A motor activity test shall be conducted with TBP in accordance with § 798.6200 of this chapter except for the provisions of paragraphs (d)(1)(i) (5), and (6) of § 798.6200.

(2) For the purpose of this section as it relates to § 798.6200 of this chapter, the following provisions also apply:

(i) *Animal selection.* Testing shall be performed in laboratory rats.

(ii) *Duration of testing.* For the acute testing, the substance shall be administered over a period not to exceed 24 hours; for the subchronic testing, test species shall be exposed daily for at least 90 days.

(iii) *Route of administration.* Animals shall be exposed to TBP orally.

(C)(1) A neuropathology test shall be conducted with TBP in accordance with § 798.6400 of this chapter except for the provisions of paragraphs (d)(1)(i) (5), and (6) of § 798.6400.

(2) For the purpose of this section, as it relates to § 798.6400 of this chapter, the following provisions also apply:

(i) *Animal selection.* Testing shall be performed in laboratory rats.

(ii) *Duration of testing.* Animals shall be exposed for at least a 90-day period.

(iii) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) *Reporting requirements—(A)* The neurotoxicity tests required under paragraphs (c)(1)(i) (A), (B), and (C) of this section shall be completed and final reports submitted to EPA within 12 months of the effective date of the final rule.

(B) Interim progress reports for these neurotoxicity tests shall be submitted to EPA at 6-month intervals beginning 6 months after the effective date of the final rule, until the final reports are submitted to EPA.

(2) *Developmental toxicity—(i) Required testing.* (A) A developmental toxicity study shall be conducted with TBP in accordance with § 798.4900 of this chapter, except for the provisions of paragraph (e)(5) of § 798.4900.

(B) For the purpose of this section, as it relates to § 798.4900 of this chapter, the following provision also applies:

(1) *Route of administration.* The animals shall be exposed by gavage to TBP.

(2) [Reserved]

(ii) *Reporting requirements.* (A) The developmental toxicity study required under paragraph (c)(2) of this section

shall be completed and a final report submitted to EPA within 12 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final rule.

(3) *Reproduction and fertility—(i) Required testing.* (A) A reproduction and fertility study shall be conducted with TBP in accordance with § 798.4700 of this chapter, except for the provisions of paragraph (c)(5)(i)(A) of § 798.4700.

(B) For the purpose of this section as it relates to § 798.4700 of this chapter, the following provisions apply:

(1) *Route of administration.* Animals shall be exposed orally to TBP.

(2) [Reserved]

(ii) *Reporting requirements.* (A) The reproduction and fertility effects study required under paragraph (c)(3) of this section shall be completed and a final report submitted to EPA within 24 months of the effective date of the final rule.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals, beginning 6 months after the effective date of the final rule, until the final report is submitted to EPA.

(4) *Mutagenic effects—Gene Mutation—(i) Required testing.* (A) A detection of gene mutation in somatic cells in culture test shall be conducted with TBP in accordance with § 798.5300 of this chapter.

(B)(1) If TBP produces a positive result in the assay conducted pursuant to paragraph (c)(4)(i)(A) of this section, a sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with TBP in accordance with § 798.5275 of this chapter, except for the provisions of paragraph (d)(5)(iii) of § 798.5275.

(2) For the purpose of this section, as it relates to § 798.5275 of this chapter, the following provisions also apply:

(i) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) [Reserved]

(C) A mouse visible specific locus assay shall be conducted with TBP if the sex-linked recessive lethal test in *Drosophila melanogaster* conducted for TBP pursuant to § 798.527, and as modified in (c)(4)(i)(B) of this section, produces a positive result, and if, after a public program review, EPA issues a Federal Register notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated. This test shall be conducted in accordance with § 798.5200 of this chapter.

(ii) *Reporting requirements.* (A)(1) The somatic cells in culture assay shall be completed and the final report submitted

to EPA, within 6 months after the effective date of the final rule.

(2) If required, the *Drosophila* sex-linked recessive lethal assay shall be completed and the final report submitted to EPA within 18 months after the effective date of the final rule.

(3) The mouse visible specific locus assay shall be completed and the final report submitted to EPA within 48 months after the date of EPA's notification of the test sponsor under paragraph (c)(4)(i)(C) of this section that testing shall be initiated.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals beginning 6 months after initiation of the sex-linked recessive lethal test in *Drosophila* and the mouse visible specific locus assay respectively, if required, until the applicable final reports are submitted to EPA.

(5) *Mutagenic effects—Chromosomal aberration—(i) Required testing.* (A) An *in vitro* mammalian cytogenetics test shall be conducted with TBP in accordance with § 798.5375 of this chapter.

(B)(1) If TBP produces a negative result in the *in vitro* cytogenetics test conducted pursuant to paragraph (c)(5)(i)(A) of this section, an *in vivo* mammalian bone marrow cytogenetics test shall be conducted with TBP in accordance with § 798.5385 of this chapter, except for the provisions of paragraph (d)(5)(iii) of § 798.5385.

(2) For the purpose of this section, as it relates to § 798.5385 of this chapter, the following provisions also apply:

(i) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) [Reserved]

(C)(1) If TBP produces a positive result in either the *in vitro* or the *in vivo* cytogenetics test conducted pursuant to paragraphs (c)(5)(i)(A) and (B) of this section, a rodent dominant-lethal assay shall be conducted with TBP in accordance with § 798.5450 of this chapter, except for the provisions of paragraph (d)(5)(iii) of § 798.5450.

(2) For the purpose of this section as it relates to § 798.5450, the following provisions also apply:

(i) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) [Reserved]

(D)(1) A rodent heritable translocation assay shall be conducted with TBP if the dominant-lethal assay conducted for TBP pursuant to paragraph (c)(5)(i)(C) of this section produces a positive result, and if, after a public program review, EPA issues a Federal Register notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated. This test shall be conducted

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in accordance with § 798.5460 of this chapter except for the provisions of paragraph (d)(5)(iii) of § 798.5460.

(2) For the purpose of this section as it relates to § 798.5460 of this chapter, the following provision also applies:

(i) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) [Reserved]

(ii) *Reporting requirements.* (A)(1) The *in vitro* mammalian cytogenetics test shall be completed and the final report submitted to EPA within 6 months after the effective date of the final rule.

(2) If required, the *in vivo* mammalian bone-marrow cytogenetics test shall be completed and the final report submitted to EPA within 14 months after the effective date of the final rule.

(3) If required, the dominant lethal assay shall be completed and the final report submitted to EPA within 26 months after the effective date of the final rule.

(4) The heritable translocation assay shall be completed and the final report submitted to EPA within 25 months after the date of EPA's notification of the test sponsor under paragraph (c)(5)(i)(D) of this section that testing shall be initiated.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals beginning 6 months after initiation of the rodent dominant lethal assay and the rodent heritable translocation assay respectively, if required, until the applicable final reports are submitted to EPA.

(6) *Oncogenicity*—(i) *Required testing.* (A) An oncogenicity test shall be conducted with TBP in accordance with § 798.3300 of this chapter except for the provisions in paragraphs (b) (1)(i) and (6)(i) of § 798.3300.

(B) For the purpose of this section, as it relates to § 798.3300 of this chapter, the following provisions also apply:

(1) *Animal selection.* TBP shall be tested in Sprague-Dawley rats and in mice.

(2) *Route of administration.* Animals shall be exposed to TBP orally.

(ii) *Reporting requirements.* (A) The oncogenicity test required under paragraph (c)(6) of this section shall be completed and a final report submitted to EPA within 53 months of the effective date of the final rule.

(B) Interim progress reports shall be submitted to EPA at 6 month intervals beginning 6 months after the effective date of the final rule until the final report is submitted to EPA.

(7) *Dermal sensitization*—(i) *Required testing.* A dermal sensitization test shall be conducted with TBP in accordance with § 798.4100 of this chapter.

(ii) *Reporting requirements.* The dermal sensitization test shall be completed and the final report submitted to EPA within 6 months of the effective date of the final rule.

(8) *Oral/Dermal Pharmacokinetics*—(i) *Required testing.* A pharmacokinetics test shall be conducted with TBP in accordance with § 795.228 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetics test required in paragraph (c)(8) of this section shall be completed and the final report submitted to EPA within 12 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final rule.

(d) *Environmental effects testing*—(1) *Algal acute toxicity*—(i) *Required testing.* (A) Algal acute toxicity testing shall be conducted with TBP using *Selenastrum capricornutum* in accordance with § 797.1050 of this chapter except for the provisions in paragraphs (c)(6) (i)(A),(B), and (ii) of § 798.1050.

(B) For the purpose of this section as it relates to § 798.1050 of this chapter, the following provisions also apply:

(1) *Summary of the test.* The algal cells at the end of 24, 48, and 72 hours shall be enumerated.

(2) *Analytical measurements—chemical.* The final separation of the algal cells from the test solution shall be done using an ultrafiltration (e.g., 0.45 micrometer pore size) technique.

(3) *Analytical measurements—chemical.* The total and dissolved (e.g., filtered) concentrations of the test substance shall be measured in each test chamber and the delivery chamber before the test and in each test chamber at 0 to 96 hours to ascertain whether it is in solution.

(ii) *Reporting requirements.* The algal acute toxicity test required in paragraph (d)(1) of this section shall be completed and the final report submitted to EPA within 9 months of the effective date of the final rule.

(2) *Fish acute toxicity*—(i) *Required testing.* (A) Fish acute toxicity testing shall be conducted with TBP using *Salmo gairdneri* (rainbow trout) in accordance with § 797.1400 of this chapter.

(B) For the purpose of this section, as it relates to § 798.1400 of this chapter, the following provisions also apply:

(1) *Chemical measured.* The total and dissolved (e.g., filtered) concentrations of the test substance shall be measured in each test chamber and the delivery chamber before the test and in each test chamber at 0, 48, and 96 hours to ascertain whether it is in solution.

(2) *Test procedures.* The test shall be performed under flowthrough conditions.

(ii) *Reporting requirements.* The fish acute toxicity test shall be completed and the final report submitted to EPA within 9 months of the effective date of the final rule.

(3) *Daphnid acute toxicity*—(i) *Required testing.* (A) Daphnid acute toxicity testing shall be conducted with TBP using *Daphnia magna* or *D. pulex* in accordance with § 797.1300 of this chapter.

(B) For the purpose of this section, as it relates to § 798.1300 of this chapter, the following provisions also apply:

(1) *Chemical measured.* The total and dissolved (e.g., filtered) concentrations of the test substance shall be measured in each test chamber and the delivery chamber before the test and in each test chamber at 0, 24, and 48 hours.

(2) *Test procedures.* The test shall be performed under flowthrough conditions.

(ii) *Reporting requirements.* The daphnid acute toxicity test shall be completed and the final report submitted to EPA within 9 months of the effective date of the final rule.

(4) *Gammarus acute toxicity*—(i) *Required testing.* (A) *Gammarus* acute toxicity testing shall be conducted with TBP using *G. lacustris*, *G. fasciatus*, or *G. pseudolimnaeus* in accordance with § 797.1310 of this chapter.

(B) For the purpose of this section, as it relates to § 798.1310 of this chapter, the following provisions also apply:

(1) *Chemical measured.* The total and dissolved (e.g., filtered) concentrations of the test substance shall be measured in each test chamber and the delivery chamber before the test and in each test chamber at 0, 24, and 48 hours to ascertain whether it is in solution.

(2) *Test procedures.* The test shall be performed under flowthrough conditions.

(ii) *Reporting requirements.* The *Gammarus* acute toxicity test shall be completed and the final report submitted to EPA within 9 months of the effective date of the final test rule.

(5) *Daphnid chronic toxicity*—(i) *Required testing.* (A) Daphnid chronic toxicity testing shall be conducted with TBP using *Daphnia magna* or *D. pulex* in accordance with § 797.1330 of this chapter, if the algal EC50, the EC50 or LC50 for rainbow trout or daphnid, or the gammarid 48-hour EC50 determined in accordance with paragraphs (d) (1), (2), (3), and (4) of this section satisfy the following criteria: Any such value is ≤ 1 mg/L or any fish or aquatic invertebrate EC50 or LC50 ≤ 100 mg/L and 24 hour to

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96 hour EC50 or LC50 ratio >2 or daphnid or other aquatic invertebrate EC50 or LC50 <100 mg/L and 24-hour to 48-hour EC50 or LC50 ratio >2 .

(B) For the purpose of this section, as it relates to § 797.1330 of this chapter, the following provisions also apply:

(1) *Chemical measured.* The total and dissolved (e.g., filtered) concentrations of the test substance shall be measured in each test chamber and the delivery chamber before the test and in each test chamber at 0, 7, 14, and 21 days to ascertain whether it is in solution.

(2) *Test procedures.* The test shall be performed under flowthrough conditions.

(ii) *Reporting requirements.* (A) The daphnid chronic toxicity test, if required, shall be completed and the final report submitted to EPA within 21 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA 6 months after the initiation of the test.

(6) *Fish early-life stage toxicity—(i) Required testing.* A fish early-life stage toxicity test shall be conducted with TBP in accordance with § 797.1600 of this chapter, using the fish with the lower LC50 value [either the rainbow trout (*Salmo gairdneri*) or the fathead minnow (*Pimephales promelas*)], if the algal EC50, the rainbow trout EC50 or LC50 or the gammarid or daphnid 48-hour EC50 or LC50 determined in accordance with paragraphs (d) (1), (2), (3), and (4) of this section satisfy the following criteria: Any such value is <1 mg/L, or any fish or aquatic invertebrate EC50 or LC50 <100 mg/L and the 24-hour to 96-hour EC50 ratio >2 , or daphnid or other aquatic invertebrate EC50 or LC50 <100 mg/L and 24 hr/48 hr EC50 or LC50 ratio >2 .

(ii) *Reporting requirements.* (A) The fish early-life stage toxicity test shall be completed and the final report submitted to EPA within 21 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA 6 months after the initiation of the test.

(7) *Benthic sediment invertebrate bioassay—(i) Required testing.* (A) A benthic sediment invertebrate bioassay shall be conducted on TBP with the midge (*Chironomus tentans*) if chronic toxicity testing is required pursuant to paragraph (d)(5) of this section and if the log Koc calculation obtained by measuring the sediment and soil adsorption isotherms determined under paragraph (e)(2) of this section is greater than or equal to 3.5 but less than or equal to 6.5. The total aqueous sediment concentrations and interstitial water concentrations of the test substance shall be measured in each test chamber

at 0, 4, 7, 10, and 14 days. The aqueous concentrations of the test substance in the delivery chamber shall be measured at 0, 4, 7, 10, and 14 days. TBP-spiked clean freshwater sediments containing low, medium, and high organic carbon content shall be used. The benthic sediment invertebrate bioassay shall be conducted according to the test procedure specified in the American Society for Testing and Materials, Special Technical Publication 854 (ASTM STP 854) entitled, "Aquatic Safety Assessment of Chemicals Sorbed to Sediments," by W.J. Adams, R.A. Kimerle, and R.G. Masher, published in *Aquatic Toxicology and Hazard Assessment: Seventh Symposium*, ASTM STP 854, pp. 429-453, R.D. Caldwell, R. Purdy, and R.C. Bahner, Eds., 1985, which will be incorporated by reference. (This published procedure will be available for inspection at the Office of the Federal Register, Room 9401, 1100 L St. NW., and in the EPA OPTS Reading Room, Rm. G004 NE Mall, 401 M St., SW., Washington, DC if EPA issues the final rule.) Copies of the incorporated material may be obtained from the Document Control Officer (TS-793), Office of Toxic Substances, EPA, NE-C004, 401 M St., SW., Washington, DC 20460, and from the American Society for Testing and Materials (ASTM), 1916 Race Street, Philadelphia, PA 19103.

(B) [Reserved]

(ii) *Reporting requirements.* (A) The benthic sediment invertebrate bioassay, if required, shall be completed and the final report submitted to EPA within 21 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA for the benthic sediment invertebrate bioassay 6 months after the initiation of the test.

(8) *Plant uptake and translocation—(i) Required testing.* Plant uptake and translocation testing shall be conducted with TBP in accordance with § 797.2850 of this chapter.

(ii) *Reporting requirements.* (A) The plant uptake and translocation test shall be completed and final results submitted to EPA within 12 months of the effective date of the final rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final rule.

(e) *Chemical fate testing—(1) Vapor pressure—(i) Required testing.* Vapor pressure testing shall be conducted with TBP in accordance with § 796.1950 of this chapter.

(ii) *Reporting requirements.* The vapor pressure test required in paragraph (e)(1) of this section shall be completed and the final report submitted to EPA

within 6 months of the effective date of the final rule.

(2) *Sediment and soil adsorption isotherm—(i) Required testing.* Sediment and soil adsorption isotherm testing shall be conducted with TBP in accordance with § 796.2750 of this chapter (EPA will provide the soil (2) and sediments (2) samples).

(ii) *Reporting requirements.* (A) The sediment and soil adsorption isotherm test required under paragraph (e)(2) of this section shall be completed and the final report submitted to EPA within 6 months of the effective date of the final rule.

(B) For the purpose of this section, as it relates to § 796.2750 of this chapter, the following provisions also apply:

(1) A Koc value shall be calculated for each test sediment using the equation $Koc = K / (\text{percent of organic carbon in test sediment})$.

(2) [Reserved]

(3) *Hydrolysis as a function of pH at 25 °C—(i) Required testing.* Hydrolysis testing shall be completed with TBP in accordance with § 796.3500 of this chapter.

(ii) *Reporting requirements.* The hydrolysis test required under paragraph (c)(3) of this section shall be completed and the final report submitted to EPA within 6 months of the effective date of the final rule.

(f) *Effective date.* The effective date of the final rule is [44 days after publication of the final rule in the Federal Register.]

(Information collection requirements have been approved by the Office of Management and Budget under Control Number 2070-0033.)

[FR Doc. 87-25973 Filed 11-10-87; 8:45 am]

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