

ENVIRONMENTAL PROTECTION AGENCY

48 CFR Ch. I

[OFTS 47003: FRL 1495-8a]

Acrylamide: Response to the Interagency Testing Committee

AGENCY: Environmental Protection Agency (EPA)

ACTION: Notice and requests for comments.

SUMMARY: Section 4(e) of the Toxic Substances Control Act (TSCA) established an Interagency Testing Committee (ITC) to recommend to the Administrator of the Environmental Protection Agency (EPA) a list of chemical substances and mixtures to be considered for testing. In a first revision that was transmitted to EPA on April 10, 1978 (43 FR 16684), the ITC added eight chemical substances and mixtures, including acrylamide, to its original list (42 FR 55028) published on October 12, 1977. This action prompted EPA to review and evaluate available data on the health effects of acrylamide, particularly its neurotoxicity. In view of evidence that the induction of neurotoxicity (central-peripheral axonopathies) is a consistent effect of the exposure of humans and several animal species to acrylamide, the Agency is not proposing a Section 4(a) rule to require further effects testing of acrylamide. The EPA is seeking public comment on this matter.

DATES: Written comments must be submitted on or before October 31, 1980. EPA will hold a public meeting for this rule on September 24, 1980, in Washington, D.C. The exact time and place will be announced in a future Federal Register notice. For further information on arranging to speak at the September general meeting or arranging a special meeting, see the public meeting section under "Supplementary Information."

ADDRESS: Written views and comments should bear the document control number 80T-127, and should be submitted to: Document Control Officer, Chemical Information Division, (TS-793), Room 447, Office of Pesticides and Toxic Substances, Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460.

A Support Document, which presents the scientific and regulatory rationale for the Agency's decision concerning the health effects of acrylamide, is available to the public from the Industry Assistance Office, Office of Pesticides

and Toxic Substances (TS-799), Environmental Protection Agency, 401 M St. SW, Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Jr., Director, Industry Assistance Office, Office of Pesticides and Toxic Substances (TS-799), U.S. Environmental Protection Agency, 401 M Street SW, Washington, DC 20460, Toll-free: 800-424-9065; In Washington, DC, please call 554-1404.

SUPPLEMENTARY INFORMATION:

I. Background

Section 4(e) of TSCA [Sec. 4(a); 90 Stat. 2003; (15 U.S.C. 2601 et seq.)] established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for the promulgation of testing rules under Section 4(a) of the Act. The ITC may designate up to 50 of its recommendations at any one time for priority consideration by EPA. TSCA requires EPA to respond to such designations within 12 months of the date they are made, either by initiating rulemaking under Section 4(a) or publishing in the Federal Register reasons for not initiating rulemaking.

The ITC designated acrylamide for testing in April 1978 (43 FR 16684), recommending that it be tested for carcinogenic, mutagenic, teratogenic and environmental effects and that an epidemiologic study be performed. The recommendations were based on (1) the possible entry of this highly water-soluble compound into surface water and groundwater as a result of its wide use as a chemical grout and that of its polymers in municipal and industrial wastewater treatment, paper strengthening and retention, and various other applications; (2) the severe neurotoxicity of acrylamide, which raises the possibility that other serious effects might result from long-term, low-level exposure; and (3) the potential exposure of about 20,000 workers to acrylamide during its manufacture, processing, use, and disposal and the potential widespread exposure of the general population via release of the compound to the environment.

In a notice published in the Federal Register on May 14, 1979 (44 FR 28095), EPA responded to the ITC recommendations explaining its reasons for not initiating rulemaking proceedings on acrylamide within 12 months of its designation by the ITC. The Agency stated that it had not yet fully evaluated the ITC recommendations or proposed test standards that would need to be included in any test rule and indicated that it would either propose testing subsequently or publish its decision not

to require testing. Since that time, a federal court ruled that EPA's response was legally inadequate. *Natural Resources Defense Council v. Costle*, 79 Civ. 2411 (S.D.N.Y., February 4, 1980). Hence, this notice of EPA's tentative decision is intended to serve as EPA's response under Section 4(e) of TSCA to the ITC designation of acrylamide for health effects testing. EPA is not publishing a final decision at this time because it believes public comment on the policy underlying its decision would be useful.

II. Assessment of Acrylamide's Toxicity

EPA has completed its review of the health effects of acrylamide, basing its evaluation on the following, publicly available material: (1) the ITC dossier and its references, (2) studies and reports identified by an EPA supplementary literature search, (3) public comments submitted in response to publication of the notice in the Federal Register on April 10, 1978 (43 FR 16684) which was a revision of ITC's original list, (4) materials supplied by acrylamide manufacturers, and (5) a contract report prepared for the Agency by the Midwest Research Institute (MRI).

The MRI Report (Conway et al. 1979) evaluated studies related to mutagenicity, teratogenicity, carcinogenicity, as well as neurotoxicity and other health effects. EPA, having reviewed MRI's work and a report by Shiraishi (1978) discussing chromosomal aberrations from acrylamide exposure, has focused its more detailed evaluation upon the relatively well-characterized neurotoxic properties of this compound in reaching its tentative decision discussed below.

It has been found that acrylamide is neurotoxic, producing peripheral axonopathies (Spencer and Schaumburg 1976). The animal species in which this effect was demonstrated include rats (Edwards 1975, Fullerton and Barnes 1966, Hashimoto and Aldridge 1970, Suzuki and Pfaff 1973), mice (Bradley and Asbury 1970), cats (McCollister et al. 1964, Kuperman 1958, Leswing and Ribelin 1969, Schaumburg et al. 1974), dogs (Hamblin 1956, Thomann et al. 1974), baboons (Hopkins 1970), and monkeys (McCollister et al. 1964). In addition, there are at least 48 published cases of the occupational toxicity and 5 cases of the nonoccupational toxicity of acrylamide to humans (NIOSH 1976, U.S. EPA 1976, Conway et al. 1979), many of whom manifested a measurable degree of neurotoxicity (central-peripheral axonopathy).

In humans, the predominant signs of neurotoxicity are related to peripheral

nerve involvement and, to a lesser extent, central nervous system involvement. A variety of other signs and symptoms also are generally reported, the most common ones occurring in the skin, hands, and feet. The onset of effects is delayed following initial exposure, and the effects may be reversible, although this is not always the case.

Based on laboratory data, EPA has concluded that acrylamide is a potent neurotoxicant at very low levels. This conclusion has been substantiated by a 1-year (oral administration) study in cats indicating a no-effect level of 0.3-1.0 mg/kg/day.

III. Tentative Decision Not To Require Testing

EPA does not plan to require the health effects testing recommended by the ITC. Instead, EPA plans to evaluate acrylamide for possible regulatory controls.

As previously stated, acrylamide causes significant neurological effects at very low levels. Thus, it is likely that any control adopted on the basis of acrylamide's neurotoxicity will provide a considerable degree of protection from other potential health hazards. Under such circumstances, the Agency does not believe it is in the public interest to perform a complete assessment of nonneurological effects. Rather, EPA believes that its rulemaking activities should be devoted to more pressing testing needs concerning chemicals about which much less is known. Thus, EPA has not conducted an in-depth evaluation of other health effects and does not plan to require testing for them.

EPA recognizes that in rejecting the alternative to require testing for effects which are not fully characterized, it is leaving gaps in the toxicity data base the Agency is trying to create. As a result, EPA may in some cases fail to reduce the risk of a health hazard to the extent it could if the effect were fully characterized.

This is particularly true where the oncogenicity risk has not been evaluated. However, as discussed below, Dow Chemical Company plans to conduct oncogenicity testing. Thus, EPA believes that, as a matter of priorities and resource allocations, the Agency should not develop a test rule for acrylamide to resolve remaining issues about its toxicity but instead should seek data on chemicals for which the need for data is greater.

EPA will reevaluate this decision if Dow fails to recommence the anticipated testing. Dow had started a 2-year chronic toxicity oncogenicity study using CDF Fischer 344 rats in June 1979.

Doses of 0.01-2 mg/kg/day were administered orally. Because of unexpected difficulties in maintaining the proper dose levels, however, Dow terminated the study as of February 1980. EPA understands that Dow will resume the testing shortly. Although the proposed Dow study does not fully satisfy EPA's test standards for these studies, i.e., one rodent species will be used, EPA anticipates that it will provide useful information concerning toxic effects other than neurotoxicity.

The Agency also is aware that a functional neurologic study in primates is under way at the University of Rochester sponsored by Dow Chemical Company and other chemical manufacturers. This study may provide information that will allow the "no-effect level" for the general population to be determined more precisely.

For these various reasons, EPA believes that additional testing resources should not be expended at this time to evaluate the health effects of acrylamide. EPA will initiate a preregulatory assessment of acrylamide based upon existing toxicity data.

EPA solicits comments on its proposed rationale, as applied to acrylamide specifically and as a precedent for the future. In particular, EPA wishes comments on its plan to limit its own assessment of a chemical's overall toxicity and to refrain from requiring testing where (1) one effect is already well established, and (2) possible control measures are likely to reduce significantly the risk from other effects.

IV. Environmental Effects

The environmental effects of acrylamide have not been evaluated completely. Its high water solubility, known toxicity to mammals, and possible slow degradation rate under certain environmental conditions (e.g., low temperatures or low oxygen levels) indicate that the compound may pose a hazard upon its release to the environment. If, after a complete analysis of available data, the Agency feels that there is insufficient information regarding the chemical fate or ecotoxicological effects of acrylamide to make an adequate hazard evaluation, it will then propose additional testing of acrylamide under Section 4(a). A separate Support Document addressing the environmental release and effects of acrylamide is forthcoming.

V. Public Meetings

EPA will hold a general public meeting on September 24, 1980, in Washington, D.C. to provide the public an opportunity to present comments and

questions on the notice as required by Section 4(b)(5) to EPA officials who are directly responsible for developing the rule and supporting analyses. The public meeting will start with a short summary by EPA of the proposed rules and will be followed by oral presentations from the floor. A time limit of 15 minutes per person, company, or organization may be imposed depending upon the number of requests. EPA will allot speaking times in advance of the meeting on a first-come basis, although the Agency reserves the right to alter the order depending upon the nature of the particular comments and other relevant factors. For the benefit of all concerned, EPA encourages the elimination of redundant comments. If time permits, following these prepared presentations, EPA will receive any other comments from the floor. Presenters are invited, but not required, to submit copies of their statements on the day of the meeting. All such written materials will become a part of EPA's record for this rulemaking. In addition, the Agency will transcribe each meeting and will include the written transcripts in the public record. The exact location and time of this meeting will be announced later in the Federal Register and the press.

In addition to the general public meeting, EPA personnel responsible for developing these proposals will be available at EPA's discretion to meet in public sessions at EPA in Washington, D.C., during the 105 day comment period, with interested persons from individual companies, trade associations, organized labor and citizen organizations to discuss these proposals. EPA encourages using special request meetings for discussing technical data and implementation issues. However, persons should plan to present their views at the general meeting to ensure their opportunity for comment since special meetings will be held only when EPA believes that the subject is more appropriately discussed in a special format than in a general meeting. EPA will provide facilities and make other necessary arrangements for such meetings. The Agency will make transcripts or summaries of the meetings for inclusion in the official public record. While these meetings will be open to the public, active participation will be limited to those requesting the session and designated EPA participants.

Persons who wish to present comments at the September 24, 1980 general meeting should contact EPA no later than September 12, 1980 by calling toll-free 800-424-9065 (in Washington, D.C. call 554-1404), or by writing to the address listed at the beginning of this

notice under "For Further Information Contact". Persons wishing to arrange a special meeting should follow the same procedure.

VI. Public Record

EPA has established a public record for this rulemaking (docket number 80T-127) which is available for inspection in the OPTS Reading Room from 9:00 a.m. to 5:00 p.m. on working days (447 East Tower, 401 M Street, S.W., Washington, D.C. 20460). This record includes basic information considered by the Agency in developing this proposal. The Agency will supplement the record with additional information as it is received. The record includes the following information.

1. Federal Register notices pertaining to this rule

- a. Proposed Notice, Acrylamide: Response to the Interagency Testing Committee (ITC).
- b. Notice of the ITC's designation of Acrylamide to the Priority List.
- c. Notice containing EPA's response to the ITC designation of Acrylamide to the Priority List.
- d. Notice of rule proposed under Section 8(d) requiring submission of health and safety information.
- e. Notice of rule proposed under Section 8(a) of TSCA requiring submission of production and exposure-related data.
- f. Cross reference to docket 80T-126.

2. Support Documents. a. Acrylamide Support Document.

3. Drafts released to public before proposal.

4. Minutes of informal public participation meetings (See this section of docket number 80T-126).

5. Communications.

a. Written: Public and Intraagency or Interagency Memorandum and Comments.

b. Telephone conversations.

c. Meetings.

8. Reports—Published and Unpublished Materials.

a. Health effects and exposure references.

b. Articles reviewed but not referenced.

VII. Related Actions

EPA is proposing the first health effects test rules under Section 4(a) of TSCA in a separate notice in today's Federal Register.

Dated: July 1, 1980.

Douglas M. Costle,
Administrator.

[FR Doc. 80-21563 Filed 7-17-80; 8:45 am]

SELLING CODE 6560-01-M

40 CFR PART 770

[OPTS 47001:FR 1495-8b]

Exemptions From Test Rules; Proposed Statement of Policy and Procedures

AGENCY: Environmental Protection Agency.

ACTION: Proposed rule.

SUMMARY: EPA is proposing policies and procedures by which manufacturers and processors subject to testing required under Section 4(a) of the Toxic Substances Control Act may apply for exemptions from testing. These exemption policies and procedures are being proposed to prevent duplicative testing under the test rules issued by EPA under Section 4 of TSCA.

DATES: Written comments must be submitted on or before October 31, 1980. EPA will hold a public meeting for this rule on September 24, 1980 in Washington, D.C. The exact time and place will be announced in a future Federal Register notice. For further information on arranging to speak at the September general meeting or arranging a special meeting see the public meeting section under Supplementary Information.

ADDRESS: Written views and comments should bear the document control number 80T-125, and should be submitted to: Document Control Officer, Chemical Information Division (TS-793), Room 447, Office of Pesticides and Toxic Substances, Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Director, Industry Assistance Office, Office of Pesticides and Toxic Substances, Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460, Toll Free 800-424-9065, Washington, DC 554-1404.

SUPPLEMENTARY INFORMATION:

Introduction

This notice proposes the general framework, policies, and procedures for consideration of all applications for exemptions from the test rules issued by the Environmental Protection Agency (EPA) under Section 4(a) of the Toxic Substances Control Act (TSCA, Pub. L. 94-469, 90 Stat. 2003; 15 U.S.C. 2601 *et seq.*). This statement of exemption policy and procedures is proposed to be generally applicable unless notice is given to the contrary in specific test rules.

Section 4 of TSCA authorizes the Administrator of EPA to require manufacturers (including importers) and/or processors of chemical

substances and mixtures to test the chemicals in accordance with applicable EPA test rules to generate data from which the effects on health and the environment of the manufacture, distribution in commerce, processing, use, or disposal of such chemicals can be determined. Section 4(a)(1)(A) requires EPA to issue test rules upon the finding that any of these activities may present an unreasonable risk of injury to health or the environment, that there are insufficient data to reasonably determine or predict the impact of the activities on health or the environment, and that testing is necessary to generate the needed data. Section 4(a)(1)(B) imposes the same conditions except that the requirement may be based on a finding that the substance or mixture is or will be manufactured in substantial quantities, and the probability of significant or substantial human exposure or entry into the environment in substantial quantities, as opposed to being based on a finding of potential unreasonable risk.

In recognition of the costs of such testing, the Congress sought to reduce unnecessarily duplicative testing by providing that any person subject to a test rule may apply to the Administrator for an exemption from the rule (Section 4(c)(1)). The exemption must be granted if the Administrator determines that the chemical substance or mixture manufactured or processed by the applicant is equivalent to a chemical substance or mixture for which test data have been submitted or are being developed and that submission by the applicant of Section 4 test data on such substance or mixture would be duplicative (Section 4(c)(2)). To provide for equitable sharing of the cost of developing the Section 4 test data, Congress required that persons who are granted an exemption must reimburse those persons who developed or are developing test data and those who helped or are helping finance the testing (Sections 4(c)(3) and 4(c)(4)). The Act also provides that two or more persons may designate one of themselves or a qualified third party to conduct testing and submit data on their behalf (Section 4(b)(3)(A)).

A manufacturer or processor of chemicals may choose to satisfy its obligation to comply with a test rule in one of three ways: (1) test the chemical itself or contract to have it tested, (2) jointly sponsor tests of the chemical, or (3) obtain an exemption from testing from EPA and reimburse the sponsors of the test. Firms may be expected to make different choices among these options

depending upon individual circumstances.

Individual testing, whether performed by the sponsor or by a third party under contract to the sponsor, may be attractive for large firms when timeliness is particularly important or when a firm desires to maintain its relationship to a particular chemical confidential. Occasionally, individual testing may also be appropriate if a particular manufacturer's or processor's product is uniquely different from the products of other firms manufacturing or processing the chemical. Individual testing may carry with it greater financial risks and costs than the other options. It will not generally be clear when a firm begins testing what portion of the testing costs will ultimately be reimbursed. Even if the amount of reimbursement is satisfactory, the sponsoring firm may need to tie up its funds until reimbursement is made—a period that may span several years.

Joint sponsorship of testing offers numerous advantages over the first option. Firms can work out the cost-sharing formula in advance of any commitment of funds so that each can estimate in advance what the testing will cost it. Such firms do not have to submit individual exemption applications under Section 4(c); however EPA must follow the same criteria in approving joint sponsorship arrangements under Section 4(b)(3)(A). Joint sponsorship also avoids having one firm tie up large amounts of its funds in testing costs until reimbursement is made. Flexible arrangements can be worked out with respect to early data acquisition and study direction so that all participants have a voice in how the study is conducted. Also, the cost of compliance for the participating firms can be reduced because only one firm needs to have extensive contact with EPA.

Finally, exemptions complement the other alternatives in that a manufacturer or processor who does not wish to "go it alone" but is not part of a joint testing program potentially can obtain an exemption from testing and reimburse the sponsor of the tests. Reimbursements can be negotiated privately between the parties in the same manner as joint-testing agreements, or they may be the result of the application of EPA rules providing for fair and equitable reimbursement. See EPA's Advance Notice of Proposed Rulemaking concerning testing reimbursement published in the Federal Register of September 19, 1979 (44 FR 54284). However, in contrast to joint sponsorship arrangements, a person

with an exemption generally has no voice in how a study is conducted.

Because TSCA provides that all persons who are granted an exemption must reimburse the sponsors of the tests (on which the exemption is based) and all persons who may have contributed to the costs of that testing, exemption policy will have a significant impact on reimbursement policy. In general, EPA will attempt to reduce the number of complex reimbursement cases under TSCA that are referred to the Agency for decision by adopting exemption policies that encourage joint sponsorship of testing. Examples include making information on planned testing available through the Industry Assistance Office and granting manufacturers an opportunity to withdraw exemption requests in order to participate in joint testing.

EPA has attempted to formulate exemption policies and procedures that will not unduly burden either industry or EPA. Although EPA will not actively match exemption applicants with test sponsors or actively play a role in joint test group formation, EPA will encourage joint test group formation by making available data, within the limits prescribed by 40 CFR Part 2 and Section 14 of TSCA pertaining to disclosure, concerning who is planning to test and who has submitted test data. Joint testing is a resource efficient means of complying with Section 4 test rules.

EPA is proposing this exemption policy not just to relieve the industry of the costs of duplicative testing, however. It will also serve to help maximize the efficient utilization of the nation's limited toxicological testing resources. If all manufacturers and processors of a chemical were individually to test their products in response to a Section 4 test rule, test facilities could rapidly become saturated with testing programs that would produce redundant information. The result would be that EPA would be delayed in requiring testing of other chemicals meeting the criteria of Section 4(a) and industry would be delayed in performing necessary testing of other products. This situation clearly would be detrimental to the environment and the public health of the American people and be contrary to the intention of Section 4 to test those substances and mixtures that may present an unreasonable risk or which result in substantial or significant exposure.

Finally, in the course of commenting on the Advance Notice of Proposed Rulemaking (ANPR) on Reimbursement, which was published in the Federal Register on September 19, 1979 (44 FR 54284), the Chemical Manufacturers Association (CMA) commented

extensively on exemptions. EPA has not had the opportunity to analyze CMA's comments before developing this proposal but will carefully review them prior to preparation of the final exemption policy notice. As appropriate, EPA will solicit further comment or hold meetings on anticipated changes to this notice and proposed rule. CMA's comments have been included as part of the public record of this rulemaking.

Requirements for an Exemption

Section 4(c) of TSCA, which is the statutory basis for granting an exemption, states:

If, upon receipt of an application [for an exemption] the Administrator determines that—

(A) the chemical substance or mixture with respect to which such application was submitted is equivalent to a chemical substance on mixture for which data has been submitted to the Administrator in accordance with a rule under subsection (a) [of TSCA] or for which data is being developed pursuant to such a rule, and

(B) submission of data by the applicant on such substance or mixture would be duplicative of data which has been submitted to the Administrator in accordance with such rule or which is being developed pursuant to such rule, the Administrator shall exempt, in accordance with [the reimbursement provisions in] paragraph (3) or (4), the applicant from conducting tests and submitting data on such substance or mixture under the rule with respect to which such application was submitted." [Section 4(c)(2) Pub. L. 94-469, 90 Stat. 2008, 15 U.S.C. 2603(c)(2).]

TSCA defines a *chemical substance* as any organic or inorganic substance of a particular molecular identity including—(i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (ii) any element or uncombined radical. [Section 3(2) Pub. L. 94-469, 90 Stat. 2004, 15 U.S.C. 2602 (2)].

The act excludes from the definition of substance mixtures (as defined by TSCA), tobacco and tobacco products (but not derivative products), nuclear materials and byproducts, firearms and ammunition, and pesticides, food, food additives, drugs, cosmetics or devices, when manufactured, processed or distributed in commerce as a pesticide, food, etc.

A *mixture* is defined by the Act as any combination of two or more chemical substances if the combination does not occur in nature and is not, in whole or in part, the result of a chemical reaction; except that such term does include any combination which occurs, in whole or in part, as a result of a chemical reaction if none of the chemical substances comprising the combination is a

new chemical substance and if the combination could have been manufactured for commercial purposes without a chemical reaction at the time the chemical substances comprising the combination were combined. [Section 3(8) Pub. L. 94-469, 90 Stat. 2004, 15 U.S.C. 2602 (8).]

Because these definitions differ somewhat from common usage, it is worthwhile to offer a few clarifying comments. First, TSCA's definition of mixture is a great deal more restrictive than the chemist's definition. TSCA defines mixtures to mean only formulary mixtures, that is, a combination of substances created by the deliberate mixing of two or more substances, or a combination of substances that could be produced commercially by mixing two or more substances. Such mixtures are distinguished by TSCA from other materials because they are not subject to the manufacturing and processing notices for new chemical substances under Section 5 of the Act and because special findings are required before testing of them may be required under Section 4(a) or before they can be subject to rules under Section 8(a). Second, all materials that are not mixtures or are not excluded by Section 3(2)(B) of TSCA are "substances". A substance may be a single pure compound, a single compound plus its impurities, or a combination of substances with their impurities. Thus, for example, under normal circumstances a combination of several isomers formed from the reaction of two pure chemical compounds is classed according to TSCA as a chemical substance, as would be the isomers which make it up.

Equivalence

The term "equivalence" is not defined by TSCA, although its legislative history gives some insight as to what Congress intended in using this term.

In making this determination [of equivalence] the conferees expect the Administrator to look at any contaminants in the chemical substance or mixture for which an exemption is being sought and ascertain whether any contaminants present might cause differences in test data which would be significant and which would, therefore, cause the Administrator to determine that the chemical substances or mixtures in that instance were not equivalent. [H.R. No. 94-1679 94th Cong., 2d Sess., 9/23/76, pp 1, Legis. Hist. 674.]

A contaminant may be an additive (discussed below) or an "impurity", which is defined in the chemical inventory regulations as "a chemical substance which is unintentionally present with another chemical substance" [40 CFR 710.2(m)]. This is the same definition as will be used under

Section 4. There are many sources of impurities including:

- (1) Unreacted starting material,
- (2) A contaminant in the starting material which persists in or gives rise to by-products in the reaction product,
- (3) A contaminant in/on the reaction vessel or other equipment,
- (4) By-products formed from the starting material or intermediate by competing reactions,
- (5) Chemical substances formed during storage, and
- (6) Chemical substances formed by reaction with environmental factors (air, water, sunlight).

Additives are substances that are intentionally added to a chemical substance to improve its stability or impart some other desirable quality. A substance becomes a mixture when it is combined with an additive so long as no chemical reaction takes place. Mixtures, including commercial chemicals which contain additives, are discussed later in this notice.

Substances. Chemical substances are marketed in a variety of grades differing chiefly by the number and amount of contaminants which range from highly pure grades such as spectral or reagent grades to one or more technical grades. In determining what chemical form to prescribe for testing, EPA will employ a case-by-case determination. EPA wishes chemicals to be tested that are representative of a broad range of products which contain the chemicals and their exposure situations. To test separately the thousands of individual products containing a commercial chemical would be prohibitively costly, time consuming, and unnecessary. Depending upon such considerations as the number, nature, and variability of the components in a technical grade chemical, the nature of the test, and what is known about the toxicity of each component, EPA may require testing of either: (1) one or more technical grade chemicals, (2) a purified grade, or (3) a technical or purified grade and one or more impurities or additives.

EPA is proposing that, unless there is evidence to the contrary, the Agency will consider one test substance to be representative of all forms of the substance subject to the test rule. In such cases the issue of equivalency as it relates to exemptions would be essentially moot. This is because the test substance and all other forms of the chemical are by definition considered to be equivalent. Thus in this case, there is no reason for an exemption applicant (hereinafter "applicant") to demonstrate the equivalence of its technical grade chemical and the test substance.

However, if the Agency requires testing of a technical grade substance and has information leading to (1) specific concerns about the effects of impurities or additives (such concern may be due to the toxicity of impurities or suspected synergism, additive effects, etc.) and (2) that the impurities or additives may differ significantly from one grade of a chemical to another, EPA is proposing to require applicants to demonstrate to EPA that their technical grade chemicals are equivalent to the test substance. EPA is interpreting "equivalence" in the sense that one or more test substances are considered representative of, or a proxy for, another in the series of required tests. EPA is proposing that claims of equivalence be substantiated by chemical analysis data, manufacturing or processing data, or biological test data, as appropriate, and that the burden of demonstrating equivalence rest on the applicant. EPA will determine in each test rule under 40 CFR 773 whether special concerns regarding impurities exist and whether applicants must submit equivalence data. EPA's proposed policy regarding the application process, denial of an exemption, reapplication and appeal are discussed in a subsequent section of this notice.

A manufacturer or processor could respond to a determination that its substance is not equivalent to the test substance by either testing its substance in full compliance with the section 4 test rule or by changing the manufacturing process, supplier of starting materials, etc. so as to eliminate the differences between its substance and the material tested.

Mixtures. Numerous product formulations exist which are mixtures of substances. Pure or technical grade chemicals that are stabilized by additives are mixtures under TSCA. In mixtures, the component which may pose an unreasonable risk of injury to health or the environment may be the most abundant component, or it may be present in small quantities.

In order to require testing of a mixture rather than its components, EPA must make the finding under Section 4(a)(2) of TSCA that the environmental and health effects resulting from the manufacture, use, etc. of the mixture "may not be reasonably and more efficiently be determined or predicted by testing the chemical substances which comprise the mixture." Thus, depending upon individual circumstances and the finding made by EPA, EPA may evaluate a mixture by requiring testing of (1) one or more pure substances comprising the mixture, (2) one or more technical grade

substances comprising the mixture, or (3) the mixture itself.

EPA is proposing that the principles established in the previous section for substances apply to the components of mixtures. Thus, if no special determination regarding impurities is made by EPA, there would be no issue of equivalency for exemption for processors or formulators of product mixtures. If such a determination is made, then an applicant would be required to show that the technical grade chemicals or the mixtures tested are equivalent to the technical grade chemicals comprising the applicant's product or the applicant's mixture, respectively. As was proposed for substances, EPA proposes to make determinations of equivalence on the basis of chemical or biological data submitted by the applicants.

Categories. Section 26(c) of TSCA states that "Any action authorized or required to be taken by the Administrator under any provision of this Act with respect to a chemical substance or mixture may be taken by the Administrator in accordance with that provision with respect to a category of chemical substances or mixtures."

EPA may issue a test rule covering a category of substances or mixtures when it believes that a number of chemicals share some significant common characteristics such as similar chemical and biological behavior and the Section 4(a) statutory criteria (See the preamble of the test rule published in today's Federal Register). Categories may be closed (containing a finite number of specified chemicals) or open (containing a potentially infinite number of chemicals) and may contain both new and existing chemicals.

The following discussion pertains to structure-based categories. Exemption policies for other types of categories will be proposed in a future rulemaking. As explained in the preamble to today's test rule, EPA is proposing to generally require testing of only a portion of the members of a structure-based category due to the expense of testing and the limited number of test facilities and personnel compared with the number of chemicals that need characterization. Therefore, EPA generally intends to select some chemicals from such a category for initial testing based on exposure and structure or structure/activity considerations.

EPA recognizes that test rules for categories of chemicals raise a number of complex issues. For this reason, EPA is proposing one approach and describing several alternatives for exemptions and reimbursements for structure-based categories to obtain a

wide range of comments on these issues. EPA may adopt any of the three approaches or variation thereof in the final rule. These three approaches by no means exhaust the possibilities, but illustrate fairly distinct options among a spectrum of alternatives.

The "whole category" approach which is being proposed for the chlorinated benzenes emphasizes the characterization of the category. In this approach manufacturers and processors of members of the category would not be responsible for testing the individual compounds which they manufacture or process but would be jointly responsible instead for testing a sample which EPA has selected as representative of the category. To illustrate this concept, if there were a category of seven compounds (1, 2, 3, 4, 5, 6, 7) which EPA believes could be adequately characterized by testing only four of the seven compounds, EPA would require that all manufacturers and processors of the seven chemicals bear equal responsibility for testing compounds 1, 3, 5, and 7. The Section 4(a) statutory finding would be made for the entire category.

Equivalence of the sample and other category members would be assumed by EPA in proposing such a test rule. This equivalence would not be on a one-to-one basis as it is for individual chemicals, such as where the manufacturers of chemical 1 assert equivalency based on the data developed on chemical 2. Rather, the sample as a whole would be considered representative of the category on the hypothesis that test results on the sample can be used to evaluate the chemicals which comprise the category. Equivalency may not exist between individual members of the category but the sample would be expected to provide sufficient data to evaluate the category as a whole.

This "whole category" approach to testing does not discriminate between manufacturers and processors whose chemicals are tested and those whose chemicals are not. Unlike Alternative 1 discussed below, the responsibility for actually funding testing falls equally on both during the course of the testing. Industry could respond to such a test rule by dividing the testing among themselves. Each firm would then apply for an exemption for those portions of the testing which it did not perform and reimburse the sponsors of such tests. A second and probably preferable response would be to form a consortium for joint sponsorship of testing.

This proposed approach is perhaps the best alternative when the hypothesis that the category can be characterized

by the sample holds. However, if this hypothesis does not hold, this approach may present considerable administrative difficulties. If chemicals 1, 3, 5, and 7 do not give results that could be extrapolated to chemicals 2, 4, and 6, manufacturers and processors of chemicals 2, 4, and 6 most likely would be reluctant to share the cost of testing chemicals 1, 3, 5, and 7. However, to permit or require a refund to manufacturers and processors of 2, 4, and 6, EPA would have to require manufacturers and processors of 1, 3, 5, and 7 to reimburse the manufacturers and processors of 2, 4, and 6 for the money they already received. As a consequence, the costs to manufacturers and processors of 1, 3, 5 and 7 would be higher than they had originally anticipated.

EPA would also have to decide whether to require testing of any or all untested category members. If the category no longer held together from the standpoint of health or environmental effects, EPA most likely would amend the rule to treat category members as individual chemicals for purposes of both existing and new testing requirements under Section 4(a), exemptions, and reimbursement.

An alternative approach (Alternative 1) would require testing of all-category members but would specify that such testing be done in two or more stages with the chemicals selected for the sample designated for testing in the first stage. In this alternative, each manufacturer or processor of a chemical in the sample is responsible for testing his own chemical. The Section 4(a) findings would again be made for the entire category. And, as in the proposed approach, the criteria for sampling would be based primarily on the potential that the designated chemicals would be structurally representative of the whole category. The category members not in the sample would be tested in the subsequent stages if the test results from the first stage could not be used to characterize the remaining category members. EPA would write the test rule in such a way that the requirement to conduct the second stage of testing would take effect automatically a specified number of months after the date from the first group were received. At that point, manufacturers and processors of the untested members of the category would obtain exemptions and reimburse those who conducted the first round of tests, or, if the data could not be extrapolated to the untested members, conduct their own testing.

To illustrate, if there were seven members in the category, and the first sample consisted of chemicals 1, 3, 5 and 7, producers of chemical 1 would pay for the testing of chemical 1, procedures of chemical 3 for 3 and so forth. If the data from those tests were then used as a basis for granting exemptions to chemicals 2, 4, and 6, producers of 1, 3, 5 and 7 would be partially reimbursed for their costs at that time. Reimbursement would be based on sharing of all costs among the manufacturers and processors of all chemicals.

This approach simplifies the reimbursement process by avoiding the redistribution of funds that would be provided for in the proposed approach if the category were not characterized by the test sample. However, there are disadvantages to this approach as well. First, this approach does not accurately express EPA's intentions with respect to testing categories in a majority of circumstances. EPA does not generally intend to test all members of a category, even when the category is not characterized by the test sample, because EPA believes the public is better served by testing a wider range of chemicals than exhaustively characterizing a number of closely related substances. Second, this approach is inapplicable to large or open-ended categories. EPA could not actually require for testing of all members in such categories due to the immense resources required. (Open categories are potentially infinite in size even though the number of known category members is finite.) Finally, the simpler reimbursement that this option offers results in a disadvantage to those manufacturers and processors who are required to test in the first stage because they receive no reimbursement from the other manufacturers and processors in the category until the end of testing. On the other hand, persons sponsoring the initial testing do not have an automatic entitlement to reimbursement; they are responsible for testing their own chemicals and receive reimbursement from producers of chemicals 2, 4, and 6, only if the data described from the first stage prove to be relevant to 2, 4, and 6.

A variant that would avoid the latter problem would be to require testing of chemicals 1 through 7 in a single stage, with each manufacturer or processor responsible for testing his own chemical, but to grant conditional exemptions to producers of chemicals 2, 4, and 6 that could be revoked if the data from 1, 3, 5, and 7 could not be extrapolated to 2, 4, and 6. Persons would be required to provide reimbursement on the basis of

the conditional exemption. However, if the data from 1, 3, 5, and 7 could not be used to characterize 2, 4, and 6, this variant would entail the same administrative problems concerning reallocation of money as the approach EPA is proposing.

Alternative 2 to testing categories lies at the other end of the spectrum from the proposed approach. In this approach the chemicals may be analyzed as a category for determining potential hazard or risk, but are tested as individual chemicals. The Section 4(a)(1)(A) findings are made only for the chemicals to be tested.

Using this approach, if EPA believed that laboratory or economic resources should not be expended on testing the whole category, EPA would again choose a smaller number of chemicals to be tested. However, the emphasis in choosing them would be on those likely to pose the greatest risk, and not on the chemicals that were most likely to provide data representative of the category. Primary emphasis would be given to testing the chemicals suspected of the highest toxicity or produced in the greatest quantities or resulting in the most exposure. However, consideration of structural representation of the category may influence the sample, particularly if there were a choice between testing two of the most high-exposure (risk) chemicals and one was considered to be more representative of the category.

If chemicals 1, 3, 5, and 7 were the ones selected for testing, only manufacturers and processors of those chemicals would be subjected to the rule and required to test. Manufacturers and processors of 1 would share the cost of testing only 1. While persons producing chemicals 2, 4, and 6 would not be required to test or reimburse producers of chemicals 1, 3, 5, and 7; this would be chosen for testing primarily or solely on their own merit, and not as a representative sample of 1, 2, 3, 4, 5, 6, and 7. While the data produced from chemicals 1, 3, 5, and 7 may be relevant to evaluating 2, 4, and 6 and would be evaluated in that light as well, the operating presumption would be that 1, 3, 5, and 7 would be tested as individuals, and that any additional benefit to be gained from them as "representatives" would be useful but not central to their selection for testing.

As advantage of this approach is its administrative simplicity. Further, it would assure that those chemicals which warrant the most concern are tested. A disadvantage is that less information may be gained about the category as a whole because of the deemphasis on choosing a sample that

would be "representative." The emphasis on testing individuals would likely make it harder to have an effective link between section 4 and the premanufacturing notification requirements of section 5 of TSCA, although EPA could pursue such options as defining criteria specifying when other existing or new chemicals in the chemical group would be tested.

In conclusion, there are clearly many factors that will bear upon the selection of the final approach. Among the most important considerations will be the following: (1) how the section 4 findings, the category definition, and the choice of test substance interact, (2) how to maximize the amount of information obtained for the lowest cost, (3) concern for financial equity: who pays for the testing and at what point in time, (4) how to minimize the administrative problems of reallocating money, and whether the rule will need to be amended if exemptions are revoked or if money is to be reallocated, and (5) the degree to which a sample may be representative of the category.

Certain provisions could be implemented with any approach to address potential inequities or other problems. For instance, a provision could be attached to the proposed option to limit a manufacturer's or a processor's testing costs so that he would pay no more than the amount that would be paid if testing were required on an individual chemical basis. This could be addressed in the reimbursement rule.

EPA is requesting comments on each of these alternatives.

Duplicative data

The other finding that EPA must make to grant an exemption is that submission of data by the applicant would be duplicative of data which have been submitted or which are being developed.

From a technical standpoint this is a complex issue. The results of toxicological testing are sensitive to a large number of variables besides the precise chemical species. Such variables include the dose and route of its administration, and the species, strain, age, sex and state of health of the animals. Although the EPA test standards and good laboratory practice standards attempt to minimize the variance due to the above factors, significant test variance may still remain.

EPA believes that one properly designed and executed study will normally provide a sufficient basis for making regulatory decisions. Thus, EPA is proposing that as long as the test substances are equivalent, EPA will

consider all tests meeting its standards to be duplicative of each other. This is not to say that all tests designed to meet the standards will be the same, or that the data produced would be identical—that would be highly unlikely. Rather, additional tests would be duplicative in the sense that there would be duplicative compliance with the test rule. However, if a test does not appear to be in compliance with the test rule and standard, EPA may be unable to conclude that further testing would be duplicative.

The Exemption Process

Study Plans

An exemption can be granted either on the basis of data previously submitted to EPA or on the basis of knowledge that test data are being developed. Exemptions based on prospective data may be terminated if satisfactory data are not developed. [Section 4(c)(4)(B), 15 U.S.C. 2603(c)(4)(B)]. To permit the granting of exemptions prospectively, EPA is requiring the submission of Study Plans from test sponsors so that it can have some assurance that testing is being initiated and will be likely to conform to required standards or procedures. (See Section III.F. of preamble to test rule for further discussion of this point.) In addition, the study plan requirement will give other persons subject to the rule the knowledge that another firm is sponsoring tests and information of the test methodology. Through the Industry Assistance Office, EPA plans to make study plans available to the public within the limits prescribed by Section 14 of TSCA pertaining to disclosure of confidential data in order to assist other members of the industry in applying for exemptions or in forming joint testing groups.

EPA has already proposed study plan requirements in certain of the proposed long-term health effects test standards (chronic, oncogenic, reproductive effects). Persons planning to test a chemical substance or mixture for those effects would be required to submit a Study Plan 90 days before starting the tests (44 FR 27338, 27347, May 9, 1979; 44 FR 44090, July 28, 1979). EPA did not propose study plan requirements for the other health effects in the belief that there was less utility to advance review of study plans for short-term test. However, EPA now believes that exemption needs make it necessary to require study plans for all effects; but, unlike the requirements for chronic and reproductive effects to submit a study plan 90 days before the initiation of testing, study plans for all other health

effects covered in the July, 1979 proposal may be submitted when testing actually begins.

EPA has also concluded that the study plans need to contain additional information to meet EPA's needs in the exemption area. As proposed previously, the study plan would include the identity of sponsors, the study protocol, rationale for species and strain selection, data on the sponsors manufactured substance (if applicable), dose selection, route of exposure, data on the test substance, schedule for testing and reporting data, and other related information (44 FR 27349, May 9, 1979). EPA now proposes to add the following requirements:

(1) identification of the test rule, (2) in the case of joint sponsorship, the identity of the principal sponsor and other sponsors, (3) where applicable, a description of the culture medium and its source, and (4) for test rules which require submission of equivalence data for exemptions, (a) an attestation that the substance manufactured or processed is equivalent to the test substance and (b) information on the process by which the test substance was manufactured. The identification of the test rule by name and CFR citation is being added to aid EPA and exemption applicants in relating the Study Plan to the test rule requirements. For enforcement and reimbursement purposes EPA needs to know who is sponsoring a test or participating in a joint sponsorship arrangement. EPA will ordinarily limit its contacts to the principal sponsor. The third item being required, a description of the culture medium, is an amendment to the required test protocol information. The selection of the culture medium is an important experimental detail governing whether the tissues or organisms will grow. Furthermore, information on the components of the tissue culture may permit EPA scientists to make some judgements and provide advice on the potential for interaction between media constituents and the test substance. The attestation of equivalency is being proposed as a means of assuring EPA that joint sponsors assure that the chemical that is selected for testing is representative of the chemicals which they actually produce or process. EPA is requiring information on the process by which the test substance was manufactured for use as an additional criterion in making equivalence determinations.

The full study plan, as modified today, will appear in § 770.2, § 772.113-1(f), § 772.100-2(b)(2), and § 772.112-21 to § 772.119-1 of the final health effects

standards. This discussion and the section on reporting in the preamble to the proposed test rule are intended to provide notice and opportunity for comment on this proposed change.

Applications for Exemptions

EPA plans to require every person seeking an exemption to file an application which cites or provides documentation concerning the study plan on which it bases its exemption application and, where required, explains why the applicant believes its product is equivalent to the test substance. In all such cases the burden will be on the applicant to present a justification for granting the exemption.

The specific information that must be included in the application is as follows:

(a) The test rule and specific testing requirement(s) from which an exemption is sought.

(b) Name, address, and telephone number of applicant.

(c) Name, address, and telephone number of appropriate individual to contact for further information.

(d) The citation or documentation of the study plan, study or studies upon which an exemption may be based.

(e) The following information, if equivalence is required to be shown:

(1) The chemical identity of the test substance or mixture on which this application is based. The chemical identity should include all available characteristics and properties of the test substance or mixture such as the boiling point, melting point, chemical analysis (including identification and amount of impurities) spectral data, etc.

(2) The chemical identity of each technical grade substance or mixture manufactured and/or processed by the applicant for which the exemption is sought. The chemical identity should include all characteristics and properties of the applicant's substance or mixture such as boiling point, melting point, chemical analysis (including identification and amount of impurities) spectral data, etc., that may be relevant in determining that the applicant's substance or mixture is equivalent to the test substance or mixture.

(3) A description of the process by which each technical grade substance or mixture for which an exemption is sought is manufactured and/or processed prior to use or distribution in commerce by the applicant.

(4) Any relevant biological test data (Ames tests, etc.) or studies which may bear on a demonstration of equivalency.

(5) The basis of the applicant's belief that the applicant's substance or mixture is equivalent to the test substance or mixture that the sponsor

manufactures or processes for purposes of satisfying the requirements of the applicable test rule.

The necessity for the above information has been described previously to enable EPA to make judgments concerning the equivalence of the substances tested and the substances of persons seeking exemptions.

When both manufacturers and processors are required to test and EPA requires the submission of equivalence data, EPA is proposing in general to require only manufacturers to submit such data. Processors may cite the equivalence data of the manufacturer of the technical grade chemical or mixture which they process. This requirement is based on the recognition that it is in the interest of economy to have only one party generate and submit equivalence data per chemical. The manufacturer is generally in the best technical position to do this and, although the costs for developing equivalence data are expected to be modest, he generally can pass a portion of the costs of data generation and submission to the processors. When EPA requires the submission of equivalence data and only processors are required to test (i.e., the finding of potential unreasonable risk or exposure is based on processing) or when EPA's concern for impurities requires the testing of a formulated product or processed form of a chemical because such concern stems from processing and use, EPA is proposing to require processors to independently submit equivalence data.

Approval of application. EPA is proposing to base its decision on whether to grant an exemption on the information contained in the application for exemption, in appropriate Study Plans submitted in response to the test rule and cited in the exemption application, and on actual data submitted from completed tests, if any. If the sponsor's protocol complies with the test standards, the data generated appear consistent and reasonable and the test substance and the applicant's substance are determined to be equivalent, the exemption will be granted. Equivalence was discussed in a previous section.

EPA will notify applicants in writing as to whether their exemption has been granted or denied. All denials will include the reasons for denial. If a denial was based upon insufficient data to demonstrate equivalency, EPA is proposing that the applicant may resubmit an amended application. An applicant may appeal a denial of an exemption. EPA is proposing not to make a decision to exempt an applicant

if a valid Study Plan or test data on a chemical have not been received by EPA from a test sponsor because EPA considers such information essential to assure the Agency that an adequate study has been completed, is under way, or is seriously being undertaken.

Joint sponsorship applications. Section 4(b)(3)(A) of TSCA authorizes the Administrator to permit two or more persons subject to a test rule to designate one person to conduct tests and submit data on their behalf. Submission of similar information to that required for Section 4(c) exemptions will be required of joint sponsors. In order to promote joint sponsorship of testing, EPA will minimize the administrative burdens by dealing principally with the single party designated by the test sponsors hereafter known as the principal sponsor. The data required for joint sponsorship approval must be filed with the first Study Plan submitted by the joint test group.

Termination of Exemptions

TSCA provides that if an exemption is granted prospectively, that is, on the basis of one or more persons developing test data rather than on the basis of test data that have been submitted to EPA, that EPA must terminate the exemption if no one has complied with the test rule. Termination proceedings will begin as soon as EPA is reasonably certain that the test rule is not being complied with.

If EPA determines that the test rule has not been fully complied with either because: (a) no one subject to the rule has started testing, (b) no data or only partial data were submitted or (c) data were not generated according to EPA test standards or in accordance with good laboratory practice, EPA will provide written notice by certified mail of its preliminary findings to each exemptee. (EPA is not likely to pursue this course where the deviations from the regulations are minor.) The notice will offer the exemptee the opportunity for a hearing to rebut EPA's preliminary findings. If an exemptee requests a hearing, a hearing will be held at which all exemptees requesting a hearing will be afforded an opportunity to make a presentation giving the reasons why the exemptions should not be terminated. EPA is proposing that if it does not receive written notice of an exemptee's desire to have a hearing within 30 days of the date that the certified letter was received by the exemptee, it will make a final determination of invalidity, terminate the exemption and so notify the exemptee.

Confidentiality

Confidentiality Issues

The issue of confidentiality of information will have a particular bearing on the exemption process. Under Section 14(a) of TSCA, information that is reported to EPA under TSCA may not be disclosed by EPA if it constitutes trade secrets or confidential commercial or financial information that would be exempt from disclosure under the fourth exemption of the Freedom of Information Act (5 U.S.C. 552(b)(4) for "trade secrets and commercial or financial information obtained from a person and privileged or confidential"). Section 14(b) provides that data from health and safety studies for certain chemical substances may not be withheld from disclosure except to the extent the data would reveal confidential manufacturing or processing processes or confidential proportions of substances in a mixture. Certain forms of disclosure of otherwise confidential information are authorized by Section 14(a), including Section 14(a)(4) which provides that confidential business information "may be disclosed when relevant in any proceeding under this Act, except that disclosure in such a proceeding shall be made in such a manner as to preserve confidentiality to the extent practicable without impairing the proceeding."

Because of particular concern with the problems of confidentiality, EPA has raised the issue of confidentiality for specific comment in past rulemaking activities under TSCA. In the case of this rulemaking, EPA is proposing for comment policies and procedures for exemptions from Section 4 testing rules. These proposals raise specific confidentiality issues which are discussed in this section. EPA solicits public comment on all the aspects of the confidentiality issues raised.

Identity of principal study sponsors and joint sponsors. In past rulemaking activities under Sections 8 and 5 of TSCA, EPA has become aware that for certain chemicals the link of a specific chemical with the person who manufactures or processes it is considered confidential business information by that person. Manufacturers have shown, and EPA has agreed, on both inventory reports under Section 8 and premanufacture notifications received under Section 5 that there are cases where disclosure of the fact that a particular company manufactures or processes a particular chemical substance would reveal confidential commercial information about that company which might be of value to competitors. That same

problem could occur in the exemption process.

In Study Plans, the principal study sponsor would identify itself and any joint sponsors as manufacturers or processors of the particular chemical substance. EPA recognizes that this information could, in certain circumstances, be confidential and that it, therefore, would be exempt from disclosure under Section 14(a) of TSCA except as discussed below. EPA solicits comments on how often, if at all, the identity of the principal study sponsor and joint sponsors are likely to be confidential.

If the identity of the principal study sponsor is confidential and not disclosed, it would have a complicating impact on the exemption process. In many cases, the Agency believes that exemption applicants will have an interest in identifying study sponsors in order to decide whether to seek an exemption and in order to negotiate with the study sponsors concerning either joint sponsorship or data reimbursement. In the absence of such information, the ability of study sponsors and exemption applicants to negotiate would be severely limited. This issue has already been raised in comments received under the Advance Notice of Proposed Rulemaking for testing reimbursement (September 19, 1979, 44 FR 54284). EPA solicits any additional comments on the problems of confidentiality with respect to the identity of study sponsors and the exemption process.

Among the comments already received concerning data reimbursement was the suggestion that EPA use its authority under Section 14(a)(4) to disclose certain confidential information. EPA is considering the need to use Section 14(a)(4) to disclose confidential study sponsor identities in order to facilitate the exemption process and the data reimbursement process. There are three approaches under consideration:

(a) No disclosure of confidential study sponsors. The benefit of this approach would be limited to granting protection to study sponsors. The detriments include additional burdens on EPA in the granting of exemptions and reaching reimbursement decisions, the lack of ability for direct negotiations, possible duplication of testing efforts, and a general slowing of the process.

(b) Disclosure of the identities of principal study sponsor, whether confidential or not. This would allow exemption applicants to identify the principal study sponsor as well as allowing principal study sponsors to identify each other. This disclosure

would allow exemption applicants and study sponsors to enter discussions for joint sponsorship or testing reimbursement. This would tend to limit needless duplication of testing and speed the administrative process of granting exemptions and determining reimbursement. This approach might lead to competitive harm from the disclosure of the identity of confidential study sponsors and might lead to a reluctance on the part of some companies to become study sponsors.

(c) Selective disclosure of the confidential principal study sponsors when a specific exemption application was received for a particular study plan or in the context of a specific reimbursement proceeding.

All of the three solutions present problems. However, industry may be able to provide alternative solutions which do not rely on such disclosures. Industry could set up neutral third parties such as trade associations through whom study sponsors and exemption applicants could communicate. Alternatively, industry could choose nonconfidential study sponsors to take the lead for specific testing. EPA has not identified any need to reveal confidential identities of joint sponsors other than the principal sponsor under the authority of Section 14(a)(4).

EPA solicits comments on all of these matters, particularly with regard to the disclosure of confidential principal study sponsor identities under Section 14(a)(4).

Identity of exemption applicants. As discussed above, there may be situations where the identity of an exemption applicant would be confidential under Section 14(a). For the same reasons discussed above, confidentiality might complicate the exemption and reimbursement process. As with principal study sponsor identities, EPA is considering disclosure under Section 14(a)(4) of confidential exemption applicant identities using the same three approaches discussed above. EPA solicits comments with regard to disclosure of confidential exemption applicant identities under Section 14(a)(4).

Identity of laboratory conducting the test. If the identity of the laboratory reported as conducting the tests in a study plan is the same as the study sponsor, then the confidentiality of that identity is covered by the discussion in the previous item. If the identity of the laboratory is different from the identity of the study sponsor, EPA has not identified any situations in which the laboratory identity would be confidential. EPA solicits any comments

on the potential confidentiality of laboratory identity.

Identification of the test rule. EPA does not anticipate any confidentiality claims with respect to the identification of the test rule in Study Plans and exemption applications. All of the confidentiality concerns focus on other items of information.

Identity and chemical analysis of the test substance. When the Agency has specified the test substance which should be used, EPA does not anticipate a confidentiality problem concerning the identity of the test substance. The specific description and grade of the test substance would be specified in the rule, and the study sponsor would only be confirming the use of a test substance which met the specified criteria.

In the situation where the Agency has not required that a specific test substance be used, the identity of the test substance, as well as that of manufactured or processed substances that are said to be equivalent, may be considered confidential by the submitter of the data. Although, instances in which equivalency arguments must be made will be the unusual case, confidentiality claims in those cases can significantly complicate an applicant's ability to demonstrate equivalence. EPA solicits comment on how often the identity of the test substance is likely to be considered confidential.

Consistent with position the Agency has taken in rules proposed under Sections 8(a) and 8(d), the Agency has reached a tentative conclusion that the identity of the test substance is data from health and safety studies as contemplated in Section 14(b) of TSCA and, therefore, would have to be disclosed unless it is within the two narrow exceptions to Section 14(b). The Agency does not believe this conclusion would have a major impact on disclosure of test substance identities. This is because the Agency has examined the types of confidentiality concerns that would be raised by the specific identity of the test substance and has concluded that most of these concerns fall within one of the specific exceptions in Section 14(b). Most concerns about the confidentiality of the test substance identity would derive from concern that disclosure would reveal a confidential manufacturing process. This is one of the two specific exceptions to the Section 14(b) disclosure requirement.

Additional concerns about the confidentiality of chemical identity have arisen in the Agency's rulemaking for premanufacture notification under Section 5 of TSCA. To the extent that study plans contain information

concerning a test substance that would be the subject of a premanufacture notice under Section 5, the Agency will follow for purposes of the exemption process the approach to chemical identity confidentiality which is decided in the final Section 5 rules which are scheduled for promulgation this fall.

With respect to identities of test substances which are not within the Section 5 rules, the Agency is proposing to treat those identities as confidential only if they meet the test of Sections 14(a) and fall within one of the two exceptions to Section 14(b). If these criteria are not met, the test substance identity would be disclosed as data from health and safety studies under Section 14(b). The Agency requests comment on this interpretation.

If the Agency were to hold some test substance identities as confidential in Study Plans because they meet the criteria of Section 14(a) and (b), the ability of exemption applicants to identify the Study Plans upon which they base their exemption applications would be greatly reduced. The policy of Section 4 of TSCA is to reduce duplicative testing and the resulting overuse of limited testing resources and to minimize the economic consequence of testing. If claims of confidentiality as to chemical identities were to effectively impair the ability of EPA to grant exemptions and thereby reduce duplicative testing of chemical substances, this statutory policy could not be implemented. Accordingly, if the chemical identity of the test substance were found to be confidential pursuant to Section 14(b), EPA would need a way of evaluating exemption applications short of full public disclosure. EPA solicits comments on these several options it is considering as well as others that might exist, together with comment on the issue of whether any such options are either necessary or appropriate.

First, EPA could set up a system for potential exemption applicants to obtain the identities of confidential test substances, under authority of Section 14(a)(4), by making a showing that they are *bona fide* manufacturers or processors of the chemical substance in question. If the applicant could show EPA that it was a *bona fide* manufacturer or processor, EPA would identify the test substance, and the applicant could seek an exemption.

Second, EPA could accept exemption applications whether or not the applicant knew the identity of the test substance in a specific Study Plan. If EPA determined that the applicant's substance was equivalent to the test substance for which a Study Plan had

been submitted, EPA would grant the exemption. If not, EPA would deny the exemption.

Third, EPA could encourage the study sponsors to choose, where possible, nonconfidential test substances that would be equivalent to the actual substance manufactured or processed but which would not reveal the confidential aspects of the manufactured or processed substances.

All of these options attempt to address the problem which might be presented were the identity of test substances to be claimed confidential by minimizing disclosure while allowing for the granting of exemptions. Each of these options has positive and negative aspects. The first option would require applicants to show that they are *bona fide* manufacturers or processors of the substance in the rule. If they make such a showing, they would be given the confidential test substance identity. Knowing this identity they could show that the substances they manufactured or processed were equivalent. This would create some burden for EPA in the *bona fide* inquiry process, but it would reduce EPA's burden of finding equivalence because the applicant would be required to make a case for equivalence which EPA would review. It would also result in disclosure of confidential information whether or not there was equivalence to the very persons from whom the test sponsor may wish to keep it.

Under the second option, the applicant would make an application knowing that there was a Study Plan for a specific chemical substance but not knowing the identity of the actual test substance. EPA would then be required to determine whether the applicant's substance was equivalent to the test substance or not. If it were, EPA would only have to tell the applicant that there was equivalence and also notify the study sponsor. (There might still be problems if the identities of the applicant and the study sponsor were confidential, but this issue is discussed above and would not directly affect the choice among options here.) If the Agency found equivalence, there would be no need to disclose the actual identity of the test substance to the applicant, thereby protecting the study sponsor's interest. However, if the Agency determined that there was not equivalence, the applicant might seek to challenge that finding. In the absence of knowledge about the actual identity of the test substance, the applicant would be unable to present its case in favor of equivalence. In that situation, the Agency would have to consider some

form of disclosure under the authority of Section 14(a)(4), in order to enable the applicant to pursue its appeal.

The third option might alleviate the need for the other options in most cases if the study sponsor could choose a nonconfidential test substance and show its equivalence to the substance actually manufactured or processed. The applicant would also have to show the equivalence of the substances it actually manufactured or processed to the test substance. This would not require the disclosure of the confidential substances, but it would be dependent upon the equivalence of the nonconfidential test substance to the substances actually manufactured or processed, which might not always be possible. In that event another solution would be necessary.

In conjunction with, or in lieu of, the above options, industry itself may be able to reach negotiated solutions to the disclosure of test substance identities. Many of these solutions would be dependent upon other information being nonconfidential. These possibilities should be addressed in any comments.

The manufacturing or processing for the test substance. In some cases the identity of the test substance cannot be specified without stating the manufacturing or processing process. For the reasons discussed above, the Agency has reached a tentative conclusion that in those cases where the identity is dependent upon the description of the manufacturing or processing process, that description would constitute data from health and safety studies under Section 14(b). However, if that description were confidential under Section 14(a), clearly it would fall within one of the exceptions of Section 14(b). Consequently, there are likely to be situations where the description would be confidential under Section 14(a) and (b). The question of whether or not such confidential descriptions should be disclosed as part of the exemption process under Section 14(a) and (b) is essentially the same as for disclosure of the identity of the test substance discussed above. The options available would be the same. The Agency solicits comments on these matters and particularly the potential disclosure of confidential manufacturing processes under the various options discussed above.

Protocol information. Consistent with the position the Agency has taken in rules proposed under Sections 8(a) and 8(d), the Agency has reached a tentative conclusion that the protocol information is data from health and safety studies as contemplated in Section 14(b) and,

therefore, would have to be disclosed unless it was within one of the two narrow exceptions to Section 14(b). The Agency has examined potential confidentiality concerns for protocol information and has not identified any concerns other than to the extent the protocol information might contain references to other confidential information such as manufacturing process or test substance chemical identity. Consequently, the Agency is proposing that disclosure of confidential protocol information be governed by the same approaches discussed above. EPA solicits comment on the confidentiality concerns, if any, that may occur for protocol information and the use of the various options for disclosing that information.

Information concerning chemical substances actually manufactured or processed and their manufacturing or processing processes. EPA is aware that information concerning the chemical analysis of substances actually manufactured or processed, including impurities and contaminants, may reveal information concerning the manufacturing or processing process. This is clearly true of actual descriptions of the manufacturing or processing processes used. The proposal would require and exemption applications to contain such information to show equivalence when such a showing is necessary. If the information concerning manufacturing or processing processes is confidential under Section 14(a), EPA would not be able to disclose it except as provided in Section 14(a)(4). EPA solicits comments on this assumption. Particularly, EPA is concerned with finding out whether this information is likely to be confidential in the form provided, whether the confidentiality concerns could be met by keeping the submitter's identity confidential, whether there would be a need to disclose this information to other parties, and whether this information on equivalence would, at any time, constitute data from health and safety studies under Section 14(b). At this time EPA has not identified any need to disclose such information under Section 14(a)(4).

Description of basis for finding of equivalence and biological data demonstrating equivalence. For the same reasons that information concerning the chemical analysis of substances actually manufactured or processed may be confidential or information concerning their manufacturing or processing processes may be confidential, EPA is aware that the argument for equivalence made by

the study sponsor or exemption applicant might be confidential under Section 14(a). In discussing the arguments in favor of equivalence, the submitter might have to reveal confidential information. If the information is confidential, EPA would not disclose it except as deemed necessary pursuant to Section 14(a)(4). EPA does not anticipate that nondisclosure of such information generally will impair the exemption process. However, the biological data submitted to demonstrate equivalence would generally constitute health and safety data under Section 14(b) in which case it would have to be disclosed. EPA solicits comments on the assumptions in this discussion and the extent to which these items are likely to be confidential.

Substantiation of Confidentiality Claims

Under EPA's confidentiality regulations in 40 CFR Part 2, a person submitting information to EPA may claim any information confidential. In order to make the assertion of confidentiality the person need only mark the information in some appropriate fashion to indicate the confidentiality claim. In some limited situations because of administrative needs (such as the Inventory) or public participation needs or anticipation of Freedom of Information Act requests (such as in the Section 5 notices), the Agency has required or proposed to require substantiation of confidentiality claims at the time of submission of the information.

With respect to the exemption process, EPA has identified information which appears to fall within the above categories justifying substantiation of the confidentiality claims at the time of submission. EPA recognizes that requiring substantiation at the time of submission may create additional burdens on the submitter. Accordingly, EPA has tried to limit such requirements to those which have a direct bearing on the efficient and fair operation of the exemption process.

The items of information for which the Agency is proposing to require substantiation of confidentiality claims at the time of submission are: the identity of the principal test sponsor, the identity of the test substance, and the manufacturing or processing process for the test substance. As discussed above, if the identities of the test substance and/or its manufacturing or processing process are confidential, the exemption process is much more difficult to administer, and exemption applicants have a more difficult time seeking exemptions, arguing in favor of equivalence, and pursuing appeals of

decisions against findings of equivalence. Accordingly, the Agency, the exemption applicants, and the study sponsors have an apparent interest in limiting the confidentiality of this information to those cases where the confidentiality is legally supportable. The Agency anticipates that it would have to make confidentiality determinations for all test substance identities and manufacturing or processing processes for test substances claimed confidential at or near the time Study Plans are submitted in order to enable exemption applicants to have the maximum information to pursue their applications. The same types of concerns would require substantiation for principal test sponsor identities.

The Agency solicits comments on the proposal to require substantiation of confidentiality claims for these three items of information in Study Plans and also whether there is any need to require substantiation for other items of information in the exemption process at the time of submission.

Public Meetings

EPA will hold a general public meeting on September 24, 1980, in Washington, D.C. to provide the public an opportunity to present comments and questions on these proposed rules as required by Section 4(b)(5) to EPA officials who are directly responsible for developing the rule and supporting analyses. The public meeting will start with a short summary by EPA of the proposed rules and will be followed by oral presentations from the floor. A time limit of 15 minutes per person, company, or organization may be imposed depending upon the number of requests. EPA will allot speaking times in advance of the meeting on a first-come basis, although the Agency reserves the right to alter the order depending upon the nature of the particular comments and other relevant factors. For the benefit of all concerned, EPA encourages the elimination of redundant comments. If time permits, following these prepared presentations, EPA will receive any other comments from the floor. Presenters are invited, but not required, to submit copies of their statements on the day of the meeting. All such written materials will become a part of EPA's record for this rulemaking. In addition, the Agency will transcribe each meeting and will include the written transcripts in the public record. The exact location and time of this meeting will be announced later in the **Federal Register** and the press.

In addition to the general public meeting, EPA personnel responsible for developing these proposals will be

available at EPA's discretion to meet in public sessions at EPA in Washington, D.C., during the 105 day comment period, with interested persons from individual companies, trade associations, organized labor and citizen organizations to discuss these proposals. EPA encourages using special request meetings for discussing technical data and implementation issues. However, persons should plan to present their views at the general meeting to ensure their opportunity for comment since special meetings will be held only when EPA believes that the subject is more appropriately discussed in a special format than in a general meeting. EPA will provide facilities and make other necessary arrangements for such meetings. The Agency will make transcripts or summaries of the meetings for inclusion in the official public record. While these meetings will be open to the public, active participation will be limited to those requesting the session and designated EPA participants.

Persons who wish to present comments at the September 24, 1980 general meeting should contact EPA no later than September 12, 1980 by calling toll-free (200) 424-9065 (in Washington, D.C. call 554-1404), or by writing to the address listed at the beginning of this preamble under "For Further Information Contact". Persons wishing to arrange a special meeting should follow the same procedures.

Public Record

All comments received in response to this notice will be available for inspection in the OPTS Reading Room (Docket No. 80T-125) in Room 447 E, 401 M Street SW., Washington, D.C. 20460 from 8:00 a.m. to 4:00 p.m. Monday through Friday, except legal holidays.

The comments of the Chemical Manufacturers Association to the Advance Notice of Proposed Rulemaking on Reimbursement bears on this rulemaking and, accordingly, will be included in the Public Record.

Related Actions

EPA is proposing the first health effects test rules under Section 4(a) of TSCA in a separate notice in today's Federal Register.

EPA published in the Federal Register on September 16, 1979 (44 FR 54282) an Advance Notice of Proposed Rule Making concerning reimbursements required to be made by persons granted an exemption under Section 4(c) of TSCA.

Dated: July 1, 1980.

Douglas M. Costle,
Administrator.

It is proposed that title 40 of the Code of Federal Regulations be amended by designating the existing material under proposed Part 770 (44 FR 44054, July 26, 1979) Subpart A, reserving Subparts B thru D, and proposing to add a new Subpart E to read as follows:

PART 770—TEST RULES FOR CHEMICAL SUBSTANCES AND MIXTURES

Subpart E—Exemptions

Sec.	
770.400	Scope, purpose and authority.
770.401	Applicability.
770.402	Definitions.
770.405	Filing of application.
770.406	Content of application.
770.407	Joint sponsorship of testing.
770.410	Approval or denial of applications for exemption or approval of joint sponsorship.
770.420	Submission of equivalence data.
770.430	Appeal from denial of exemption application.
770.431	Termination of exemption.
770.440	Statement of financial responsibility. [TSCA 15 U.S.C. 2603(b)(3)(A), 2603(c)]

Subpart E—Exemptions

§ 770.400 Scope, purpose and authority.

(a) This subpart sets forth the requirements for submission and approval of applications for exemption and for approval of joint sponsorship of testing under Sections 4(b)(3)(A) and 4(c) of the Toxic Substances Control Act [TSCA, 15 U.S.C. 2603(b)(3)(A), 2603(c)].

(b) (1) Section 4(c) of TSCA permits any person subject to a test rule promulgated under Section 4(a) to request an exemption. The Administrator is directed to approve an application for an exemption if he determines that the chemical to which the application pertains is equivalent to one for which data have been or are being developed pursuant to the same testing rule, and that submission of data by the applicant would be duplicative.

(2) Section 4(b)(3)(A) of TSCA authorizes the Administrator to permit two or more persons subject to a test rule to designate one of themselves or a qualified third party to conduct testing and submit data on their behalf.

(3) Sections 4(c)(3)(A) and 4(c)(4)(A) of TSCA provides that persons receiving exemptions must reimburse all those who have contributed or are contributing to financing the development of the data on the basis of which the exemption was received. This reimbursement is to be for a portion of the costs incurred. If the persons

concerned cannot agree on the amount and method of reimbursement, EPA is required to order the person granted the exemption to provide fair and equitable reimbursement to the appropriate parties.

§ 770.401 Applicability.

This part is applicable to manufacturers and processors of chemical substances and mixtures who seek an exemption from test requirements of Part 773 of this chapter or who elect to jointly sponsor such testing.

§ 770.402 Definitions.

For the purpose of this subpart: "Additive" means a chemical substance that is intentionally added to another chemical substance to improve its stability or impart some other desirable quality.

"Equivalence data" means chemical data or biological test data which show two substances or mixtures to be equivalent.

"Equivalent" means that one or more substances or mixtures is able to represent or substitute for another in a test or series of tests.

"Exemption" means an exemption from the testing requirement of a TSCA Section 4 test rule in Part 773 of this chapter.

"Impurity" means a chemical substance which is unintentionally present with another chemical substance. "Joint sponsor" means a person who sponsors testing pursuant to Section 4(b)(3)(A) of TSCA.

"Joint sponsorship" means the joint sponsorship of testing by two or more persons in accordance with Section 4(b)(3)(A) of TSCA.

"Principal sponsor" means an individual sponsor or the joint sponsor who assumes primary responsibility for the direction of a study and oral and written communication with EPA.

"Reimbursement period" means the period of time during which persons granted exemptions from test rules are required to reimburse persons who have contributed or are contributing to financing the development of data on which exemptions are based. This period is established on a case by case basis pursuant to Section 4(c)(3)(B) of TSCA.

"Sponsor" means the person or persons who design, direct and finance the testing of a substance or mixture designated for testing in a Section 4 test rule in Part 773 of this Chapter.

"Test substance" means the chemical substance or mixture that is specified for use in actual testing.

§ 770.405 Filing of applications.

(a) *Who may file.* Any person seeking an exemption from a test rule promulgated under Section 4(a) of TSCA.

(b) *What may be claimed.* A person may apply for an exemption from all or one or more specific testing requirements testing requirements to which the person is subject as set forth in Part 773 of this chapter.

(c) *Where to file.* All applications and appeals must be submitted to the Document Control Officer (TS-793), Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460, Attn: [File Number]. The File Number is the code of Federal Regulations (CFR) section number of the subject chemical (e.g., 773.130 for chloromethane).

§ 770.406 Content of application.

(a) The test rule and specific testing requirement(s) from which an exemption is sought.

(b) Name, address, and telephone number of applicant.

(c) Name, address, and telephone number of appropriate individual to contact for further information.

(d) The citation or documentation of the Study Plan, study or studies upon which an exemption may be based.

(e) If required by § 770.420 of this part:

(1) The chemical identity of the test substance or mixture on which this application is based. The chemical identity should include all available characteristics and properties of the test substance or mixture such as the boiling point, melting point, chemical analysis (including identification and amount of impurities) spectral data, etc.

(2) The chemical identity of each technical grade substance or mixture manufactured and/or processed by the applicant for which the exemption is sought. The chemical identity should include all characteristics and properties of the applicant's substance or mixture such as boiling point, melting point, chemical analysis (including identification and amount of impurities) spectral data, etc., that may be relevant in determining that the applicant's substance or mixture is equivalent to the test substance or mixture.

(3) A description of the process by which each technical grade substance or mixture for which an exemption is sought is manufactured and/or processed prior to use or distribution in commerce by the applicant. Processing as opposed to manufacturing information is required only if processors are required to submit

equivalence data individually pursuant to § 770.420.

(4) Any relevant biological test data (Ames tests, etc.) or studies which may bear on a demonstration of equivalency.

(5) The basis for the applicant's belief that the applicant's substance or mixture is equivalent to the test substance or mixture that the sponsor manufacturers or processes for purposes of satisfying the requirements of the applicable test rule.

§ 770.407 Joint sponsorship of testing.

Persons subject to test rules who jointly sponsor testing are not required to file an application for an exemption but must file a Study Plan.

§ 770.410 Approval or denial of applications for exemption or approval of joint sponsorship

(a) The Administrator will approve any applications if he determines that:

(1) the chemical substance or mixture with respect to which the applications were submitted is equivalent to a chemical substance or mixture for which data have been or are being submitted in accordance with a test rule, and

(2) submission of data by the applicant on such chemical substance or mixture would be duplicative of data which have been or are being submitted to the Administrator in accordance with a test rule.

(b) The Administrator will notify the applicant by certified mail of his determination within 30 days.

§ 770.420 Submission of equivalence data.

(a) If EPA does not require the submission of equivalence data in Part 773 of this Chapter for the substance or mixture subject to the test rule, the information specified in § 770.406(e) will not be required to be submitted.

(b) If EPA requires the submission of equivalence data in Part 773 of this Chapter for the substance or mixture, a showing of the equivalency of the applicant's substance and the test substance is required as a condition for an exemption and for EPA approval of joint sponsorship of tests.

(1) Manufacturers applying for an exemption shall be required to submit the information specified in § 770.406(e).

(2) When both manufacturers and processors are subject to a test rule, a processor applying for an exemption may cite any applicable information required by this section that is supplied by the manufacturer of the chemical substance that the processor processes.

(3) If only processors are subject to a test rule, processors applying for an exemption shall be required to submit the information required by this section.

(4) If EPA specifies testing of formulated products or processed forms of the chemical, both manufacturers and processors applying for an exemption shall be required to submit the information specified in § 770.406(e).

§ 770.430 Appeal from denial of exemption application.

(a) Within 30 days after receipt of notification that EPA has denied an application for exemption or approval of joint sponsorship, the applicant may file an appeal with the Document Control Officer.

(b) The appeal shall indicate the basis for the applicant's request for reconsideration.

(c) The Administrator will notify the applicant of his decision within 60 days.

(d) The filing of an appeal from the denial of an exemption or approval of joint sponsorship shall not act to stay the applicant's legal obligation under Section 4 of TSCA.

§ 770.431 Termination of exemption.

(a) EPA shall terminate a prior approval of an exemption application if it determines that:

(1) The test which provided the basis for approval of the exemption application has not been started, or

(2) The test is not being conducted, or the data being generated, in accordance with the test standards and good laboratory practices in 40 CFR 772.

(b) EPA will first provide 30 days written notice for an opportunity for a hearing to those persons whose exemption was based upon the non-complying test.

(c) An exemptee may request EPA to terminate its exemption. Such requests should be in writing, submitted to the Document Control Officer and should state the reasons for the request.

§ 770.440 Statement of financial responsibility.

Each applicant for an exemption shall submit the following sworn statement with his application:

I understand that if this application is granted before the reimbursement period described in Section 4(c)(3)(B) of TSCA expires, I must pay fair and equitable reimbursement to the person or persons who incurred or shared in the costs of complying with the requirement to submit data and upon whose data the granting of my application was based.

[FR Doc. 80-21564 Filed 7-17-80; 8:45 am]

BILLING CODE 5650-01-M

Chloromethane and Chlorinated Benzenes Proposed Test Rule; Amendment to Proposed Health Effects Standards

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Under Section 4(a) of the Toxic Substances Control Act (TSCA), the Environmental Protection Agency (EPA) is proposing that manufacturers and processors of chloromethane and all chlorinated benzenes except hexachlorobenzene conduct health effects testing in accordance with previously proposed Section 4(b) test standards. The health effects testing proposed for chloromethane is oncogenicity and structural teratogenicity. EPA is proposing that all manufacturers and processors pay for testing a sample of six of the chlorinated benzenes: mono-, 1,2- and 1,4-di-, 1,2,4-tri-, 1,2,4,5-tetra-, and pentachlorobenzene. All except pentachlorobenzene are to be tested for structural teratogenicity and subchronic/chronic effects, all except 1,2,4-trichlorobenzene are to be tested for reproductive effects, and all except mono- and the two dichlorobenzenes are to be tested for oncogenicity. Testing will be in accordance with already proposed test standards except for a limited number of chemical-specific modifications proposed in this rule. The Administrator of EPA will use the test data to assess the risks of injury to human health presented by these chemicals.

EPA is also proposing to amend the previously proposed health effects standards to increase reporting requirements for Study Plans.

DATES: Written comments should be submitted on or before October 31, 1980. EPA will hold a public meeting for this rule on September 24, 1980, in Washington, D.C. The exact time and place will be announced in a future Federal Register notice. For further information on arranging to speak at the September general meeting or arranging a special public meeting see Section XIII of this preamble.

ADDRESSES: Written views and comments should bear the document control number 60T-126 and should be submitted to: Document Control Officer, Chemical Information Division (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, 401 M Street, S.W.,

Washington, D.C. 20460. The support documents described herein are available on request from the Industry Assistance Office.

FOR FURTHER INFORMATION CONTACT: John Ritch, Industry Assistance Office, Office of Pesticides and Toxic Substances (TS-799), Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460; Toll-free telephone number: 800-424-9065 (In Washington, D.C. call 544-1404).

SUPPLEMENTARY INFORMATION:

Introduction

Under Section 4(a) of the Toxic Substances Control Act (TSCA) (Pub. L. 94-469; 90 Stat. 2006; 15 U.S.C. 2603) EPA is proposing health effects testing requirements for chloromethane and certain chlorinated benzenes. These rules will not require testing for all health effects recommended by the Interagency Testing Committee (ITC); accordingly, this notice and accompanying documents also explain EPA's decision not to require testing for certain effects and its plans to propose rules for other effects after public comment is received on issues raised in today's proposal.

This preamble outlines EPA's legal authority to require testing and its approach to implementing Section 4, explains the proposed rules and EPA's policies on significant issues, summarizes the basis for EPA's determinations concerning the need to test, identifies issues for comment, and covers other pertinent points. In addition, EPA has prepared four support documents which are available from the Industry Assistance Office. The Support Documents for Chloromethane and the Chlorinated Benzenes describe the basis for EPA's findings in detail. The Economic Analysis Support Document assesses the ability of the chloromethane and chlorinated benzenes markets to sustain the cost of testing. The Exposure Support Document explains EPA's approach to exposure assessment for purposes of Section 4 of TSCA.

EPA has also proposed health effects test standards in the Federal Register on May 9, 1979 (44 FR 27334) and July 28, 1979 (44 FR 44054) which are designed to be incorporated into this rule by reference. Documents pertaining to those proposals describe the purpose of the various tests proposed today, how they are to be done, how much they will cost, and other related matters. Those documents, and the ones supporting today's proposal, must be read together with this preamble to obtain a complete

explanation of the basis for EPA's determinations.

The following is an outline to the remainder of this preamble.

- I. Statutory Framework and Implementation.
 - A. Section 4(a) findings.
 - B. Test rules and standards.
 - C. Issuance of test rules and standards.
 - D. Effective period of rule.
 - E. Testing responsibilities, exemptions, and reimbursement.
 - F. Implementation of exemption and reimbursement provisions.
- II. Recommendations of the interagency Testing Committee.
- III. Goals and Policy Considerations.
 - A. Goals of Section 4 implementation.
 - B. Section 4(a)(1)(A) findings.
 - C. Choice of test material.
 - D. Use of categories.
 - E. Responsibility for testing.
 - F. Reporting requirements and deadlines.
 - G. Confidentiality.
- IV. Chloromethane: Basis for Determinations.
 - A. Introduction.
 - B. Exposure profile.
 - C. Proposed findings for oncogenicity and structural teratogenicity.
 - D. Decision to defer proposal of a test rule for neurotoxicity, behavioral teratogenicity, and mutagenicity.
 - E. Decision not to require testing for systemic effects, reproductive effects, metabolism, and epidemiology.
- V. Chlorinated Benzenes: Basis for Determinations.
 - A. Introduction.
 - B. Exposure profile.
 - C. Proposed findings for oncogenicity, structural teratogenicity, reproductive effects, and subchronic/chronic effects.
 - D. Decision to defer proposal of a test rule for neurotoxicity, behavioral teratogenicity, mutagenicity, and metabolism.
 - E. Decision not to require testing for acute toxicity and epidemiology.
- VI. Summary of Proposed Rule.
 - A. Chloromethane:
 1. Effects to be tested.
 2. Test substance.
 3. Route of administration.
 4. Persons required to test, exemptions.
 5. Reporting requirements.
 - B. Chlorinated Benzenes:
 1. Effects to be tested.
 2. Test substances.
 3. Route of administration.
 4. Persons required to test, exemptions.
 5. Reporting requirements.
- VII. Economic Analysis of Proposed Rule and Alternatives.
- VIII. Availability of Test Facilities and Personnel.
- IX. Compliance and Enforcement.
- X. Issues for Comment.
 - A. Scientific issues pertaining to proposed rule.
 1. Chloromethane.
 2. Chlorinated Benzenes.
 - B. Scientific issues pertaining to deferred rules.
 1. Chloromethane.
 2. Chlorinated Benzenes.
 - C. General issues.
- XI. Environmental Impact Statement.

XII. Public Participation.
 XIII. Public Meetings.
 XIV. Public Record.

I. Statutory Framework and Implementation

Section 4 of the Toxic Substance Control Act authorized the Administrator of EPA to require manufacturers (including importers) and processors of identified chemical substances and mixtures to test the chemicals in accordance with applicable EPA test rules [Section 4(a), (b)]. TSCA states that each Section 4(a) test rule must identify the chemical substances and mixtures for which testing is required, provide standards for the development of test data ("test standards"), and, for chemicals which are not new chemicals, designate deadlines for the submission of data developed under the rule [Section 4(b)(1)].

A. Section 4(a) Findings

In order to require that a chemical be tested in accordance with EPA test standards, the Administrator must make three findings relating to the chemical's risk potential, the insufficiency of data available to EPA, and the need to test.

First, the Administrator must find either that the manufacture, distribution in commerce, processing, use, disposal, or some combination of these activities involving the chemical may present an unreasonable risk of injury to health or the environment [Section 4(a)(1)(A)(i)], or that the chemical is or will be produced in substantial quantities and that there is or may be significant or substantial human exposure to or substantial environmental release of the chemical [Section 4(a)(1)(B)(i)].

Second, the Administrator must find that existing data and experience relating to the chemical are insufficient to reasonably determine or predict the effects on health or the environment of the manufacture, distribution in commerce, processing, use, or disposal of the chemical or of any combination of these activities [Section 4(a)(1)(A)(ii) and (B)(ii)].

The third finding is that testing is necessary to develop the requisite data [Section 4(a)(1)(A)(iii) and (B)(iii)].

These findings may be made with respect to individual chemicals or categories of chemicals. Section 26(c)(1) provides that any action authorized or required to be taken by EPA under any provision of the Act may be taken in accordance with that provision with respect to a category of chemical substances or mixtures. Section 26(c)(2)(A) explains that the term "category of chemical substances"

means a group of chemical substances, the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or the environment, or the members of which are in some other way suitable for classification as such for purposes of the Act (except that the term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances).

The Administrator may require testing of mixtures only if, in addition to the foregoing findings, he finds that the necessary information cannot reasonably and more efficiently be obtained by testing the separate components in the mixture [Section 4(a)(2)]. Also, while TSCA does not generally apply to chemicals manufactured, processed, or distributed in commerce for use as pesticides, food additives, drugs, and cosmetics, such chemicals may be tested under Section 4 if they are also manufactured, processed, or distributed in commerce for uses covered by TSCA.

B. Test Rules and Standards

The rules required by Section 4 must (1) identify the chemicals to be tested, (2) provide the date by which test data must be submitted, (3) specify which tests are to be conducted, and (4) prescribe standards for the development and analysis of test data. [Sections 4(b) and 3(12)(A)]. The Act states that carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects and any other effect which may present an unreasonable risk of injury to health or the environment are effects for which test standards may be prescribed [Section 4(b)(2)(A)]. The Act further specifies that the characteristics of chemicals for which such standards may be prescribed include persistence, acute toxicity, subacute toxicity, chronic toxicity, and any other characteristic which may present such a risk [Section 4(b)(2)(A)].

To the extent necessary to assure reliable and adequate data or such health and environmental effects, test standards may also prescribe the manner in which data are to be developed, any test protocol or methodology to be employed in the development of such data, and such other requirements as are necessary to provide such assurance [Section 3(12)(B)]. The Act specifies that the methodologies that may be prescribed in such standards include epidemiological studies, serial or hierarchical tests, *in*

vitro tests, and whole animal tests [Section 4(b)(2)(A)].

C. Issuance of Test Rules and Standards

EPA has chosen to implement Sections 4(a) and 4(b) in separate but related rulemakings. In general, a "test rule" imposes testing requirements on specific chemicals, whereas a "test standard" indicates the testing method to be used. In today's action implementing Section 4(a), EPA is proposing a test rule which identifies the specific chemicals to be tested and test standards to be followed, establishes deadlines and reporting requirements for the submission of data to EPA, and specifies the persons who will be required to conduct tests and submit data. This proposal reflects EPA's preliminary determination that the development of test data is necessary to determine whether the identified chemicals present an unreasonable risk of injury to human health or the environment.

In two previous notices implementing Section 4(b), EPA proposed the health effects test standards and Good Laboratory Practices which are to be referenced in the test rule proposed today. Standards for oncogenicity, other chronic effects, and combined chronic effects were published in the Federal Register of May 9, 1979 (44 FR 27334). Standards pertaining to (1) acute oral toxicity, (2) acute dermal toxicity, (3) acute inhalation toxicity, (4) primary eye irritation, (5) primary dermal irritation, (6) dermal sensitization, (7) subchronic oral dosing, (8) subchronic 90-day dermal toxicity, (9) subchronic inhalation toxicity, (10) teratogenicity, (11) reproductive effects, (12) mutagenicity-gene mutations, (13) mutagenicity-heritable chromosomal mutations, (14) mutagenicity-effects on DNA repair or recombination, and (15) general metabolism, were published in the Federal Register of July 28, 1979 (44 FR 44054). In addition, the Agency's proposed test standards relating to Good Laboratory Practices (GLP) for Health Effects (Animal Bioassays) were published in the Federal Register of May 9, 1979 (44 FR 27362). Standards for neurotoxicity (neurologic and behavioral effects) testing, behavioral teratogenicity testing, certain types of metabolism testing, for additional mutagenicity testing and environmental effects testing have not yet been proposed.

These test standards, when final, are intended to be generic standards that will be incorporated by reference into each proposed and final test rule. However, because of the need to ensure that the generic test standards are

appropriate to a specific chemical, the Administrator may propose individual modifications of the test standards in specific test rules. In the course of commenting on a specific test rule, the public may also recommend changes to the test standards that it believes are necessitated by the particular characteristics of the chemical for which testing has been proposed. EPA will consider all such comments carefully but will not reevaluate the appropriateness of the generic standards except as they relate specifically to the proposed testing of that chemical. Comments that raise general testing standard issues will be taken into account when EPA conducts the required yearly review of the adequacy of the standards (Section 4(b)(2)(B)). At that time, EPA will solicit comment on and propose appropriate revisions to the generic standards.

By conducting this annual review and by tailoring the generic standards to the characteristics of specific chemicals as necessary, EPA believes sufficient flexibility is provided to assure that testing requirements for chemicals will be scientifically appropriate and as consistent as possible with nationally and internationally agreed upon guidelines. While chemical-specific modifications to test rules and standards will not be routinely considered after promulgation, the Agency will consider them upon a showing of compelling necessity.

This scheme for integrating the "test rules" and "test standards" will apply somewhat differently for this first set of test rules and test standards. Because final health effects test standards have not yet been promulgated, the test rule proposed today incorporates proposed test standards. The final test rule will incorporate the final test standards, along with any chemical-specific modifications applicable to chloromethane and the chlorinated benzenes. EPA will incorporate the record of the test standard rulemaking into this proceeding (with the exception of effects for which testing is not being proposed).

In commenting on today's proposal, there is no need to repeat comments made previously on the general appropriateness of the proposed test standards and good laboratory practice standards. Comments may be limited here to the appropriateness of the proposed test standards, as modified, in the test rule to the testing of chloromethane and the chlorinated benzenes. Persons wishing to reiterate previous comments are encouraged to

reference, rather than repeat, prior submissions.

It has been suggested that in order to comment on the proposed test rule meaningfully, there must be an opportunity to review the final standards. EPA disagrees. While EPA has chosen to propose test standards in a separate earlier rulemaking, there is no legal requirement that test standard issues be resolved first. The same opportunity for comment exists that would be available if EPA had decided to propose and promulgate all the requirements in the test rules and standards in one rulemaking. Further, EPA staff will be available to discuss questions relating to the relationship of the test rules to the test standards.

D. Effective Period of Rule

Section 4(b)(1)(C) requires EPA to specify the period of time within which persons required to test must submit the data to EPA. This period does not apply to new chemicals; submission requirements for them are governed by Sections 5(b) and 5(d).

Section 4(b)(4) governs the expiration of the rule. Testing requirements do not end as soon as the first data are submitted, but expire at the end of the reimbursement period. The reimbursement period begins when the first data are submitted and ends after five years or at the expiration of a period of time equal to the time necessary to develop the data, whichever is longer [Section 4(c)(3)(B)]. In the case of categories of chemicals, the rule expires when the reimbursement period for the last chemical in the category to be tested expires. In addition, EPA may repeal the rule at any time.

E. Testing Responsibility, Exemptions, and Reimbursement

Section 4(b)(3)(B) specifies that the activities for which the Administrator makes the Section 4(a) findings (manufacture, processing, distribution, use, and/or disposal) determine whether the responsibility to conduct the required tests and submit the resulting data is borne by (1) each person who manufactures or intends to manufacture the chemical, (2) each person who processes or intends to process the chemical, or (3) both manufacturers and processors. Because TSCA defines "manufacture" to include "import into the customs territory of the United States" [Section 3(7)], the term "manufacturer" encompasses both manufacturers and importers.

Section 4 contains provisions designed to avoid duplicative testing. Section 4(b)(3)(A) provides that the

Administrator may permit two or more of the manufacturers and/or processors who are required to conduct tests and submit data to designate one such person or a qualified third person to conduct the tests and submit such data on behalf of the persons making the designation. In addition, Section 4(c) specifically provides that any person required to test may apply to the Administrator for an exemption from the requirement. If the Administrator determines that a chemical for which an exemption application is submitted is equivalent to a chemical for which data have been submitted or are being developed pursuant to a test rule and that submission of data by the applicant would be duplicative of data that have been submitted or are being developed pursuant to a test rule, the Administrator must exempt the applicant from conducting tests and submitting data 1 [Section 4(c)(2)]. Persons receiving exemptions must reimburse those who actually did, are doing, or previously contributed to the cost of the required testing for a portion of the costs incurred in complying with the rule [Sections 4(c)(3)(A) and 4(A)].

If the persons submitting the test data and those granted exemptions based on those data cannot agree on the amount and method of reimbursement, EPA must order the person granted the exemption to provide fair and equitable reimbursement. Reimbursement rules to be adopted by the Agency are to be developed in consultation with the Justice Department and the Federal Trade Commission. Relevant factors to be taken into account are the competitive position and the market share of the persons providing and receiving reimbursement. The Administrator's final order is reviewable in Federal district court [Sections 4(c)(3)(A) and 4(A)].

F Implementation of Exemption and Reimbursement Provisions

The Agency has published in today's Federal Register a proposed Statement of Exemption Policy and Procedure, setting forth its intended approach to Section 4(c) exemption questions. In addition, the Agency published an Advance Notice of Proposed Rulemaking (ANPRM) relating to reimbursement issues under Sections 4(c)(3) and 4(c)(4) in the Federal Register of September 19, 1979 (44 FR 54284). EPA plans to publish a proposed rule on reimbursement in the fall of 1980.

As discussed later (III.E.), there is some interdependence among the exemption and reimbursement provisions, the allocation of responsibility for testing [Section

4(b)(B)(3)], and the selection of chemicals within a category for inclusion in a test rule. In general, the issues raised by these provisions are quite complex from both an administrative and economic perspective. In response to the ANPRM on reimbursement, EPA has recently received submissions from the Chemical Manufacturers' Association, firms and other trade groups which address many of these issues. EPA has not had an opportunity to fully analyze these comments but will consider the implications that they may have on this rulemaking.

II. Recommendations of Interagency Testing Committee

Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for testing. The ITC may designate up to 50 substances at any one time for priority consideration by EPA. TSCA requires EPA to respond to such designations within 12 months of the date they are made either by initiating rulemaking under Section 4(a) or publishing in the Federal Register reasons for not initiating rulemaking.

As of April 1980, the ITC had designated 39 chemicals and categories of chemicals for priority consideration by EPA. Today's proposal concerns health effects testing for one chemical substance, chloromethane, and two categories of substances, the lower and higher chlorinated benzenes, recommended by the ITC. In addition, in a separate notice appearing in today's Federal Register, EPA announces its tentative decision not to require health effects testing for acrylamide, another substance designated by the ITC.

Chloromethane was designated on the Priority List in the ITC's First Report published in the Federal Register October 12, 1977 (42 FR 55026). The ITC recommended that testing be undertaken for carcinogenicity, mutagenicity, teratogenicity, and other chronic effects, placing particular emphasis on its concern about chloromethane's effects on the central nervous system, liver, kidney, bone marrow, and the cardiovascular system. Monochlorobenzene and the dichlorobenzenes were also placed on the list in the First Report. The ITC recommended testing for carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects and epidemiology. The higher chlorinated benzenes, tri-, tetra-, and penta-, were added to the list in the ITC's Third Report, published in the Federal Register October 30, 1978 (43

FR 50630), and testing was recommended for the same effects.

The publication of today's proposal serves as EPA's response to the ITC's health effects testing recommendations for these chemicals. EPA previously responded to the ITC's designation of chloromethane and the lower chlorinated benzenes by publishing an explanation in the Federal Register that it was not yet prepared to initiate rulemaking for any of the chemicals designated in the first two lists (43 FR 50134, October 26, 1978; 44 FR 28095, May 14, 1979). However, a district court recently ruled that EPA's responses to the first two ITC lists did not meet the legal requirements of Section 4(e) of TSCA. *Natural Resources Defense Council v. Costle*, 79 Civ. 2411 (S.D.N.Y., Feb. 4, 1980). The court ordered EPA to submit a plan for complying with the ITC's designations; EPA submitted the compliance plan on March 6, 1980.

EPA's proposed compliance plan calls for EPA to publish Advance Notices of Proposed Rulemaking, proposed rules, or announce decisions not to test at sequenced intervals over the next four years. This plan was based on EPA's current process for developing test rules. Since the submission of the compliance plan to the Court, EPA has initiated a reexamination of the process by which EPA assesses ITC recommendations and issues test rules. EPA is seeking ways to issue test rules more rapidly and efficiently, and will submit a new compliance plan to the Court on September 15, 1980, reflecting the changes to be made as a result of this reexamination. EPA will publish the final schedule in the Federal Register. The schedule addresses both health and environmental effects. (Today's proposal does not include environmental effects, because the evaluation of environmental effects and proposal of environmental effects standards has not progressed at the same speed as for health effects.)

In general, because the ITC has designated all chemicals as having equal priority, EPA's schedule reflects its attempt to evaluate the ITC chemicals in the order that they were presented to the Agency. The availability of information and difficulty of assessment however, influence the order in which EPA will make decisions concerning ITC recommended chemicals. In addition, as is the case with the two chlorinated benzenes groups recommended by the ITC, the Agency may evaluate together several recommendations proposed by the ITC at different times.

III. Goals and Policy Considerations

A. Goals of Section 4 Implementation

In enacting TSCA, Congress expressed concern about how little is actually known about the health and environmental effects of exposure to the multitude of chemicals present in significant quantities in the environment. Thus, Section 4 of TSCA implements Congress' stated intent that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures" [Section 2(b)(1)].

In fulfilling that intent, EPA has two primary goals: (1) to require testing of selected high priority chemicals to determine reliably whether or not such substances pose an unreasonable risk to health or the environment; and (2) to make such testing requirements as efficient and cost effective as possible.

To achieve this latter goal, EPA is pursuing several avenues. For example, the Agency is carefully reviewing the massive volume of comments on the proposed generic test standards to determine, among other things, whether any changes in the standards could eliminate any unnecessary specificity that may increase the cost of the test or the demand for trained personnel. Along the same lines, EPA will modify the generic test standards if necessary to make them suited to the particular chemical(s) contained in a Section 4 test rule. Thus, the standards for testing which the Agency adopts should be both scientifically sound and not unnecessarily costly.

EPA and other research institutions such as the Department of Health and Human Services' National Toxicology Program are also taking steps to stimulate the development of new and improved test methods. Such methods would ideally improve upon the scientific predictive power of current tests and lead to more cost-effective testing. For example, as sound hazard identification screening tests become available, EPA intends to prescribe sequential approaches to testing. Ideally, such a sequential approach would utilize the results of less expensive tests as screening aids to set priorities more knowledgeably and to reduce the need for conducting more expensive detailed tests.

Given the cost of testing and the limited testing resources available, EPA seeks to employ Section 4 testing requirements such that the maximum

amount of public health and environmental benefit can be achieved per unit of testing resource used. An example of this is EPA's intention, whenever it is scientifically appropriate, to limit the number of members within a designated chemical group that will be subject to Section 4 testing requirements. One way of accomplishing this is to sample structure-based category members based on the possibility that testing of a small number of category members can characterize the entire category. When this approach is possible, the testing resources saved will be available to evaluate a greater range of different chemicals.

Another approach, requiring testing for one effect at a time rather than one rule requiring concurrent testing for several effects, was considered as a means of saving testing resources. EPA has rejected this approach for two reasons. First, the length of time it would require to characterize potentially hazardous substances would likely lead to long delays in action to control exposure to such substances. EPA currently estimates that 4 1/4 years will be required to characterize the chlorinated benzenes for all effects for which testing is being proposed. Performing this testing in a sequence rather than concurrently would at a minimum require 9 years. Second, EPA believes that individual rulemaking would be required for each effect under this approach. Individual rulemaking for each effect would be a further resource burden for EPA and industry and would likely add an additional four years to complete the full test sequence making the total time 13 years.

B. Section 4(a)(1)(A) Findings

This discussion explains EPA's approach to each of the findings EPA must make before requiring testing under Section 4(a)(1)(A). Although this discussion is presented specifically in the context of health effects, the same principles apply to environmental effects as well. This discussion is not intended to address environmental effects since test for these effects are not included in today's rule.

1. "May present an unreasonable risk". As noted in Section I.A. of this preamble, one of the findings that the Administrator must make under Section 4(a)(1)(A) is that one or more activities involving a given chemical may present an unreasonable risk of injury to human health or the environment. This involves consideration of several factors; namely, that the chemical (1) may present a hazard, (2) may present a risk, and (3) may present an unreasonable risk. The

distinctions between these concepts as well as EPA's approach, are described below.

(a) May present a hazard. EPA considers a variety of factors to be suggestive of the potential health effects or hazard of a substance. Sometimes, evidence of one effect suggests that another effect may occur. One common example of this is mutagenic activity, which is considered to be suggestive of oncogenic (carcinogenic) effects (e.g., results demonstrating a chemical's ability to produce mutations in bacteria (Ames test) are considered relevant to a consideration of oncogenic potential). Knowledge of a chemical's physical and chemical properties is also very helpful; these properties can indicate, for example, whether a chemical is likely to be excreted from the body or accumulate in fat tissue, causing long term effects. Another major clue is whether the chemical is structurally related to another chemical with known adverse health effects. Evidence of potential hazard may also be suggested by previous tests which resulted in inconclusive or unreliable results. Further, anecdotal and clinical reports of injury, may indicate that particular kinds of hazards may exist.

For most of these factors, and others not mentioned, EPA's conclusion that the chemical may present a hazard will not be based on definitive scientific data. This is inevitable; if EPA knew in detail the types of hazards a chemical posed, there would be no need to test. Thus, determinations of hazard potential under Section 4 by their very nature must involve reasonable scientific assumptions, extrapolations, and interpolations.

(b) May present a risk. EPA uses the term "risk" to include both hazard and exposure potential. The hazard potential of a chemical is only part of the risk equation. Because toxicity is of little concern to EPA if there is no human exposure to the chemical, EPA looks at both toxicity and exposure in determining whether to test or regulate chemicals. There is usually an inverse relationship between hazard and exposure—the more severe the potential hazard, the less exposure that is necessary to conclude that there is a potentially serious risk, and vice versa.

While there is a need to show a potential for exposure in order to make a Section 4(a)(1)(A) finding, the exposure threshold is much lower than that under Section 4(a)(1)(B). This is because the former (may present an unreasonable risk) finding was intended to focus on those instances where EPA has a scientific basis for suspecting potential toxicity and reflects that the

potential for risk to humans may be significant even when the potential for exposure seems small as, for example, when the chemical is discovered to be hazardous at very low levels. In contrast, the 4(a)(1)(B) finding was intended to allow EPA to require testing, not because of suspicions about the chemical's safety, but because there may be substantial or significant human exposure to a chemical whose hazards have not been explored.

To make the "may present a risk" finding as part of a "may present an unreasonable risk" finding under Section 4(a)(1)(A), it is sufficient for the Agency to show that there is a reasonable likelihood that exposure may arise because of activities associated with the manufacturing, processing, distribution, use or disposal of the chemical. If evidence establishing that exposure actually has occurred were available, such information would be of obvious importance to the Agency in determining whether to require testing. (EPA's methodological approach to exposure assessment is set forth in detail in the Exposure Support Document.) However, monitoring or other specific exposure information will be unavailable in many cases and, therefore, the Agency will be compelled to rely upon reasonable conclusions about exposure potential.

(c.) May present an unreasonable risk. When it is found that a chemical "may present a risk," it is necessary that some consideration be made of the likelihood that the risk be unreasonable in order to require testing under Section 4(a)(1)(A). The term "unreasonable risk" is not defined in the statute. Congress specifically decided against defining "unreasonable risk," despite recommendations that it do so. Some guidance for making an unreasonable risk determination can be found in the House Report, however, which states that the determination of unreasonable risk is a judgement which involves balancing the severity of harm and the probability that the harm will occur against the effects of the proposed regulatory action on the availability of the benefits of the chemical. The report also states that the balancing process does not include a formal cost-benefit analysis and may reflect that a risk may be judged to be unreasonable if caused by a "lesser probability of greater harm" or "greater probability of lesser harm." [H. Rept. No. 94-1341, 94th Cong., 2nd. Sess., 7/14/76, at 13-14 Legis. Hist. 421-22.]

Thus, it can be concluded from both the legislative history and the use of the term in the statute that "unreasonable

risk" is not an inherent quality of a specific substance but is dependent upon a number of factors which must be considered in the context of a specific regulatory action.

It is clear that the Congress intended the test for unreasonable risk under Section 4 be much less stringent than under Section 6. [H. Rept. No. 94-1341, 94th Cong., 2d Sess., 7/14/76, at 14-15, Legis. Hist. 422-23.] Congress required only that EPA determine that a chemical "may present an unreasonable risk" under Section 4, not that the substance does pose an unreasonable risk, which is the requirement under Section 6 where a chemical is to be regulated. An unreasonable risk determination for purposes of Section 4 arises from an analysis that differs from such an analysis under Section 6. In large part, this is because a test rule will not ordinarily deprive the public of the benefits of the chemical subject to the rule. Unlike Section 6 rules which could prohibit the manufacture and processing of the chemical, the economic impact of test rules is generally limited to the costs of testing.

The fact that EPA could not know the nature and extent of any risk before the testing is performed to determine the hazard of the chemical means that EPA could not in any case determine in advance what kind of regulatory options it would pursue. Such considerations are routinely discussed when EPA develops rules under Section 6, but in issuing test rules the Agency will not attempt to hypothesize the many control measures that might eventually be taken to reduce the risk of the tested substance if testing revealed that the substance posed an unreasonable risk. Because there are a large number of control options available with respect to nearly any substance and because the degree of risk shown by testing would affect the choice of control options, anticipating which ones would be adopted would be speculative. Under TSCA alone, there are a wide variety of regulatory options ranging from prohibition or restriction of the manufacturing, distribution, use or disposal of the product, to labeling, recordkeeping and reporting requirements. Authorities exercised by EPA other than TSCA as well as authorities exercised by other agencies such as OSHA could also be used and voluntary reduction or elimination of the risk could be undertaken by industry.

Therefore, EPA proposes to pursue the following policy for purposes of Section 4(a)(1)(A). If there is substantial evidence that exposure to a chemical may lead to a serious health effect or

increase in mortality and that people may be exposed to the chemical, EPA will presume that the activities in question (manufacturing, processing, using, transporting, disposing) "may present an unreasonable risk" unless the rule is likely to result in a significant loss to society of the benefits of the substance. In the latter instances, if EPA's analysis shows that the costs of testing may cause manufacturers or processors to cease or severely restrict their commercial activities, EPA will weigh this potential adverse impact against the benefits of testing before presuming that the chemical may present an unreasonable risk. Whether this balancing is necessary will depend upon the economic impact of each rule. Because no such adverse impact is likely from this first rule, this area is not explored in depth.

A consequence of this policy is that EPA has considerable flexibility in making the exposure finding to support testing under Section 4(a)(1)(A). Thus, when serious effects such as oncogenicity, cardiovascular damage, teratogenicity, mutagenicity, or neurotoxicity are suspected, the exposure information on which EPA will base its findings may be quite limited. This flexibility seems well founded since, if the testing reveals a serious hazard, some restrictions undoubtedly would be considered appropriate to reduce the risk when weighed against the alternative of doing nothing. Of course, economic, technological, and other considerations would influence the degree to which the risk could be reduced or eliminated. Even if there were an extraordinary case where no control options existed at present, the knowledge that people were exposed to a very hazardous chemical may create a substantial incentive to develop substitute products and processes.

2. Insufficiency of data. Whether EPA makes a risk-based [Section 4(a)(1)(A)(i)] or exposure-based [Section 4(a)(1)(B)(i)] finding in deciding whether to test, EPA must also find that there are insufficient data and experience upon which the effects of the chemical on health or the environment can reasonably be determined or predicted. This requirement was intended to assure that EPA would not demand unnecessary or duplicative testing. [See, e.g., H. REP. NO. 94-1341, 94th Cong., 2d Sess. (1976)].

EPA has taken several steps to ensure that the Agency does not require duplicative data from the proposed test rules. The Agency has sent a letter to all EPA offices and other Federal Agencies which requests information on the

chemicals recommended to the Agency by the Interagency Testing Committee. A copy of this letter and the responses received by the Agency are available in the Public Record. The Agency has also pursued testing information on these chemicals through the National Toxicology Program whose Executive Committee includes representatives from other Federal Agencies. In order to further minimize the likelihood of requiring duplicative testing, the Agency intends to continue to seek out information which might affect final testing requirements after test rules have been proposed. In this context, the Agency has proposed (44 FR 77470 Dec. 31, 1979) a rule under Section 8(d) which will require the submission of any unpublished health and safety studies on chemicals recommended by the ITC.

In the main, however, EPA's current approach to making this second finding has been to review the literature to see whether studies have been done for the effects under consideration. EPA has critically evaluated the design, execution and results of each relevant study to determine whether the study alone, or in combination with others, provides sufficient data to assess the chemical's hazards; that is, does the available information provide the basis for defining the hazard component of a decision whether the chemical does or does not present an unreasonable risk? Much of this analysis has been done in conjunction with the determination that the chemical may present an unreasonable risk since the combined effect of the Section 4(a)(1)(A)(i) and 4(a)(1)(A)(ii) findings is the determination that existing information is sufficient to raise the question of potential risk but insufficient to resolve it.

EPA recognizes that many existing studies do not provide the degree of accuracy or the amount of information that EPA would like. EPA does not require that existing studies meet current EPA test standards in order to be accepted as sufficient. In deciding whether it is necessary to seek further testing for effects for which some data exist, EPA has considered such factors as the benefits of obtaining more data and greater certainty, the likelihood that additional testing would resolve any uncertainties, the cost and economic impact of new testing, the nature of the effects of concern, and competing testing priorities for other chemicals about which even less is known. When EPA does conclude that the data are insufficient and more testing is needed, it may be because the studies that have been completed have resulted in

equivocal results, or because the existing studies, whether of good or bad quality, do not furnish enough information for EPA to judge the magnitude of risk to people who are or may be exposed to the chemical or to estimate a level below which the risk can be reduced to a reasonable level. Thus, EPA may determine that testing is necessary to obtain additional data on dose-response relationships, on different animal species, or for some other similar reason. At the same time it is proposing testing, EPA may pursue interim regulatory measures in appropriate instances if the existing information indicates a risk significant enough to justify that course while additional data are being developed. The decision about when to seek a more complete data base necessarily will be determined by the facts pertaining to the particular chemical under consideration.

One final consideration to note is that EPA recognizes that the burden of proof to demonstrate that a chemical has no effect is greater than that to demonstrate that there is an effect. Therefore, EPA pays particularly close attention to the possibility of "false negative" results. "False negative" is a statistical concept used to describe instances in which it is wrongly concluded that a chemical does not cause an adverse effect. This can happen where a test is designed or conducted in such a way as to preclude its detecting toxic effects occurring at levels that might be significant in terms of human exposure. For instance, in a test where a chemical is fed to 50 animals, and a 5 percent significance level is used to judge the results, if the chemical is one which causes cancer at the dose administered in only 10 percent of the animals, there is somewhat more than a 50 percent probability that the test results will not reveal that the chemical causes cancer. (The significance level of a test is also the probability of a false positive, an instance where it is wrongly concluded that the chemical does cause an adverse effect.) Thus, the absence of observed effects in such a study could not be relied upon to support the conclusion that the chemical is not harmful. Were the sensitivity of the test (ability to detect effects) improved (for example, by increasing the number of animals) more confidence could be attributed to the negative results. Thus, it is very important that EPA carefully assess negative findings before concluding that the existing data are sufficient and further testing is unnecessary.

3. *Necessity for testing.* Before the Administrator may issue a final test rule under TSCA Section 4(a)(1)(A), he must

find that the testing that will be required "is necessary to develop such data," that is, that the testing ordered needs to be undertaken, and if undertaken will provide data relevant to a determination as to whether activities involving the chemical present an unreasonable risk of injury to health or the environment.

The first aspect of this finding will largely flow from the previous determinations that there are insufficient data and experience to reliably determine or predict the chemical's effects and that there is a basis for concern as to the possibility of such risks. In addition, the Agency must take into consideration ongoing testing of a chemical in determining whether additional testing should be required. In order to do that, EPA has examined the protocol and any interim data results of each relevant ongoing study known to the Agency to decide whether the study is likely to produce data which would obviate the need for further testing. The same considerations used by the Agency in evaluating whether there are sufficient data and experience to assess the chemical have been used to evaluate the adequacy of ongoing testing. Where EPA has been able to conclude that the ongoing study is likely to meet its needs, there is no need to require additional testing. However, if the final data ultimately generated by the ongoing study do not allow EPA to carry out a reliable risk assessment, EPA at that time will reconsider its decision not to propose a rule. Where EPA's review of an ongoing study indicates that serious defects in the design or execution of the study already exist that are likely to prevent an adequate assessment of the risk upon receipt of the final data, EPA may require additional testing immediately.

There are alternatives to this approach. EPA could, on the grounds that there was no assurance satisfactory data would be produced, disregard tests currently being performed in deciding whether to require testing. EPA has rejected this course since it could lead to a significant and unnecessary misallocation of resources. Alternatively, EPA could automatically defer a decision about whether to require testing until after data have been submitted from the ongoing study. This option has also been rejected; defects in the ongoing test may be immediately apparent so that reliance on it could unjustifiably delay the development of reliable data for many years, to the detriment of the public health.

After concluding that there is a need to develop data, EPA must also evaluate whether testing is capable of developing

the necessary information. Even if the Agency finds that a chemical may pose a risk from a particular effect, and that there are insufficient data and experience, EPA cannot order a chemical to be tested if no testing methodology exists which would lead to the production of the necessary data. Similarly, when EPA cannot find a suitable cohort for an epidemiology study it is unable to require such testing. The publication of a test standard for a particular effect constitutes EPA's finding that tests conducted according to that standard are capable of providing the needed data. Although EPA has not chosen to do so in this rule, in future rules, EPA may propose testing for effects for which standards are not yet proposed and reopen the comment period on the test rule, if necessary, to provide adequate opportunity for comment after proposal of the test standards. EPA also may adopt a standard for a particular chemical without addressing the broader question of its application as a "generic" test standard. Finally, in addition to its own efforts to develop test standards, EPA may initiate or recommend to other groups the initiation of research aimed at developing the information or methodologies whose lack currently precludes testing.

C. Choice of Test Material

In determining what chemical form to prescribe for testing, EPA will employ a case-by-case approach.

EPA wishes chemicals to be tested that are representative of a broad range of products which contain the chemicals and their exposure situations. To test separately the thousands of individual products containing a commercial chemical would be prohibitively costly, time-consuming, and unnecessary. Generally, for regulatory purposes, data on one commercial grade of a chemical are considered representative of the toxicological properties of other grades of the chemical.

In specific cases, however, EPA may wish to have a purer than commercial grade tested. Examples of such situations are, first, when a contaminant or impurity in the commercial products also is suspected of causing the toxicological effect of concern and is likely to interfere significantly with the ability of the test to determine whether the primary component alone causes the effect. A second case involves those circumstances in which the Agency wishes to test only a few members of a chemical group and extrapolate the results to other members of the group. In this instance, a purer form of the test chemicals could result in fewer

confounding factors when extrapolating in structure-activity analysis.

D. Use of Categories

Section 26(c) of TSCA states that:

Any action authorized or required to be taken by the Administrator under any provision of this Act with respect to chemical substance or mixture may be taken by the Administrator in accordance with that provision with respect to a category of chemical substances or mixtures.

Chemicals may be classified as a category in any way "suitable" as such for purposes of this Act" except that chemicals may not be grouped together as a category solely on the basis of their being new chemicals [TSCA § 26(c)].

Thus, the Agency may use the authority granted in Section 26, in conjunction with the provisions of Section 4, to require the testing of chemical categories by the manufacturers and/or processors of the chemicals in that category. Categories may be closed (containing a finite number of chemicals) or open (containing a potentially infinite number of chemicals). Closed and open categories may contain both "new" and "existing" chemicals. "Existing" chemicals are those on the chemical inventory developed under Section 8(b) of the Act; "new" chemicals are not on the inventory and the Agency must be notified under Section 5 at least ninety days before they are to be manufactured commercially.

There are various types of appropriate groupings that could constitute a category under TSCA. For example, categories may be structurally based, or may be based on exposure considerations or usage patterns. Because the category contained in this test rule (the chlorinated benzenes) is a structurally-based one, this discussion is focused on treatment of such categories. Because this category is a closed one, all of whose members appear on the TSCA Inventory, the relationship of the Section 4 testing requirements to the Section 5 requirements for new chemicals falling within a category under a Section 4 test rule is not explored in this discussion.

The three findings that EPA must make under Section 4(a)(1)(A) were discussed in Section III.B. They relate to (i) potential unreasonable risk, (ii) insufficiency of data, and (iii) a need to test to generate data. These findings could be made on an individual chemical basis or a category basis. EPA believes the Section 4(a)(1)(A) findings can be made for the entire category (generic finding) rather than for each specific category member (chemical-specific finding). The basis of this view

is the language of Section 26(c) which states that "any action * * * required to be taken * * * with respect to an individual substance * * * may be taken with respect to a category of substances * * *".

In the case of a structure based category, the structural features that are presumed to give rise to a hazard that leads to the potential risk are generally a characteristic for category membership. Such categories satisfy the Section 4(a)(1)(A) criteria if there is also potential exposure to the members of the category and if there are insufficient data to evaluate the category.

In making the Section 4(a)(1)(A)(i) part of the findings EPA recognizes that production and exposure among members of a chemical family will vary; some may be produced in small quantities or appear only as by-products, while others may be produced in millions of pounds per year. All members may be of concern however. By-products, for example, which are not commercially produced may nevertheless result in significant exposure if they remain in commercial chemicals as impurities or if they are separated and not properly disposed of. Other substances may not be produced currently but could well serve as substitutes for those chemicals now in commercial production. EPA will consider these kinds of factors when proposing a category definition and will exclude a chemical from the requirements of the final rule if data are provided during the public comment period which indicate that a chemical included in a proposed category does not meet Section 4(a)(1)(A)(i) criteria.

EPA plans to make the Section 4(a)(1)(A)(ii) finding on a category basis as well. EPA recognizes that there may be sufficient data on certain effects for some members of the category, and that, consequently, under such circumstances it may be unfair to require all manufacturers and/or processors of chemicals in the category to bear equal responsibility for testing the representative sample. However, EPA believes that questions of financial responsibility are best resolved in reimbursement proceedings and do not affect the Section 4(a) findings; however, EPA would exclude from the Section 4(a) category those individual chemicals for which there were sufficient data on all effects.

The last finding (Section 4(a)(1)(A)(iii)), requires EPA to conclude that testing is necessary to develop the missing data. In the case of a structure-based category, EPA believes that testing of each member is not necessary to achieve that end if a representative

sample can be selected that will enable EPA to evaluate the whole category.

It is important to note that in many cases other categories besides the one chosen by EPA may be capable of definition. For instance, EPA may choose to limit the category definition so as not to include all chemicals that have in common a particular characteristic which could permit them to be grouped together. Such factors as the amount of time necessary to analyze data relating to a category may influence the Agency's decision as to how broadly the category should be defined, even if the category could be more broadly defined using the same or similar factors for delineating category membership.

As discussed in Section III.A. of this document, for policy reasons EPA generally will seek ways to avoid requiring full-scale testing on all members of a structure-based category. Scientifically, testing all members of the category would provide the most information about the category. However, EPA's approach of requiring testing of only some members of a structurally-based category:

(a) Avoids overloading test facilities and personnel with testing relating to only one category, thereby allowing testing for significantly more chemical substances or categories;

(b) Reduces the potentially adverse economic effects of concentrating testing requirements on a small segment of industry, an impact which might result from requiring testing on all category members;

(c) If a proper sampling approach is taken, (1) may permit reasonable scientific extrapolation based on the data received, enabling assessment and, where appropriate, regulation of the category (or appropriate subsets) without the necessity for conducting full-scale testing on all of its members, and (2) should provide guidance on which additional chemicals should be tested if it is concluded that further testing is needed.

EPA has carefully considered various approaches which it might utilize to sample structurally-based categories. From an economic and regulatory support standpoint, production volume alone could serve as a useful single factor for determining which substances should be tested. All substances within the category produced in excess of some arbitrary amount (such as one million pounds) could be tested. This would generally serve to produce information on the individual chemicals for which the economic impact of testing would be lowest and, to the extent that production volume correlates with exposure, the

potential for subsequent regulation the highest.

On the other hand, from the scientific standpoint of characterizing the effects of the category as a whole, sampling based solely on production volume may produce a biased sample. The scientific goal should be to select a sample that would provide the most information about the entire category. Furthermore, it is also more economical to get the most information per testing dollar spent, a goal that can best be achieved by careful sample selection.

Other variables could be factored into a sampling decision. The use of the substances, particularly as it affects exposure, might be taken into consideration. Market economic factors could also be considered. For example, it might be considered preferable to test a lower volume chemical with a relatively inelastic demand curve (i.e., even a large rise in price would only cause a small drop in demand) than a high production chemical with an extremely elastic demand curve (i.e., a small increase in price would cause a huge drop in demand).

When EPA analyzed this issue, it did so keeping in mind the ultimate planned use of the data derived from test rules, i.e., support of risk assessment. EPA has decided for policy reasons that the primary goal of testing a structure-based category should be to develop data that will allow the Agency to make regulatory or unreasonable risk decisions concerning the category as a category, rather than making such decisions for the individual category members as individual chemicals. The Agency, therefore, has adopted as its preferred approach under Section 4 of TSCA one whose goal is to develop data that are likely to be capable of extrapolation to all category members or to an appropriate subset, and to enable EPA or other regulatory agency to take control action without testing each category member.

The action which EPA takes on a structure-based category as a result of data obtained on the test sample will vary depending on the nature of the test data. If, for example, all members of the test sample produce negative results on the required tests, no further testing of the untested category members would generally be required. If all members of the test sample produce a consistent pattern of positive results on the required tests, the category as a whole will be assessed for regulatory action on the basis of these results. In this case, EPA does not anticipate requiring further testing. The situation becomes more complex when the test data in the sample show mixed results. In this case,

EPA will assess the aggregate test results to see what further action should be taken.

The importance of extrapolation of data from a tested sample does not mean that factors such as production volume and exposure are irrelevant in the selection of a test sample. EPA must ensure that adequate data are generated to support possible regulatory action against those chemicals that pose the greatest risk within a given structural category, which are likely to be those chemicals with the highest exposure potential. Thus, EPA will balance the need to characterize the entire category with the need to have a solid data base on the highest production and/or exposure members.

While EPA favors an approach based upon a sampling of category members, there will undoubtedly be situations where limited testing on all category members (e.g., acute toxicity, metabolism, or short-term mutagenicity screens), might be required in order to help further delineate the category for ultimate assessment purposes. In addition, metabolism and related testing may be warranted in some cases to provide an additional empirical basis for relating the results for tested chemicals to untested members of the group. The decision as to when to utilize such an approach cannot be made as a matter of generic policy, but must be made on an *ad hoc* basis. The factors relevant to these determinations include the number of members in the category, the closeness of the structural relationship among category members, the currently available information on category members, and the availability, suitability and cost of such tests.

In addition to the considerations described above, a central element of EPA's approach to structure based categories is the relationship between the selection of the test sample, the Section 4(a) findings, and exemptions and reimbursement. These factors are closely linked so that the approach to one affects the approach to the others. EPA is proposing one approach and considering two alternative approaches to testing, exemptions and reimbursement in conjunction with categories under TSCA Section 4. EPA may adopt any one of these in the final rule.

The proposed approach has been selected as most compatible with EPA's goal of characterizing an entire category on the basis of test results from a sample of category members. In this approach manufacturers and processors of members of the category would not be responsible for testing the individual compounds which they manufacture or

process but would be jointly responsible instead for testing a sample which EPA has selected as representative of the category. To illustrate this concept, if there were a category of seven compounds (1,2,3,4,5,6,7) which EPA believes could be adequately characterized by testing only four of the seven compounds, EPA would require that all manufacturers and processors of the seven chemicals bear equal responsibility for testing compounds 1,3,5 and 7. The Section 4(a) statutory finding would be made for the entire category.

Equivalence of the sample and other category members would be assumed by EPA in proposing such test rule. This equivalence would not be on a one-to-one basis as it is for individual chemicals, such as where the manufacturers of chemical 1 assert equivalency based on the data developed on chemical 2. Rather, the sample as a whole would be considered representative of the category on the hypothesis that test results on the sample can be used to evaluate the chemicals which comprise the category. Equivalency may not exist between individual members of the category but the sample would be expected to provide sufficient data to evaluate the category as a whole.

This "whole category" approach to testing does not discriminate between manufacturers and processors whose chemicals are tested and those whose chemicals are not. Unlike Alternative 1 discussed below, the responsibility for actually funding testing falls equally on both during the course of the testing. Industry could respond to such a test rule by dividing the testing among themselves. Each firm would then apply for an exemption for those portions of the testing which it did not perform and reimburse the sponsors of such tests. A second and probably preferable response would be to form a consortium for joint sponsorship of testing.

This approach is perhaps the best alternative when the hypothesis that the category can be characterized by the sample holds. However, if this hypothesis does not hold, this approach may present considerable administrative difficulties. If chemicals 1,3,5, and 7 do not give results that could be extrapolated to chemicals 2,4, and 6, manufacturers and processors of chemicals 2,4, and 6 most likely would be reluctant to share the cost of testing chemicals 1,3,5, and 7. However, to permit or require a refund to manufacturers and processors of 2,4, and 6, EPA would have to require manufacturers and processors of 1,3,5,

and 7 to reimburse the manufacturers and processors of 2, 4, and 6 for the money they already received. As a consequence, the costs to manufacturers and processors of 1, 3, 5 and 7 would be higher than they had originally anticipated.

EPA would also have to decide whether to require testing of any or all untested category members. If the category no longer held together from the standpoint of health or environmental effects, EPA most likely would amend the rule to treat category members as individual chemicals for purposes of both existing and new testing requirements under Section 4(a), exemptions, and reimbursement.

An alternative approach (Alternative 1) would require testing of all category members but would specify that such testing be done in two or more stages with the chemicals selected for the sample designated for testing in first stage. In this alternative, each manufacturer or processor of a chemical in the sample is responsible for testing his own chemical. The Section 4(a) findings would again be made for the entire category. And, as in the proposed approach, the criteria for sampling would be based primarily on the potential that the designated would be structurally representative of the whole category. The category members not in the sample would be tested in the subsequent stages if the test results from the first stage could not be used to characterize the remaining category members. EPA would write the test rule in such a way that the requirement to conduct the second stage of testing would take effect automatically a specified number of months after the data from the first group were received. At this point, manufacturers and processors of the untested members of the category would obtain exemptions and reimburse those who conducted the first round of tests, or, if the data could not be extrapolated to the untested members, conduct their own testing.

To illustrate, if there were seven members in the category, and the first sample consisted of chemicals 1, 3, 5 and 7, producers of chemical 1 would pay for the testing of chemical 1, producers of chemical 3 for 3 and so forth. If the data from those tests were then used as a basis for granting exemptions to chemicals 2, 4, and 6, producers of 1, 3, 5 and 7 would be partially reimbursed for their costs at that time. Reimbursement would be based on sharing of all costs among the manufacturers and processors of all chemicals.

This approach simplifies the reimbursement process by avoiding the redistribution of funds that would be

provided for in the proposed approach if the category were not characterized by the test sample. However, there are disadvantages to this approach as well. First, this approach does not accurately express EPA's intentions with respect to testing categories in a majority of circumstances. EPA does not generally intend to test all members of a category, even when the category is not characterized by the test sample, because EPA believes the public is better served by testing a wider range of chemicals than exhaustively characterizing a number of closely related substances. Second, this approach is inapplicable to large or open-ended categories. EPA could not actually require testing of all members in such categories due to the immense resources required. (Open categories are potentially infinite in size even though the number of known category members is finite.) Finally, the simpler reimbursement that this option offers results in a disadvantage to those manufacturers and processors who are required to test in the first stage because they receive no reimbursement from the other manufacturers and processors in the category until the end of testing. On the other hand, persons sponsoring the initial testing do not have an automatic entitlement to reimbursement; they are responsible for testing their own chemicals and receive reimbursement from producers of chemicals 2, 4, and 6, only if the data described from the first stage prove to be relevant to 2, 4, and 6.

A variant that would avoid the latter problem would be to require testing of chemicals 1 through 7 in a single stage with each manufacturer or processor responsible for testing his own chemical, but to grant conditional exemptions to producers of chemicals 2, 4, and 6 that could be revoked if the data from 1, 3, 5, and 7 could not be extrapolated to 2, 4, and 6. Persons would be required to provide reimbursement on the basis of the conditional exemption. However, if the data from 1, 3, 5, and 7 could not be used to characterize 2, 4, and 6, this variant would entail the same administrative problems concerning reallocation of money as the approach EPA is proposing.

Alternative 2 to testing categories lies at the other end of the spectrum from the proposed approach. In this approach the chemicals may be analyzed as a category for determining potential hazard or risk, but are tested as individual chemicals. The Section 4(a)(1)(A) findings are made only for the chemicals to be tested.

Using this approach, if EPA believed that laboratory or economic resources

should not be expended on testing the whole category, EPA would again choose a smaller number of chemicals to be tested. However, the emphasis in choosing them would be on those likely to pose the greatest risk, and not on the chemicals that were most likely to provide data representative of the category. Primary emphasis would be given to testing the chemicals suspected of the highest toxicity or produced in the greatest quantities or resulting in the most exposure. However, consideration of structural representation of the category would influence the sample, particularly if there were a choice between testing two of the most high-exposure (risk) chemicals and one was considered to be more representative of the category.

If chemicals 1, 3, 5, and 7 were the ones selected for testing, only manufacturers and processors of those chemicals would be subjected to the rule and required to test. Manufacturers and processors of 1 would share the cost of testing only 1. While persons producing chemicals 2, 4, and 6 would not be required to test or reimburse producers of chemicals 1, 3, 5, 7, this would be chosen for testing primarily or solely on their own merit, and not as a representative sample of 1, 2, 3, 4, 5, 6, and 7. While the data produced from chemicals 1, 3, 5, and 7 may be relevant to evaluating 2, 4, 6 and would be evaluated in that light as well, the operating presumption would be that 1, 3, 5, and 7 would be tested as individuals, and that any additional benefit to be gained from them as "representatives" would be useful but not central to their selection for testing.

An advantage of this approach is its administrative simplicity. Further, it would assure that those chemicals which warrant the most concern are tested. A disadvantage is that less information may be gained about the category as a whole because of the deemphasis on choosing a sample that would be "representative." The emphasis on testing individuals would likely make it harder to have an effective link between section 4 and the premanufacturing notification requirements of section 5 of TSCA, although EPA could pursue such options as defining criteria specifying when other existing or new chemicals in the chemical group would be tested.

In conclusion, there are clearly many factors that will bear upon the selection of the final approach. Among the most important considerations will be the following: (1) how the section 4 findings, the category definition, and the choice of test substance interact, (2) how to

maximize the amount of information obtained for the lowest cost, (3) concern for financial equity: who pays for the testing and at what point in time, (4) how to minimize the administrative problems of reallocating money, and whether the rule will need to be amended if exemptions are revoked or if money is to be reallocated, and (5) the degree to which a sample may be representative of the category.

Certain provisions could be implemented with any approach to address potential inequities or other problems. For instance, a provision could be attached to the proposed option to limit a manufacturer's or a processor's testing costs so that he would pay no more than the amount that would be paid if testing were required on an individual chemical basis. This could be addressed in the reimbursement rule.

EPA is requesting comments on each of these alternatives.

E. Responsibility for Testing

As discussed in Section I.E. of this preamble, Section 4(b)(3)(B) of TSCA requires that EPA designate which activity in the life cycle of the chemical gives rise to the exposure that forms the basis of the Section 4(a)(1)(A) or Section 4(a)(1)(B) finding. However, if the exposure may result from both manufacturing and processing activities, findings concerning potential exposure from the chemical's distribution in commerce, use, and/or disposal may, for practical purposes, be irrelevant under Section 1(b)(3)(B). This is because the conclusion that distribution, use, or disposal may or may not result in exposure does not affect a manufacturer's or processor's responsibility to test if it is already required to do so because of exposure arising from its own manufacturing or processing activities. However, if the exposure potential arises from activities further downstream, findings concerning distribution, use and disposal will be important.

EPA will utilize the same approach to exposure for purposes of Section 4(b)(3)(B) as it does for assessing exposure potential for the purpose of making Section 4(a)(1) findings. As in the case where findings are made under Section 4(a)(1)(A), if EPA has information showing actual exposure, the Agency will use it; but if such data are unavailable, EPA will utilize the data that exist to make reasonable deductions concerning exposure potential. (See Support Document on Exposure.)

In most cases, EPA expects that other activities besides manufacturing may

present exposure opportunities and, therefore, an exposure risk, so that processors will usually be required to test along with manufacturers. This may present practical problems, however, because the statutory definition of processing is quite broad. Section 3(11) of TSCA defines a processor as "any person who processes a chemical substance or mixture." The term "process" is in turn defined in Section 3(10) to mean

The preparation of a chemical substance or mixture, after its manufacture, for distribution in commerce—

(A) In the same form or physical state as, or in a different form or physical state from, that in which it was received by the person so preparing such substance or mixture, or

(B) As part of an article containing the chemical substance or mixture.

("Processor" means any person who processes a chemical substance or mixture.) It should be noted that the term "processor" under TSCA has a much broader meaning than the common or industry's meaning. The following examples illustrate activities that would cause a person to be considered a processor under TSCA.

Example 1. A person reacts chemicals X and Y to produce a new chemical substance, Z. This person is a processor of X and Y and a manufacturer of Z. This example is closest to industry's meaning of the term.

Example 2. A person who purchases or manufactures chemicals and then mixes or reacts them is a processor of each chemical if the mixtures or compounds are distributed in commerce. Processors that fall within this example include producers of paints, automotive products (e.g., antifreeze, oil additives, etc.) and specialty cleaners and floor wax preparations. This example covers a large segment of the processor class.

Example 3. A person who heats and mixes powdered resins, fillers, pigments, and plasticizers to form a homogeneous mix which is then formed into sheets of a desired thickness would be a processor of each component because the components are distributed in commerce as part of an article. Tire manufacturers and producers of rubber and plastic articles would fall within this example. Processors in this example are similar to those in example 2, except that the products that are distributed in commerce are articles rather than chemicals.

Example 4. A person who purchases steel cans and then coats the cans with a resin would be a processor of the resin, since the resin is now a part of an article which is distributed in commerce.

Similarly, a person who purchases printing ink and then applies the ink to paper or boxes would be a processor of the ink which has become a part of an article. Also tanneries and textile mills would be processors of the dyes used to color the leather and fabric. Persons in these examples add chemicals to previously produced articles.

The above examples are not meant to be inclusive. They are only provided to illustrate the breadth of the TSCA definition of processor and assist persons in determining whether their activities fall within the TSCA meaning of "process". The 1977 Census of Manufacturers indicates that there are approximately 11,000 establishments in Standard Industrial Classification (SIC) 28, Chemicals and Allied Products. Examples 1 and 2 would fall within SIC 28. Processors in example 3 are in SIC 30 Rubber and Miscellaneous Plastic Products, and number approximately 12,000 establishments. The types of processors in example 4 are in SIC 27 Printing and Publishing, SIC 228 Textile Finishing SIC 3111 Leather Tanning and Finishing, and SIC 3479 Metal Coating and Allied Services, and account for approximately 45,000 establishments.

The Agency is concerned that, if all processors covered by the Act were subject to a test rule, there would be difficulties experienced by both EPA and the industry in administering the exemption and reimbursement provisions of TSCA Section 4. Consequently, EPA has examined various alternatives for exempting certain kinds of processors from all test rules or specific ones. Examples of them are (1) excluding some processors from coverage on the basis that their principal activity is not of a nature that has traditionally been considered processing within the chemical industry, (2) restricting coverage of the rule to members of the chemical industry, e.g. SIC 28., (3) excluding processors who incorporate the substance or mixture into an article of commerce, (4) excluding all processors downstream of the point at which the subject chemical is reacted or formulated into a substance or mixture with a new identity, and (5) excluding those processors who are small businesses.

Each of these has substantial advantages and disadvantages, and EPA does not attempt to resolve them in this proposal. At a public meeting on September 25, 1979, and in subsequent conversations, members of the chemical industry expressed an interest in deciding how to allocate costs and testing responsibilities most fairly. Although the comments recently

submitted by the Chemical Manufacturers' Association on the advance notice of proposed rulemaking on data reimbursement deal with this question they do not offer a solution to the problem of who is subject to the rule. EPA is requesting comments on the approach which it should take under Section 4 with respect to processors, including comments on the five alternatives listed above and any other approaches which would limit the applicability of Section 4 test rules, yet be equitable and provide flexibility.

F. Reporting Requirements and Deadlines

In the proposed health effects standards, EPA proposed requiring study plans and quarterly reports for chronic and reproductive effects, and final reports for all effects (44 FR 27351, May 9, 1979; 44 FR 27351, July 26, 1979). Based upon the experience EPA has gained in the last year in developing this rule and an exemption policy, EPA is now proposing to expand the study plan requirement to all effects and to require the submission of additional information. The new requirements are proposed not only as part of today's rules for chloromethane and the chlorinated benzenes but as part of the generic test standards which apply to all chemicals subject to Section 4 test rules. Hence, this discussion is intended to serve as notice of EPA's intent (1) to modify Sections 772.113-1(f), 772.116-3(c), and 772.100-2(6)(2) of the proposed test standards to include the changes discussed below, and (2) to propose that Study Plans be submitted for the other effects for which standards were proposed at 40 CFR 772.

- Study Plan requirements. The study plan requirement as originally proposed and as modified today is intended to serve two primary purposes. First, the various test standards referenced in this rule provide varying degrees of specificity concerning test methodology. Study Plans containing the information described above will assure the Agency that testing which is being undertaken comports with applicable test standards. This will permit the Agency to fulfill its general responsibility to assure that testing is performed pursuant to the rule. It will also allow EPA and the test sponsor to discuss areas of mutual interest that are not specifically covered by this rule. EPA cannot formally reject Study Plans, but can reject final reports based on inadequacy of testing methodology (i.e., failure to comply with the test standard). However, the Agency would prefer to avoid the waste of resources, loss of time, and controversy

that rejection of final reports would entail.

A second reason for requiring submission of Study Plans is to permit the granting of exemptions to test rule requirements under Section 4(c) of TSCA. As described previously, the Agency may grant an exemption only if it finds that the testing would be duplicative of data already submitted or being developed pursuant to the test rule. In the case of data already submitted, this finding can be addressed in straightforward manner. If the exemption request is based upon duplication of testing in progress or about to be undertaken by some other person, then the Agency plans to base its decision on a review of the relevant Study Plans. These plans will enable EPA to find that further testing would be duplicative and that testing will be conducted in accordance with the test rule.

The previously proposed study plans do not meet EPA's exemption-related needs adequately. There is no requirement to submit study plans for most effects even though EPA intends to use the plans to decide whether or not to grant an exemption. Thus, EPA is proposing to require submission of study plans for all health effects. However, in contrast to the previously proposed requirement to submit study plans 90 days before the initiation of testing, EPA does not intend to require early submission of study plans for health effects other than chronic or reproductive effects. EPA believes that for shorter tests a required 90-day early submission may be unnecessarily disruptive to the conduct of the tests, thus, EPA will require that Study Plans be submitted no later than the initiation of testing, with a request that they be supplied in advance of testing to permit their early review.

The other change to the Study Plan requirement entails the submission of more information than that proposed previously. EPA now proposes to add the following requirements (1) identification of the test rule, (2) in the case of joint sponsorship, the identity of the principal sponsor and other sponsors, (3) where applicable, a description of the culture medium and its source, and (4) for test rules which require submission of equivalence data for exemptions, (a) an attestation that the substance manufactured or processed is equivalent to the test substance and (b) information on the process by which the test substance was manufactured. The information to be submitted as part of the proposed Study

Plans requirement is set forth in full below.

(a) All Study Plans are required to contain the following information:

(1) Identity of the test rule.
(2)(i) The name and address of the test sponsors.

(ii) The name, and address of the responsible administrative officials and project manager(s) in the principal sponsor's organization.

(iii) The name, address, and telephone number of the appropriate individual for oral and written communications with EPA.

(iv) (A) The name and address of the testing facility including responsible administrative officials and project manager(s).

(B) Brief summaries of the training and experience of each professional involved in the study including Study Director, Veterinarian, Toxicologist(s), Pathologist(s) and Pathology Assistants.

(3) Identity and data on the substances or mixtures being tested including appropriate physical constants, spectral data, chemical analysis and stability under test and storage conditions.

(4) Study protocol information as required in Part 772 including information describing the culture medium and its source, if applicable.

(5) Schedule for initiation and completion of major phases of long term tests, schedule for submission of interim progress and final reports to EPA.

(b) If a demonstration of equivalency is required in order to obtain exemptions from testing, sponsors will have to attest that the chemicals which they manufacture or process are equivalent to the test substance and describe the process by which the test substance is manufactured.

The reasons for these additional requirements are discussed in the Proposed Statement of Exemption Policy and Procedures published in today's Federal Register.

- Interim Quarterly Summary Reports. The requirement to submit "Interim Quarterly Summary Reports" for long term studies was proposed in the Federal Register on May 9, 1979, (44 FR 27339, and 27351). Such reports are intended to provide the current status of the study including all significant findings and problems as well as resolutions initiated or proposed. As discussed in the statement on Exemption Policy, EPA has the authority to terminate exemptions from test rule requirements based upon a finding that the sponsor engaged in testing has not complied with the test rule. Periodic interim reporting will enable EPA to continually monitor compliance with the

test rule so that, if necessary, appropriate action can be taken without unnecessary loss of time.

• **Final Test Reports.** EPA has published in the Federal Register on May 9, 1979 (44 FR 27334) and July 28, 1979 (44 FR 44054) the requirements for the Final Test Reports as a part of the proposed test standards.

• **Time Period.** 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. In determining deadlines for submission of Study Plans, Interim Quarterly Summary Reports (where applicable), and Final Reports for each type of test, EPA has considered and allowed a reasonable amount of time for a number of factors which will effect the time period needed for satisfactory testing. These factors include coordination among persons subject to the rule to permit agreement on joint testing programs; development of Study Plans; set-up and execution of required tests; analysis of test results; and

preparation of Final Reports. The time frame for these factors as they relate to each type of health effects test are detailed in Table 1. In each case, the final test rule will specify an elapsed-time date by which all Final Test Reports must be submitted to EPA, calculated from the effective date of the test rule. EPA believes that the time periods which are being proposed will allow ample opportunity to satisfactorily comply with the test rule (see Sections VI and X).

The Agency encourages a coordinated response from persons subject to the rule and has allotted time for such coordination for each proposed schedule. A coordinated response might take the form of joint sponsorship of testing or coordinated submission of Study Plans and requests for exemptions. EPA believes that the utilization of such mechanisms by persons subject to the rule will lead to more efficient use of both sponsor and EPA resources.

(iv) Subchronic/Chronic Effects:

Activities:	Time allotted (mos)
Acquisition and acclimation of test animals and test substance; development of protocol for acute toxicity range-finding tests.	2
Performance of acute toxicity range-finding tests; selection of dose levels for subchronic tests; development of Study Plan for subchronic tests.	1
Total	3

G. Confidentiality

Section 770.4 of the health standards on chronic effects proposed in the Federal Register of May 9, 1979 (44 FR 27334), would establish general procedures for handling information submitted to EPA in compliance with this subpart. As proposed, when information submitted is covered by a claim of confidentiality asserted in accordance with these rules, EPA will disclose that information publicly only to the extent permitted by the Act, 40 CFR 770.4, and EPA's Public Information rules, 40 CFR Part 2. Under these rules EPA will notify the submitter of confidential information before the Agency makes disclosure. If a person asserts a claim but fails to submit a sanitized copy or the required substantiations, he will be given an opportunity to correct this problem before EPA releases the information.

EPA will review all confidentiality claims asserted for information included in reports submitted to meet test rule requirements. In accordance with Section 14(b) of the Act, EPA will grant confidentiality for such information only if the Agency determines that release would disclose confidential information concerning the processes used in manufacturing or processing of a chemical substance or mixture, or the confidential proportions of a mixture.

EPA will require submission of a sanitized copy of a health and safety study for which the submitter asserts a claim of confidentiality and substantiation of that claim at the time of submitting the information. The reasons for this policy were discussed in the May 7, 1979 proposal (44 FR 27345).

IV Chloromethane: Basis for Determinations

A. Introduction

The ITC recommended that chloromethane be tested for carcinogenicity, mutagenicity, teratogenicity, and other chronic effects. EPA has decided to propose test rules

Table 1

Chemical and required tests	Chloromethane		Chlorinated benzenes		Reproductive effects	Sub-chronic/chronic effects
	Oncogenic effects	Structural teratogenic effects	Oncogenic effects	Structural teratogenic effects		
Activities and Allotted Times (months):						
1. Coordination among test Sponsors	1	1	1	1	1	1
2. Study Plan Preparation ²	8	4	8	4	5	3
3. 90-day Pre-test Reporting Requirement	3		3		3	
4. Test Performance ¹	30	1½	30	1½	14	13
5. Analysis of test results, preparation of Final Report	11	4½	11	4½	6	5
6. Final Report Deadline	53	11	53	11	29	12

¹ Time periods reflect time to perform tests in accordance with EPA's test standards.

² Study Plan Preparation: The time period allotted for Study Plan Preparation for each testing requirements is discussed below and is designed to permit the necessary activities precedent to initiation of the required testing. These activities vary among the different testing requirements, but generally involve such things as acquisition and acclimation of test animals and performance of "range-finding" tests to determine appropriate dose levels.

(i) Oncogenic Effects:

Activities:	Time allotted (mos)	Time allotted (mos)
Acquisition and acclimation of test animals; preparation of test protocol and performance of four-14 day acute toxicity range-finding tests; preparation of protocol for subchronic toxicity range-finding tests.	2	1
Performance of subchronic toxicity range-finding tests.	3	1
Performance of pathology analysis of subchronic test animals; selection of dose levels for chronic toxicity tests; acquisition of test animals and development of Study Plan for chronic toxicity tests.	3	
Total	8	4

(iii) Reproductive Effects:

Activities:	Time allotted (mos)
Acquisition and acclimation of test animals and test substance, preparation of test protocol and performance of 14-day acute toxicity range-finding tests; preparation of protocol for subchronic range-finding tests.	2
Performance of subchronic range-finding tests.	1
Performance of pathology analysis of subchronic test animals; development of Study Plan for reproductive effects tests...	2
Total	5

(ii) Structural Teratogenic Effects:

Activities:	Time allotted (mos)
Acquisition and acclimation of test animals; preparation of test protocol for acute range-finding tests.	2

for oncogenicity,¹ and structural teratogenicity. In addition, EPA plans to require testing for neurotoxicity (neurologic and behavioral effects), behavioral teratogenicity, and possibly mutagenicity at a future date. Today EPA is seeking comment on certain issues pertaining to those effects and is not proposing testing for those effects because appropriate test standards, or, in the case of mutagenicity, complete test sequences, for such effects have not yet been developed. EPA does not see a need to require testing for systemic effects (acute or chronic toxicity), or metabolism. However, should additional information come to the attention of the Agency about effects for which testing has not been required, EPA will reevaluate its decision and, if necessary, propose testing. The ITC did not recommend an epidemiology study for chloromethane; EPA considered the possibility of requiring an epidemiology study but decided not to do so.

In the remainder of this discussion, EPA summarizes pertinent facts concerning chloromethane, the reasons for EPA's determination regarding each effect, and the basis for EPA's conclusion that the statutory criteria for testing have been satisfied for oncogenicity and structural teratogenicity. Detailed scientific support for these conclusions is contained in the Chloromethane Support Document.

B. Exposure Profile

Chloromethane, CH₃Cl (methyl chloride), is a colorless, noncorrosive gas at room temperature and normal atmospheric pressure. Other physical properties of this chemical include: molecular weight, 50.49; boiling point, -23.7°C; specific gravity, 0.92 at 20°C; solubility in water, 0.74 g/100 ml at 25°C; vapor pressure, 5 atm at 20°C; and an estimated logarithm of the octanol/water partition coefficient (log P_{ow}) of 1.08.

Approximately 300 to 500 million pounds of chloromethane are manufactured annually in the United States. The major process for chloromethane manufacture (accounting for greater than 98 percent of U.S. production of the chemical) is the hydrochlorination of methanol. Direct chlorination of methane is used to produce the remaining 2 percent.

Essentially all chloromethane manufactured in the United States is consumed domestically, primarily as a

chemical intermediate in the manufacture of silicones and tetramethyllead. These and other intermediate uses together account for about 96 percent of chloromethane consumption. The major non-intermediate use, as a catalyst-solvent in the manufacture of butyl rubber, accounts for most of the remaining consumption of chloromethane in the U.S.

Because of chloromethane's almost exclusive use in chemical manufacture and processing, the greatest potential for human exposure during its life cycle occurs for workers engaged in the manufacture, processing, and use of the chemical. The 1972-1974 National Occupational Hazard Survey conducted for the National Institute for Occupational Safety and Health estimated that as many as 50,000 workers may be occupationally exposed to chloromethane at the parts per million (ppm) level found in occupational settings. For example, chloromethane exposure has been found at levels of 50 to 75 ppm in the compressor room during its manufacturing and processing. Similar levels have also been found during processing of chloromethane in the manufacture of tetramethyllead, and during the use of chloromethane in the production of polystyrene foam plastics.

The current threshold limit value (TLV) for occupational exposure to chloromethane is 100 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended lowering the present TLV to 50 ppm, on the basis of some of the literature discussed in the Chloromethane Support Document. However, certain studies suggest that an even lower level may be needed to protect the health of workers.

The occupational exposure levels are considerably higher than those that appear in non-occupational settings. Thus, while chloromethane is present in the atmosphere in parts per trillion levels from natural sources, and in the parts per billion range in urban atmospheres from manmade sources other than manufacturing, processing and use (e.g., cigarette smoke), it appears at much higher concentrations in occupational settings.

C. Proposed Findings for Oncogenicity and Structural Teratogenicity

1. Potential unreasonable risk finding.

EPA believes that exposure to chloromethane may present an unreasonable risk of oncogenic and structural teratogenic effects. This conclusion is based on the evidence presented below and in the support

documents (1) that chloromethane has the potential for causing these effects, (2) that a considerable number of workers are exposed to chloromethane during its manufacturing, processing, and use, and (3) that the costs of testing will not have a significant impact on the availability of the benefits of the chemical. The following discussion of each effect focuses, therefore, on the basis for EPA's determination that chloromethane may cause oncogenic, (tumor-causing including cancer) and structural teratogenic (causing birth defects) effects.

2. *Oncogenicity.* (a) Chloromethane may present an unreasonable risk of injury to health from oncogenic effects.

Several factors suggest that chloromethane has oncogenic potential. Chloromethane is capable of inducing gene mutations in bacteria and causing chromosomal aberrations in plants. It is also a direct alkylating agent for both human and animal tissues. Both mutagenic and alkylating properties are considered to be suggestive of potential oncogenicity. In addition, chloromethane is a member of a class of compounds, the halogenated hydrocarbons, of which several members are known to have oncogenic potential. Furthermore, chloromethane is metabolized to formaldehyde, which preliminary test results indicate is a potential oncogen. Thus, EPA has concluded that chloromethane may present an oncogenic risk to human health.

(b) There are insufficient data upon which the oncogenic effects of chloromethane can reasonably be determined or predicted, and testing is necessary to develop such data.

There is a need to test chloromethane because the data are insufficient to determine whether or not it is an oncogen. As of this date, no long-term oncogenicity study has been completed. Battelle Laboratories, under contract to the Chemical Industry Institute of Toxicology (CIIT), has started a combined oncogenicity/chronic toxicity study; however, EPA believes there are serious defects in the execution of this study that may preclude reliance on negative results as indicative of a lack of oncogenic potential. (See Chloromethane Support Document for details). Thus, EPA is proposing to require that a two-year oncogenicity study be undertaken in accordance with the proposed test standards for oncogenicity to be adopted by EPA (and in accordance with any modifications to the final generic standards contained in the final test rule). Specific modifications to the standard are

¹ As explained in the proposed oncogenicity test standards, EPA is using the term "oncogenicity" instead of "carcinogenicity" 44 FR 27337 (May 9, 1979).

discussed in Section VI of this preamble.

3. Structural Teratogenicity. (a)

Chloromethane may present an unreasonable risk of injury to health from structural teratogenic effects.

There are several reasons to believe that chloromethane may be a structural teratogen. Because chloromethane is a lipid soluble, low molecular weight gas, it is likely to cross the placenta and be available to affect the fetus. There has been one instance of fetal death associated with exposure of a pregnant woman to chloromethane. Thus, EPA believes chloromethane may cause structural teratogenic effects.

(b) There are insufficient data upon which the structural teratogenic effects of chloromethane can reasonably be determined or predicted, and testing is necessary to develop such data.

EPA is unaware of any structural teratogenicity studies that have been done on chloromethane. Consequently, EPA believes that a test rule is necessary in order to assess the risk of teratogenicity posed by chloromethane. EPA is aware that CIIT currently plans to conduct a teratogenicity study. EPA has reviewed CIIT's protocol, and is concerned about the selection procedure for dose levels selected and the species being used. Because of these concerns, EPA is proposing that structural teratogenicity tests be performed in accordance with the proposed test standards with specific modifications discussed in Section VI of this document. It should be noted that in Section X of this preamble the Agency raises for comment the issue as to whether structural teratogenicity and behavioral teratogenicity tests should be combined. EPA will reevaluate the need for a final test rule for structural teratogenicity if the problems with the CIIT proposal are resolved.

D. Decision to Defer Proposal of a Test Rule for Neurotoxicity, Behavioral Teratogenicity, and Mutagenicity

1. Neurotoxicity (neurologic and behavioral effects). Several studies show that workers in the chloromethane industry have exhibited chronic neurologic or behavioral changes from long-term exposure. It has also been found that workers exposed to chloromethane show significant decrements in complex math tasks, increases in resting tremor, and increases in the latency to visual stimuli.

Many problems have been encountered in evaluating the animal studies in the literature. Chloromethane has been tested in several species of animals where the authors concluded that 300 ppm had no apparent effect in

64 weeks of exposure on any species tested, but that 500 ppm produced serious toxicity in most species and pronounced neurologic signs in dogs and monkeys. The evidence indicates that daily exposures to concentrations of 500 ppm can be extremely dangerous even for a period of two weeks or less. More recent animal studies of chronic exposure have produced suggestive evidence of functional and pathologic effects after shorter exposure at considerably lower concentrations. One study reports effects in rats and rabbits at low levels in both acute and chronic exposures. This study reports an increase in the time to acquire a conditioned response in rats after 4 hours of exposure to as little as 114 ppm. Furthermore, after six months of exposure to 20 ppm rats show behavioral deficits. At the lower dose, pathologic changes in rabbits exposed in the same experiment occurred throughout the brain as well as in the eye. While these studies suggest that long-term exposure to chloromethane at levels well below 300 ppm may pose an unreasonable neurological risk, they lack certain information necessary for a complete evaluation of the study and are thus insufficient for the purpose of performing adequate risk assessment.

Neurotoxicity test requirements are not being proposed today because EPA is not prepared to specify appropriate test standards to be followed at this time. Instead EPA is soliciting public comments on the Agency's current views with respect to such testing. As EPA's own work progresses and comments are received, EPA intends to prepare a test rule and standard.

The primary neurobehavioral effects of concern that have been identified for testing are chronic effects on the function and morphology of the nervous system. Set forth below are EPA's current views on the most appropriate types of testing and on related issues relevant to the development of suitable test standards.

Based on a recent controlled laboratory study and worker studies, it appears that changes in complex cognitive functions and visual function as measured by behavioral tasks may be the most sensitive human indicators of exposure to chloromethane. Reports on exposed workers, including one follow-up study, suggest that chloromethane exposure may induce damage that involves the cranial nerves or other structures controlling the eye, pyramidal and extrapyramidal (two motor neuron pathways) signs, a reduced tolerance to alcohol, fatigue, and depression. The EPA is considering proposing animal

studies to determine appropriate control levels for chronic exposure. The Agency is interested in comments as to the most appropriate testing to require for such effects.

The choice of species for animal testing involves several considerations. First, one study suggests that dogs and monkeys are more sensitive than the other species the investigators tested, and that effects in these species most resemble human effects. The inappropriateness of rats as a test species is suggested in the same study by the failure to observe any overt effects in rats, but not other mammalian species, exposed to 500 ppm. The ocular conjunctivitis observed in one study in rabbits and more recently observed in another study in mice, but not observed in rats, also suggests that rats are less sensitive with respect to ocular irritations as well. However, another study in rats found behavioral effects from both acute and low level chronic exposure. The reports of neither study are adequate to determine why a discrepancy occurs between these studies. The Agency is interested in comments on the most appropriate test species for evaluating the neurobehavioral effects of chloromethane.

The Agency is also considering and requests comments concerning the appropriateness of and the best means of defining adequate post-exposure testing of subjects from all exposed groups to assess the severity of delayed effects, if any, and the persistence of any observed effects. If exposure in chronic testing is noncontinuous, these effects could be assessed in part during chronic exposure studies prior to the beginning of daily or weekly exposure.

Abuse potential is another potential neurobehavioral effect on which the Agency wishes to receive comment. The abuse potential of a chemical is the likelihood that organisms will self-administer it, i.e., it acts as a reinforcer. The EPA defines abuse potential as including those intrinsic pharmacologic properties that can be measured experimentally and abuse liability to include both abuse potential and other factors that relate to abuse (World Health Organization 1975). Abuse potential depends on a number of factors that may be independent phenomena for a given chemical. A chemical may be called a positive reinforcer if it produces pleasurable consequences that increase the probability of self-administration. Tolerance is a reduced response to a chemical following repeated exposure that can raise the probability of

increased self-administration to continue to produce the same consequences. Dependence is an altered state produced by repeated exposure that can increase the probability of self-administration to avoid or escape unpleasant consequences upon withdrawal.

Chloromethane is a nonspecific central nervous system depressant. Many chemicals in this large and structurally heterogeneous class have abuse potential in humans, including other chlorinated alkanes. In this class, chloroform, chloroethane, and 1,1,1-trichloroethane have been reported to be abused by humans.

Chloromethane has been reported to produce euphoria, as well as unpleasant effects such as headache and depression several hours after exposure. One report describes an exposed worker who stated that acute intoxication with chloromethane was considered by some workers to be of little concern because the effects resembled intoxication with ethanol. This is suggestive evidence of positively reinforcing properties. On the basis of these properties and reports, and because abuse potential will increase the risk of all types of toxicity, the EPA is concerned with this potential hazard. The Agency solicits comments on the need and appropriate methods for testing chloromethane for abuse potential.

The Agency is also interested in whether studies relating to interactions which may occur between ethanol and chloromethane should be undertaken. Human case reports of reduced tolerance to ethanol coupled with chloromethane exposure and the fact that both chloromethane and ethanol have non-specific central nervous system (CNS) depressant action have led the Agency to consider interactions with ethanol as a possible factor of concern in the assessment of the effects of chloromethane. Identifying the nature and extent of an interaction that is additive, potentiating, or inhibiting can be an important element in risk assessment. In addition, dependence on alcohol or chloromethane may modify the probability of self-administration and thus the risks associated with the other agent. The Agency is aware of the existence of a planned behavioral interaction study with ethanol, which addresses such effects in acutely exposed humans, but is not designed to characterize the significance of ethanol-chloromethane interactions in chronic exposure. EPA requests comments on the desirability of including an ethanol interaction component in any chronic neurotoxicity studies which it requires,

or in some other fashion testing for this effect. Comment on appropriate methods is also solicited.

Finally, within the workplace, as the mixed acute and chronic exposure case studies reflect, accidental acute high exposures (related to accidents or leaks in the workplace) periodically occur to workers already chronically exposed to lower levels. The Agency is also considering the appropriateness and means of assessing such mixed exposure hazards in its proposed neurotoxicity testing, and requests comments on the need for and methods which might be used to test for such effects.

2. Behavioral teratogenicity. Evidence has been developed which suggests that behavioral deficits in developing systems are associated with exposure to non-specific CNS depressant chemicals similar to chloromethane. Because of chloromethane's neurotoxic properties, it may affect the central nervous system which is known to be especially susceptible during early fetal development. A recent study has shown that exposure of rats *in utero* to dichloromethane at a dose which caused no structural defects did cause behavioral defects.

Based on this evidence, the concerns about the neurotoxic properties of chloromethane and the likelihood that it may cross the placenta and affect the fetus, EPA believes chloromethane may present an unreasonable risk of behavioral effects on the fetus.

There is a need to test chloromethane for behavioral teratogenicity because the existing evidence which indicates that there may be a behavioral teratogenic risk from chloromethane is not sufficient to characterize the extent of that risk. Consequently, EPA believes further testing is necessary for this assessment.

Behavioral teratogenicity test requirements are not being proposed today because EPA is not prepared to specify appropriate test standards to be followed at this time. Instead EPA is soliciting public comments on the Agency's current views with respect to such testing. EPA is aware that the CIIT protocol for teratogenic tests on chloromethane specifies measurement of potential behavioral teratogenic endpoints, and the Agency is considering these in its development of behavioral teratogenic standards.

The EPA believes that such behavioral teratogenicity testing should include a test for evaluation of behavioral and neurological development in the offspring of pregnant animals exposed to chloromethane (see,

e.g., Vorhees et al. 1979).² In addition to routine signs of physical development that may reflect toxicity, such as body weight, the Agency's current view is that the proposed testing should include specific tests to assess in the offspring effects of chloromethane demonstrated in adults. Acquisition of a conditioned reflex has been reported as a sensitive endpoint. Neurologic impairment of motor function in humans and other mammals also has been reported as well as impairment of visual functions in humans. These three types of endpoints should be considered as well as thorough neuropathology. The Agency is interested in comments on the suggested behavioral teratogenicity tests.

3. Mutagenicity. There is evidence from bacteria and higher plants that chloromethane is capable of causing both gene mutations and chromosomal aberrations. In bacteria, chloromethane is a direct-acting mutagen capable of inducing base pair substitutions in the DNA of *Salmonella typhimurium* strains TA 1535 and TA 100. In *Tradescantia paludosa* pollen grains, chloromethane is more effective than ethylene oxide in causing chromatid breakage. However, these data are not sufficient to assess the extent of the risk to humans of mutagenicity from chloromethane and additional testing is necessary to develop such data.

EPA believes that mutagenic risk from exposure to chloromethane can most reasonably be determined by performing a sequence of tests for both gene mutation and chromosomal aberration. In such schemes, the performance of certain tests is triggered by positive or negative results from previous tests. However, test requirements for the mutagenicity sequences are not being proposed today because as of this time EPA has been unable to develop specific criteria for sequencing decisions that are suitable for inclusion in Section 4 test standards. EPA believes that such criteria are important to insure consistency between various laboratories in their determinations of whether to stop testing or proceed to the next test in the sequence. In addition, EPA has not yet developed test standards to be followed for the DNA alkylation tests in the gene mutation sequence, which is the uppermost test in the proposed testing sequence for gene mutation.

In the interest of the public health, EPA believes that testing of chloromethane for its mutagenic effects

²Vorhees CV, Brunner RL, Butcher RE, Sobolka TJ. 1979. A developmental test battery for behavioral toxicity in rats: a preliminary analysis using MSG, calcium carageenan, and hydroxyurea. *Toxicol. and App. Pharmacol.* 50:267-282.

should not be delayed due to the Agency's current inability to put in place all elements necessary for the testing sequence. Accordingly, because the initial tests of the mutagenicity sequence are short-term tests which are not expensive to perform, EPA plans to arrange for the performance of all tests in the sequences except the final tests: DNA alkylation tests for gene mutation and the heritable translocation assay for chromosomal aberration. Based on its evaluation of the results of these EPA tests, the Agency will decide whether to propose that the final tests of each sequence be performed in accordance with EPA standards which are being or have been developed. EPA is soliciting public comments on the proposed mutagenicity testing sequences discussed below.

• **Gene Mutation Testing.** EPA believes tests should be performed which demonstrate the potential of chloromethane to induce heritable gene mutations in a higher organism. In addition, the ability of chloromethane to interact with mammalian germinal tissue should be determined. A sequence of tests is set forth which includes: the sex-linked recessive lethal test in *Drosophila melanogaster*, DNA alkylation in mouse and *Drosophila* sperm, gene mutation in mammalian cell culture and DNA alkylation in mammalian cell culture.

EPA regards the production of mutations in a dose response related manner in *Salmonella* to be sufficient evidence for the identification of a chemical as a potential mutagen. Therefore, the Agency believes that testing of chloromethane for gene mutation should begin with the *Drosophila* sex-linked recessive lethal test to confirm the mutagenicity of chloromethane. Because chloromethane has not been tested in mammalian cells in culture, the Agency believes that a negative sex-linked recessive lethal test in *Drosophila* should be followed by a test for mutation in mammalian cells in culture. A finding of gene mutation in one of these tests would be followed by tests for alkylation of mouse sperm

DNA, and, as appropriate, alkylation of *Drosophila* sperm DNA or the DNA in mammalian cell culture.

The test sequence for gene mutation is shown in Figure 1. This figure designates the tests which EPA plans to sponsor.

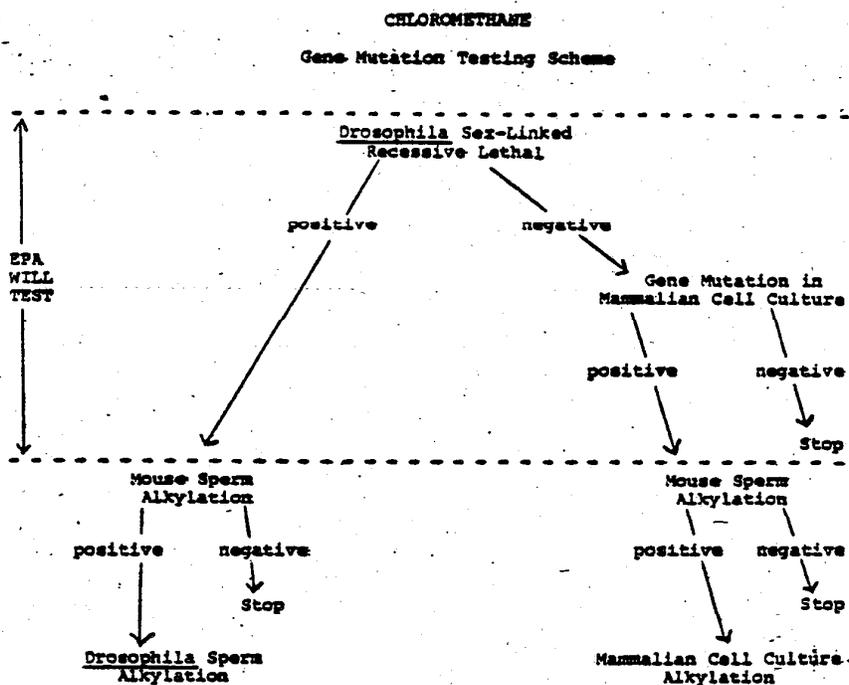


FIGURE 1

• **Chromosomal Aberration Testing.** EPA also believes that chloromethane should be further tested for its potential for causing chromosomal aberrations. A sequence of tests being considered by the Agency includes the dominant lethal assay and heritable translocation assay. EPA has set forth in the Chloromethane Support Document its reasons for not accepting the conclusions of the dominant lethal assay submitted by the Diamond Shamrock Corporation. EPA plans, therefore, to arrange for performance of another dominant lethal assay on chloromethane. This test is indicative of chromosomal effects in

mammalian germ cells. The heritable translocation test demonstrates not only the mutagenic activity of a chemical but also the heritability of such effects. This information can be used in hazard assessment. Therefore, based on the evaluation of the dominant lethal test, the Agency will decide whether to propose a test rule requiring performance of the final test in this sequence, a heritable translocation assay.

The test sequence for chromosomal aberration is shown in Figure 2. This figure designates the tests which EPA plans to sponsor.

Chloromethane

Test Scheme for Chromosomal Aberrations

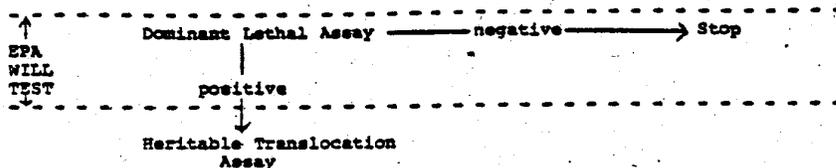


FIGURE 2

E. Decision Not To Require Testing for Systemic Effects, Reproductive Effects, Metabolism, and Epidemiology

1. Systemic effects. (acute and chronic effects)

Chronic toxicity. Although the Interagency Testing Committee (ITC) recommended testing to determine chronic effects on the liver, kidneys, bone marrow, and cardiovascular system, EPA is not proposing a test rule for these effects. This is because no-effect levels have been determined for liver, kidney, and bone marrow toxicity under a series of test conditions, and because effects on the cardiovascular system do not appear to be associated with nonlethal chronic exposure. Furthermore, the most sensitive indicator of toxicity appears to be the central nervous system for which the Agency expects to propose separate (neurotoxicity) testing. Hence, EPA finds that no further chronic toxicity testing to examine liver, kidney, and bone marrow toxicity is needed at this time.

Acute toxicity. As discussed in section IIIA of the Chloromethane Support Document, EPA believes that available human and animal data are sufficient to evaluate the acute toxicity of chloromethane. Therefore, the EPA is not proposing further testing for acute toxicity at this time.

2. Reproductive effects. EPA has found that there are no data to support a conclusion that chloromethane may present a risk of reproductive effects. Therefore EPA is not proposing testing for such effects at this time.

3. Metabolism. Although the ITC did not recommend metabolism testing, EPA considered the need to require such testing in the course of doing its hazard assessment for the health effects discussed above. EPA concluded that metabolism testing is not necessary at this time.

4. Epidemiology. An animal study and an epidemiologic study indicate that chronic exposure of humans by inhalation of chloromethane at the present TLV (100 ppm) may result in

impaired neurological functions. However, EPA believes that these studies are not sufficient to clarify the relationship between chronic exposure to chloromethane at 100 ppm and neurological impairment. While a well-designed epidemiologic study could clarify this relationship, an epidemiologic test requirement is not being proposed today because EPA lacks the specific information necessary to identify a suitable cohort. The identification of a suitable cohort is a complex process requiring specific information. NIOSH has attempted for several years to locate a cohort for an epidemiologic study on chloromethane but thus far has been unsuccessful. EPA will examine the information provided under the rule proposed under Section 8(a) of TSCA to determine whether a suitable cohort can be found. If EPA obtains information identifying a suitable cohort, the Agency will evaluate the need for proposing an epidemiologic study for chloromethane considering in its evaluation any test results obtained from required animal tests. In the case of chloromethane, EPA

is soliciting public comment on the feasibility and desirability of an epidemiologic study.

V. Chlorinated Benzenes: Basis for Determinations

A. Introduction

The ITC recommended that the mono-, di-, tri-, tetra-, and penta-chlorinated benzenes be tested for carcinogenicity, mutagenicity, teratogenicity, and other chronic effects, and that epidemiological studies be undertaken. The Committee also recommended that the chlorinated benzenes be tested for environmental effects which, as stated previously, are not addressed in today's notice.

EPA is proposing rules today for oncogenicity, structural teratogenicity, reproductive effects and subchronic/chronic effects testing of some or all of the chlorinated benzenes recommended for testing by the ITC. At a later date, EPA plans to require testing for neurotoxicity (neurologic and behavioral effects), behavioral teratogenicity, metabolism, and possibly mutagenicity. Because appropriate test standards or, in the case of mutagenicity, complete test sequences for such effects have not yet been developed, EPA is not proposing testing now and is instead seeking comment on issues pertaining to those effects. EPA does not see a need to require testing for acute toxicity and has decided that it is not feasible to require epidemiology studies at this time. However, should additional information come to the attention of the Agency about effects for which testing has not been required, EPA will reevaluate its decision and, if necessary, propose testing. The Agency's proposed testing is summarized in Table 2.

Chemical	Oncogenicity	Structural teratogenicity	Reproductive effects	Sub-chronic/chronic	Neurotoxicity	Behavioral teratogenicity	Mutagenicity	Metabolism	Acute toxicity	Epidemiology
Monochlorobenzene.....	—	X	X	X	D	D	D	D	—	—
o-Dichlorobenzene.....	—	X	X	X	D	D	D	D	—	—
p-Dichlorobenzene.....	—	X	X	X	D	D	D	D	—	—
1,2,4-trichlorobenzene.....	X	X	—	X	D	D	D	D	—	—
1,2,4,5-tetrachlorobenzene.....	X	X	X	X	D	D	D	D	—	—
Pentachlorobenzene.....	X	—	X	X	D	D	D	D	—	—

X=Proposed testing. —=Not proposed. D=Decision to propose testing deferred.

This proposed regulation considers the chlorinated benzenes, also referred to as chlorobenzenes, as a group in accordance with the provisions of Section 26(c) of TSCA. For membership in the category, a substance must be a benzene derivative in which one to five hydrogen atoms are replaced by chlorine. Thus, the category "chlorinated benzenes" includes monochlorobenzene, p-dichlorobenzene, 1,2,3-

trichlorobenzene, 1,2,4-trichlorobenzenes, 1,3,5-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, 1,2,3,5-tetrachlorobenzene, 1,2,4,5-tetrachlorobenzene and pentachlorobenzene.

It should be noted that while hexachlorobenzene is a member of the chlorinated benzenes family, it was not included in the ITC's recommendations.

The Agency has not considered hexachlorobenzene as part of this rulemaking because it has been evaluated through a separate process within the Office of Pesticides and Toxic Substances (OPTS) and the Agency. After the OPTS review of hexachlorobenzene, it was referred to the Office of Solid Waste for action under the Resource Conservation and Recovery Act for control of the major source of hexachlorobenzene release to the environment. These regulations were published in the Federal Register of May 19, 1980 (45 FR 33068). Therefore, the term "chlorinated benzenes" as used in this rule does not include hexachlorobenzene.

B. Exposure Profile

The commercially most significant chlorinated benzenes include monochlorobenzene (approximately 303 million pounds per year domestic production in 1978), *o*-dichlorobenzene (approximately 55 million pounds in 1978), *p*-dichlorobenzene (approximately 68 million pounds in 1978), 1,2,4- and 1,2,3-trichlorobenzene (approximately 28 million pounds together in 1973), 1,2,4,5-tetrachlorobenzene (approximately 18 million pounds, 1973 consumption estimate), 1,2,3,4-tetrachlorobenzene (approximately 12 million pounds in 1973) and pentachlorobenzene (1-10 million pounds in 1977). *m*-Dichlorobenzene, 1,3,5-trichlorobenzene, and 1,2,3,4- and 1,2,3,5-tetrachlorobenzenes are currently produced as by-products in the synthesis of other chlorinated benzenes. Trichlorobenzenes are also produced for use as starting material for tetrachlorobenzenes. All of the chlorinated benzenes are on the TSCA inventory.

The liquid chlorobenzenes find widespread use as solvents and synthetic intermediates. Monochlorobenzene is an intermediate in the production of chloronitrobenzene, herbicides, diphenyl oxide, DDT, silicones and other chemicals. *o*-Dichlorobenzene is similarly used as a chemical intermediate and solvent. Some solvent uses of particular concern to EPA are its use for auto engine degreasing and inclusion in formulated products such as toilet bowl and drain cleaners. The major uses of 1,2,4-trichlorobenzene are as a dye carrier, herbicide intermediate, and functional fluid, especially in transformers. (Examples of a functional fluid include heat transfer fluid, dielectric, hydraulic fluid, etc.)

The solid chlorobenzenes find widespread use as synthetic intermediates and pesticides. *p*-

Dichlorobenzene is used in the home and in commercial and industrial settings as a space deodorant and also as a moth control agent. 1,2,4,5-Tetrachlorobenzene is used primarily as an intermediate in the production of the fungicide and bactericide 2,4,5-trichlorophenol and the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and as a transformer fluid. Pentachlorobenzene is used as an intermediate in the synthesis of the fungicide, pentachloronitrobenzene and is produced, and disposed of as waste, as a contaminant in other chlorobenzene manufacturing.

The processing and use of chlorinated benzenes as chemical intermediates, process solvents, and solvents in formulated products give rise to potential occupational, consumer, and environmental exposure. Inhalation of chlorinated benzene vapors and exposure to the solid forms of chlorinated benzene dust during manufacturing and processing and use have been shown to occur. The National Occupational Hazard Survey indicates that slightly more than 1 million workers may be exposed to monochlorobenzene, a similar number to *p*-dichlorobenzene, and nearly double that number to *o*-dichlorobenzene although other data indicate the survey overestimated worker exposure.³ Although this estimate of worker exposure may be high, there is nevertheless sufficient exposure to warrant testing.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended threshold limit values expressed as time-weighted averages (TWA) or short-term exposure limits (STEL) for the chlorinated benzenes as follows:

monochlorobenzene—75 ppm (350 mg/m³), TWA
o-dichlorobenzene—50 ppm (300 mg/m³), TWA
p-dichlorobenzene—75 ppm (450 mg/m³), TWA
p-dichlorobenzene—110 ppm (475 mg/m³), STEL
 1,2,4-trichlorobenzene—5 ppm (40 mg/m³), TWA

The Occupational Safety and Health Administration (OSHA) has adopted the TWA standards for monochlorobenzene and *p*-dichlorobenzene. For *o*-

³ Additional figures showing much less employee exposure to the chlorinated benzenes were submitted to the Agency on February 25, 1980, by the Synthetic Organic Chemical Manufacturers Association (SOCMA); however, several aspects of the SOCMA report indicate that its exposed worker estimates may underestimate exposure. No citations were included from which the data can be verified. (See the Chlorinated Benzenes Support Document for more details)

dichlorobenzene the OSHA standard is 50 ppm ceiling level (CL). OSHA has no standards for 1,2,4-trichlorobenzene or the other chlorinated benzenes.

Human exposure through the environment may also contribute to unreasonable risk. The information available indicates that many industrial uses and disposal practices may result in ultimate discharge of chlorinated benzenes into the environment rather than their recovery and reuse. It has been estimated that 30 to 50 percent of the monochlorobenzene produced annually is ultimately released into the air. Similarly, the solvent uses of *o*-dichlorobenzene and the deodorant and moth control uses of *p*-dichlorobenzene would be expected to lead to significant environmental release of these two substances. In addition, *m*-dichlorobenzene has been detected in air samples around disposal sites and industrial facilities. Both 1,2,4- and 1,3,5-trichlorobenzene have been detected in waste-water discharges and in fish. 1,2,3,5- and 1,2,3,4-tetrachlorobenzenes have been detected in freshwater fish in the Great Lakes and nearby rivers leading to concern that the higher chlorinated benzenes may bioaccumulate and present a risk of exposure through the food chain. 1,2,3,5-Tetrachlorobenzene is known to be disposed of as waste during the production of 1,2,4,5-tetrachlorobenzene.

C. Proposed Findings for Oncogenicity, Structural Teratogenicity, Reproductive Effects and Subchronic/Chronic Effects

1. Section 4(a)(1)(A) findings. EPA believes that there are several reasons for considering the chlorinated benzenes as a category for Section 4(a)(1)(A) purposes. The chlorobenzenes comprise a category of closely related chemical compounds that have been shown to cause or would be expected to cause similar biological consequences upon exposure. The chlorobenzene group is formally constructed by substituting one hydrogen of benzene after another with chlorine, in all possible structural arrangements, resulting in corresponding gradual changes in properties across the series. Proceeding from less chlorinated to more highly chlorinated benzenes, regular changes can be observed in characteristics or numerical values over a broad range of categories: chemical and physical properties, method of manufacture, use patterns, nature of impurities, and biological and environmental behavior.

Some irregularities do occur within the group that result from different steric and electronic effects among isomers of the same degree of substitution, but these are not significant enough to

negate the overall consistency of the group's behavior. In general, the chlorinated benzenes have low water solubility and this solubility decreases as the number of chlorines increases. The group exhibits moderate to high octanol/water partition coefficients, which increase as the degree of chlorination increases. This is significant because a high octanol/water partition coefficient is an indicator of a chemical's potential to accumulate in fatty tissues, however, it appears that all chlorinated benzenes are metabolized via epoxidation, dechlorination and/or oxidation by non-epoxide mechanisms, with various chlorophenols among the major products. In some cases different chlorobenzenes are metabolized to a common chlorophenol. The electron-withdrawing character of the chlorine atom relative to carbon renders monochlorobenzene less reactive than benzene toward electrophilic attack (e.g., nitration, chlorination), with each additional chlorine substituent somewhat lowering the reactivity of the compound. Some variations do occur within the group that are due to different steric and electronic effects among isomers of the same degree of substitution; nevertheless, the overall trends in physicochemical properties are consistent.

The available information on metabolism and toxicity suggests that these shared physical and biochemical characteristics are responsible for causing similar adverse health effects. For example, in animal studies, all of the chlorobenzenes tested have effects on the liver, several have effects on the kidneys, and all those tested lead to changes in the hematopoietic system. Further the data that are available on the metabolism of chlorobenzenes to support the conclusion that most if not all of the compounds undergo epoxidation, dechlorination, and/or oxidation by non-epoxide mechanisms, with various chlorophenols among the major products. In some cases, different chlorobenzenes are metabolized to a common chlorophenol.

This is not to imply that all category members will necessarily have identical effects or similar potencies for a given effect, but the Agency believes that scientific principles and available data and experience lead to a reasonable presumption that the biological behavior of these 11 chemicals will present a coherent picture of toxicity.

In addition to exhibiting a common, potential hazard, all the chlorinated benzenes raise exposure concerns. As discussed in the previous section, many of the chlorinated benzenes are

produced in quantities ranging in millions of pounds a year. Others commonly appear as by-products of other chlorinated benzenes. The broad variety of uses potentially leads to occupational, consumer, and environmental exposure to the entire category. Further, there may also be exposure to several chlorinated benzenes simultaneously since the commercial methods for producing and handling the chemicals ensures that most commercial chlorobenzenes will contain other chlorobenzenes as impurities or by-products and that chlorobenzene production wastes will also contain various chlorobenzenes. Further, the estimation of relative environmental levels of the various chlorobenzenes is complicated by the possibility that some interconversion of isomers might occur in the environment. (This could be the result either of conversion to more highly chlorinated compounds during water treatment by chlorination or of reductive dechlorination by photodegradative mechanisms or by microorganisms to form the less-chlorinated derivatives. There is little information on this point, although interconversions by dechlorination apparently do occur to some extent during the mammalian metabolism of some chlorinated benzenes [Section III. B.1.c.(1) of the Support Document]). Thus, for all of the above reasons, EPA concludes that the chlorinated benzenes may present an unreasonable risk of injury to health.

EPA is also making the Section 4(a)(1)(A) (ii) and (iii) findings for the category of chlorinated benzenes. EPA finds that data and experience are insufficient to characterize the chlorinated benzenes and that additional testing is necessary to permit their characterization. EPA recognizes that 1,2,4-trichlorobenzene has been adequately tested for subchronic effects and pentachlorobenzene, for teratogenicity, and that monochlorobenzene, *o*-dichlorobenzene and *p*-dichlorobenzene are being tested for oncogenicity. However, these data will not be sufficient to characterize all chlorobenzenes. Rather than requiring testing of all chlorinated benzenes for effects for which there are insufficient data, EPA believes that scientific principles and available data and experience lead to a reasonable presumption that the biological behavior of the 11 chlorinated benzenes will present a coherent picture of toxicity and that biological data on a well-chosen sample of category members can be used to characterize the behavior of untested members. However, as

explained elsewhere in this preamble, manufacturers and processors of all chlorinated benzenes are subject to the rule and responsible for testing or sharing the costs of testing. Whether the costs of testing should be borne more by manufacturers and processors of one chlorobenzene than another to ensure financial equity shall be addressed in the reimbursement rule rather than proposed here, although comment on this issue would be appreciated.

In the remainder of this discussion, EPA summarizes pertinent facts concerning the chlorobenzenes, and gives the specific basis for EPA's conclusion that the statutory criteria for testing have been satisfied for oncogenicity, structural teratogenicity, reproductive effects and subchronic/chronic effects. Detailed scientific support for EPA's conclusions are contained in the Chlorinated Benzenes Support Document.

2. *Oncogenicity.* (a) The chlorinated benzenes may present an unreasonable risk of injury to health from oncogenic effects.

Several factors suggest that the chlorinated benzenes have oncogenic potential. Exposure to chlorinated benzenes has been associated with leukemia in humans in several cases. They are structurally similar to a known leukemogen and oncogen, benzene, and a known oncogen, hexachlorobenzene. Chlorinated benzenes are thought to be metabolized to arene oxides, a class of compounds with oncogenic potential. In addition, they have been shown to produce positive results in mutagenicity tests which are suggestive of oncogenicity. Lastly, hexachlorobenzene and chlorinated benzene metabolites have been shown to have tumor-promoting potential. Thus, EPA has concluded that the chlorinated benzenes may present an oncogenic risk to human health.

(b) There are insufficient data upon which the oncogenic effects of the chlorinated benzenes can reasonably be determined or predicted, and testing is necessary to develop such data.

Although few animal models have been developed which are capable of detecting chemically induced leukemia, long-term testing for oncogenic effects from exposure to chlorinated benzenes is necessary to adequately characterize the risk of other oncogenic effects (i.e. tumors). The potential of the chlorinated benzenes to produce tumors has been demonstrated by the results of mutagenicity and tumor promoting tests.

There is a need to test the chlorinated benzenes because data are insufficient to determine whether or not they are oncogenic. As of this date, no long term

oncogenicity study has been completed. However, the National Cancer Institute (NCI) is currently testing monochlorobenzene and *o*-dichlorobenzene in long-term bioassays. *p*-Dichlorobenzene is scheduled to be placed on test beginning in June 1980. Therefore, EPA is not proposing that monochlorobenzene, *o*-dichlorobenzene, or *p*-dichlorobenzene be tested for oncogenicity. While the NCI protocol differs from the oncogenicity testing standards proposed by EPA, the Agency is tentatively accepting these differences in testing approaches. When the results of the NCI tests become available, the Agency will include them in its continuing evaluation of these chemicals. These results will be made available in the public record when the test data are received by the Agency. Oncogenicity data on these three chlorobenzenes alone are not sufficient to characterize the chlorinated benzenes category for the potential to cause oncogenic effects because testing the lower chlorinated benzenes does not span the structural spectrum of the category. Thus, EPA has concluded that it is necessary to require that two-year oncogenicity studies be undertaken on additional chlorinated benzenes in accordance with the proposed test standards for oncogenicity adopted by EPA (and any modifications to the final generic standards in the final test rule). See Section VI.B.2. of this preamble for a discussion of the test substances proposed by EPA for testing.

3. Structural Teratogenicity. (a) The chlorinated benzenes may present an unreasonable risk of injury to health from structural teratogenic effects. Several factors indicate that the chlorinated benzenes may have structural teratogenic potential. They are related structurally to hexachlorobenzene which is teratogenic in mice and causes rib abnormalities in rats. Pentachlorobenzene causes dose related rib abnormalities in rats as seen with hexachlorobenzene. In addition, certain phenolic metabolites of the chlorinated benzenes are also known to cause embryo—and fetotoxic responses in the rat. The structurally-related hexachlorobenzene has been demonstrated to pass the placenta. Also, chlorobenzenes are nonspecific central nervous system (CNS) depressants in adults and, as such, cross the blood-brain barrier. In addition, the relatively low molecular weights and the lipid solubility of the chlorobenzenes indicate potential for rapid diffusion across the placenta. Thus, chlorinated benzenes and some of their toxic metabolites can be reasonably assumed to cross the

placenta and pose a risk to the developing embryo or fetus. For the reasons stated above, EPA believes that the chlorinated benzenes may pose a structural teratogenic risk.

(b) There are insufficient data upon which the structural teratogenic effects of the chlorinated benzenes can reasonably be determined or predicted, and testing is necessary to develop such data.

As of this date, the chlorinated benzenes have not been tested for their potential to cause structural teratogenicity, except for pentachlorobenzene. Consequently, EPA believes a test rule is necessary to assess the structural teratogenic potential of the chlorinated benzenes. EPA is proposing that structural teratogenicity tests be performed, except for pentachlorobenzene, in accordance with the proposed test standards. It should be noted that in Section X the Agency raises for comment the issue as to whether structural teratogenicity and behavioral teratogenicity tests should be combined. The EPA Health Effects Research Lab at Research Triangle Park, N.C. (RTP), has performed a teratogenicity screen on 1,2,4-trichlorobenzene for the Office of Drinking Water. However, this screen is currently undergoing the process of validation. If the screen is validated for assessing teratogenic effects, EPA will evaluate the data and determine whether any changes in the teratogenicity testing requirements are necessary. This study will be available in the public record. Also, the National Toxicology Program (NTP) has tentatively selected 1,4-dichlorobenzene for teratogenicity testing. In addition, the chlorobenzene producers, including Dow Chemical Co., are reportedly planning a jointly sponsored teratology study on monochlorobenzene, *o*-dichlorobenzene, and *p*-dichlorobenzene. These factors will be taken into consideration in adopting a final test rule for the chlorinated benzenes.

4. Reproductive Effects (a) The chlorinated benzenes may present an unreasonable risk of injury to health from reproductive effects.

Several factors indicate that the chlorinated benzenes may cause reproductive effects in humans. It has been shown that monochlorobenzene affects the ovarian weight of rats and that hexachlorobenzene affects the fertility of rats. Dose-related ovarian effects noted in monkeys exposed to hexachlorobenzene also cause concern about other chlorinated benzenes. In addition, testicular effects have been noted in a subchronic study on dogs

exposed to monochlorobenzene. Hexachlorobenzene has been demonstrated to pass the placenta, accumulate in human body fat and appear in the mothers milk. Because hexachlorobenzene is structurally similar to chlorobenzenes, it is reasonable to believe that this can occur with the other chlorinated benzenes as well. Thus, EPA believes that the chlorinated benzenes have the potential to cause reproductive effects.

(b) There are insufficient data upon which the reproductive effects of the chlorinated benzenes can reasonably be determined or predicted, and testing is necessary to develop such data.

A reproductive study on 1,2,4-trichlorobenzene has been performed by EPA's Health Effects Research Lab at Research Triangle Park (RTP), North Carolina, for the EPA Office of Drinking Water. Thus, further testing of this compound appears to be unnecessary unless evaluation of the final results of these tests indicates further testing should be done. When the final report of the RTP study has been completed, it will be made available in the public record. Existing data are insufficient to determine the effects on fertility and the offspring due to exposure to the other chlorinated benzenes. Reproductive testing is necessary to develop data which will characterize the ability of the chlorinated benzenes to cause reproductive effects. EPA is proposing that reproductive effects testing be performed in accordance with the proposed test standards.

5. Subchronic/chronic effects. (a) The chlorinated benzenes may present an unreasonable risk of injury to health from subchronic/chronic effects.

The available data indicate that all of the chlorinated benzenes are associated with damage to the liver and hematopoietic (blood forming) system. Kidney damage has been produced by at least the first three groups of chlorobenzenes (mono- through tri-).

Structurally, the chlorinated benzenes are related to benzene on one end of the spectrum and hexachlorobenzene on the other end of the spectrum. Both of these chemicals are recognized for their chronic toxic effects in humans. Experimental evidence shows that members of the group of chemicals structurally in between these two compounds are capable of producing similar health effects. In addition, other halogenated hydrocarbons are known to bioaccumulate. Similarly, several of the chlorinated benzenes have been reported as having the capacity to bioaccumulate.

In addition to evidence from animal studies and structural relationships,

human case reports have indicated that these chemicals induce severe health effects especially in the liver and hematopoietic system. Although anecdotal human case reports are not considered by EPA to be definitive evidence that these chemicals cause serious health effects, the information contributes to a total picture of their chronic health effects. Because of the above evidence, EPA believes that the chlorinated benzenes have the potential to cause subchronic/chronic effects.

(b) There are insufficient data upon which the subchronic/chronic effects of the chlorinated benzenes can reasonably be determined or predicted, and testing is necessary to develop such data.

While the available data clearly demonstrate that chronic effects occur from exposure to chlorinated benzenes, the data are not adequate to determine what level of control of exposure would eliminate the unreasonable risk of various chronic effects. A study adequate to characterize the subchronic toxicity of pentachlorobenzene has recently been completed by EPA. EPA is aware that Imperial Chemical Industries in Great Britain is carrying out a long-term inhalation study in rats on *p*-dichlorobenzene. EPA is also currently trying to obtain details on an inhalation study performed by a different group on rats exposed to 1,2,4-trichlorobenzene. If the results of these two studies become available to the Agency, EPA will evaluate them and decide whether subchronic testing of these two chlorinated benzenes is necessary. Based upon current information, however, EPA believes that with the exception of pentachlorobenzene testing is necessary to further define the risk of chronic effects posed by the chlorinated benzenes. EPA is proposing that 90 day subchronic tests be performed in accordance with the proposed test standards except that the rat should be the only species tested. The Chlorinated Benzenes Support Document contains a discussion as to the Agency's view on the sufficiency of a 90-day subchronic test for determining the potential of the chlorinated benzenes for causing chronic effects.

D. Decision To Defer Proposal of a Test Rule for Neurotoxicity, Behavioral Teratogenicity, Mutagenicity, and Metabolism

1. Neurotoxicity (neurologic and behavioral effects). Signs and symptoms of adverse effects on the nervous system have been associated with exposure to four of the chlorobenzenes (monochlorobenzene, *o*-dichlorobenzene, *p*-dichlorobenzene,

and 1,2,4,5-tetrachlorobenzene) in various species, including humans, rats, rabbits and guinea pigs. In humans exposed to monochlorobenzene, headache, dizziness, somnolence, loss of consciousness, acroparasthesia (numbness and tingling of extremities), hyperesthesia (extreme sensitivity) of the hands, spastic contractions of the fingers or the gastrocnemius muscle, twitching muscles of the head and neck, and dyspeptic (stomach) disorders have been reported. Humans exposed to *p*-dichlorobenzene, possibly contaminated with small amounts of *o*-dichlorobenzene, exhibited intensified muscular reflexes, ankle clonus (contraction of ankle muscular tissue), and loss of appetite.

Animals exposed to monochlorobenzene have shown non-specific CNS depression, chronaxie disturbances (disturbances in excitability of nervous or muscular tissue), and an elevation of blood cholinesterase. *o*Dichlorobenzene also produces signs of CNS depression. Animals exposed to *p*-dichlorobenzene develop nystagmus (rhythmic eye movements), tremors, twitches, loss of the righting reflex, rapid labored respiration, and transitory edema of the head of the optic nerve. Repeated exposure to high doses of *p*-dichlorobenzene produces weakness, tremors, weight loss, and death. Exposure to 1,2,4,5-tetrachlorobenzene causes deficits in the speed and accuracy of a conditioned reflex.

Additional data are needed for a more complete characterization and assessment of the neurotoxic hazard from exposure to the chlorinated benzenes. For the chlorobenzene compounds that have been tested for neurologic and behavioral effects, the dose-response characterization is incomplete, and available observational data are poorly quantified, subjective, and therefore, relatively insensitive. Subchronic studies of electrophysiological functions are inadequately detailed.

Neurotoxicity test requirements are not being proposed today because EPA is not prepared to specify test standards to be followed at this time. Instead, EPA is soliciting public comment on the Agency's current views with respect to such testing. EPA intends to propose such testing when appropriate EPA test standards for neurotoxicity are developed.

The following discussion sets forth the Agency's current views on testing for neurologic and behavioral effects. EPA's views on the route of administration of the various chlorobenzenes are discussed in the Support Document. EPA

believes that both acute and subchronic (repeated exposure for 90 days or longer) tests on rodents should be performed using locomotor activity, a functional observational battery, and a neurophysiological test of chronaxie (relationship between a stimulus intensity and latency of response of the excitable tissue) and conduction velocity as dependent measures. Histopathology of the nervous system of subchronically exposed animals is also recommended. The examination should include: longitudinal and cross sections of the spinal cord, i.e., thoracic and lumbar regions; cross sections of the forebrain, midbrain, and brainstem; and representative sections of the sciatic nerve. Tissue should be fixed *in situ* with formaldehyde or glutaraldehyde and paraformaldehyde.

Tests of locomotor activity have been widely used in screening drugs and have been proposed as screening tests for environmental chemicals. A recent survey by Reiter and MacPhail⁴ of locomotor activity measures discusses some of the problems involved in generating comparable data from different types of measurement devices as well as the influence of other important variables. In general, when combined with observational measurements of other central nervous system (CNS) functions automated activity devices provide more reliable and better quantified measures of locomotor activity.

Observational assessment by means of screening tests that measure objective physiological signs, unconditioned reflexes, elicited responses, and operants are essential for detecting the spectrum of a chemical's effects and providing a basis for determining its functional anatomical targets. Tilson and Cabe⁵ and Tilson, Mitchell, and Cabe⁶ present useful examples of a screening battery and a discussion of some factors important to development of screening batteries.

Among the neurobehavioral functions assessed by means other than observation which are reported in the available literature on chlorinated benzenes are acquisition of conditioned responses, chronaxie measurements of nerves or muscles, and electroencephalography. EPA is

⁴Reiter LW, McPhail RC. 1979. Motor activity: a survey of methods with potential use in toxicity testing. *Neurobehavioral Tox.* 1, Suppl. 1:53-66.

⁵Tilson HA, Cabe PA. 1978. Strategy for assessment of neurobehavioral consequences of environmental factors. *Environ. Health Perspect.* 28:287-298.

⁶Tilson HA, Mitchell CL, Cabe PA. 1978. Screening for neurobehavioral toxicity: the need for examples of validation of testing procedures. *Neurobehavioral Toxicology* 1 (suppl. 1):137-146.

considering proposing that subchronic studies of the effects of chlorobenzenes measure chronaxie and some other neural function. Among such functional tests, conduction velocity of a mixed large and small diameter fiber population is a well-known parameter for evaluating nerve damage (See Glatt et al.⁷). However, other tests such as frequent impulse series transmission (e.g., Tackmann et al.⁸) or other electrodiagnostic procedures should be considered. The Agency is interested in comments on the suggested neurotoxicity tests.

2. Behavioral Teratogenicity. Acute and repeated exposure to all of the tested chlorinated benzenes (in animals: monochlorobenzene, *ortho*- and *para*-dichloro- and 1, 2, 4, 5-tetrachlorobenzene; in humans: monochlorobenzene and *para*-dichlorobenzene) have been associated with adverse central nervous system (CNS) effects. Because chlorobenzenes are non-specific CNS depressants in adults and, as such, cross the blood-brain barrier, it can be reasonably assumed that the chlorinated benzenes or their toxic metabolites can cross the placental barrier. The CNS appears to be especially susceptible to toxic insult during its development. In addition, other non-specific CNS depressants have been shown to be associated with behavioral deficits in developing organisms. Thus, the possibility for fetal exposure to chlorinated benzenes combined with their neurotoxic potential warrants their evaluation as behavioral teratogens. On these bases, EPA concludes that chlorinated benzenes may present a potential risk of behavioral teratogenic effects. Moreover, in agreement with the concept that behavioral and anatomical evaluations are complementary approaches to central nervous system toxicity, the Agency is considering requiring behavioral teratogenicity testing.

Behavioral teratogenicity test requirements are not being proposed today because EPA is not prepared to specify appropriate test standards to be followed at this time. Instead EPA is soliciting public comment on the Agency's current views with respect to such testing. EPA intends to propose such testing when an EPA test standard for behavioral teratogenicity is developed.

⁷Glatt AP, Talaat HN, Koella WP. 1979. Testing of peripheral nerve function in chronic experiments in rats. *Pharmac. Ther.* 539-543.

⁸Tackmann W, Ullerich D, Lehmann HJ. 1974. Transmission of frequent impulse series in sensory nerves of patients with alcoholic polyneuropathy. *Europ. Neurol.* 12:317-330.

The EPA believes that such behavioral teratogenicity testing should include a test for evaluation of the neurofunctional deficits and behavioral and neurological development in offspring of pregnant animals exposed to chlorobenzenes (see, e.g., Vorhees et al.⁹). In addition to routine signs of physical development that may reflect toxicity, such as body weight, the proposed testing should include specific tests to assess in offspring known effects of chlorinated benzenes in adults. As non-specific CNS depressants, the chlorinated benzenes cause narcosis, reflex changes, and other neurological motor signs, as well as changes in food intake and body weight. Screening batteries specifically designed for examining these behaviors in developing organisms should include measures shown to be related to intoxication. Neuropathology should also be included. EPA's views on the route of administration for the various chlorobenzenes are discussed in the Chlorinated Benzenes Support Document. The Agency is interested in comments on the suggested behavioral teratogenicity tests.

3. Mutagenicity. EPA has determined that the chlorinated benzenes may pose a hazard to human health from mutagenic effects. Certain of the chlorinated benzenes have been reported to possess mutagenic activity in bacterial or eukaryotic systems that detect gene mutations, to cause reciprocal chromosomal recombination in yeast, to cause differential cell kill in DNA repair deficient strains of bacteria; and to induce C-mitosis and chromosomal breaks in plant systems. Thus it is evident that the chlorinated benzenes possess the potential to induce mutation, to interact with the chromosomal material, to cause recombination between homologous chromosomes, and to cause C-mitosis and chromosomal aberrations in plants. In addition, certain chlorinated benzenes interact with bacterial DNA to produce DNA damage as evidenced by differential cell kill. Given the weight of the evidence, EPA considers that these agents may pose a potential mutagenic risk to the human population. However, these data are not sufficient to assess the extent of the risk of mutagenicity from the chlorinated benzenes and additional testing is necessary to develop such data.

EPA believes that mutagenic risk from exposure to the chlorinated benzenes

⁹Vorhees CV, Brunner RL, Butcher RE, Sobolka TJ. 1979. A developmental test battery for behavioral toxicity in rats: a preliminary analysis using MSG, calcium carageenan, and hydroxurea. *Toxicol. and App. Pharmacol.* 50:287-282.

can most reasonably be determined by performing a sequence of tests for both gene mutation and chromosomal aberration. In such schemes, the performance of certain tests is triggered by positive or negative results from previous tests. However, test requirements for the mutagenicity sequences are not being proposed today because, as of this time, EPA has been unable to develop specific criteria for test sequencing decisions that are suitable for inclusion in Section 4 test standards. EPA believes that such criteria are important to insure consistency between various laboratories in their determinations of whether to stop testing or proceed to the next test in the sequence. In addition, EPA has not yet developed test standards to be followed for the DNA alkylation tests in the gene mutation sequence or the *in vitro* cytogenetics test for chromosomal aberration.

In the interest of the public health, EPA believes that testing of chlorinated benzenes for their mutagenic effects should not be delayed due to its current inability to put in place all elements necessary for the testing sequence. Accordingly, due to the current absence of explicit criteria for the sequences, and because the initial tests of the mutagenicity sequences are short term tests which are not expensive to perform, EPA plans to arrange for the performance of all tests in the sequences except the final tests: DNA alkylation tests for gene mutation and the heritable translocation assay for chromosomal aberration. Based on its evaluation of the results of these EPA tests, the Agency will decide whether to propose that the final tests of each sequence be performed in accordance with EPA standards which are being or have been developed. EPA is soliciting public comment on the proposed mutagenicity testing sequences discussed below.

Test sequences are set forth for both gene mutation and chromosomal aberration tests because effects on either genes or chromosomes may give rise to heritable mutations. The following tests will generate information necessary to determine if chlorinated benzenes are potential human mutagens and perform a mutagenicity hazard assessment.

—Gene Mutation Testing. EPA believes tests should be performed which demonstrate the potential of the chlorinated benzenes to induce heritable gene mutations in a higher organism. In addition, the ability of the chlorinated benzenes to interact with mammalian germinal tissue should be determined.

The test battery planned for assessing gene mutation from exposure to the

chlorobenzenes consists of the reverse mutation in *Aspergillus nidulans*, the sex-linked recessive lethal test in *Drosophila melanogaster*, DNA alkylation in mouse and *Drosophila* sperm, gene mutation in mammalian cell culture, DNA alkylation in mammalian cell culture, and tests for DNA damage and repair. EPA believes it is appropriate to use *Aspergillus* rather than *Salmonella typhimurium* in the initial mutagenicity tests based upon the test results of the chlorinated benzenes in several microbial systems. These results have shown that reverse mutations are not produced in *Salmonella* strains TA-1535, 1537, 1538, and 98 and 100 with or without metabolic activation.¹⁰ Testing in *E. coli* WP-2 also showed that the chlorinated benzenes were non-mutagenic with and without metabolic activation. In contrast to the above results, monochlorobenzene produced point mutations in *Streptomyces antibioticus* and the dichlorobenzenes produced point mutations in *Aspergillus*. Consequently, the most appropriate mutagenicity test method, in the Agency's view, to assess the potential of additional chlorinated benzenes to be mutagenic is one of the latter. Inasmuch as monochlorobenzene, *o*-, *m*-, and *p*-dichlorobenzene were investigated in *Aspergillus* whereas only monochlorobenzene was tested in *S. antibioticus*, *Aspergillus* would be the species of choice. It should be noted that not all six compounds are proposed to be tested on the entire test battery. This is because some compounds have been adequately characterized in some tests and can be started further along in the sequence. Thus, testing of monochlorobenzene, *o*-, and *p*-dichlorobenzene begins with the sex-linked recessive lethal test in *Drosophila* because these agents have already been adequately tested in assay systems for the induction of point mutations in bacteria and fungi. EPA does not believe that monochlorobenzene should be tested in mammalian cells in culture because this agent has been adequately tested in mammalian cell culture and found to be inactive in this system. Tests for mutation in mammalian cells in culture have not been performed with *o*-, and *p*-dichlorobenzene or tri-, tetra- or pentachlorobenzenes. For this reason EPA believes that these substances should be tested in this system.

¹⁰ All 11 chlorinated benzenes have been proposed for testing in the *Salmonella* test system by the National Toxicology Program (NTP). EPA will coordinate its sequenced testing with the mutagenicity testing undertaken by NTP.

EPA does not consider that tri-, tetra- and pentachlorobenzene have been adequately tested for the ability to induce point mutations. The only results of which the Agency is aware at this time show trichlorobenzene to be inactive in *Salmonella*. The Agency believes that testing of these agents should begin with a test for reverse mutations in *Aspergillus* and follow the full testing sequence. The scheme includes testing for DNA damage and repair if both *Aspergillus* and gene mutation in mammalian cell culture are negative.

The test sequences for gene mutation are shown in Figures 3-6. The figures designate the tests which EPA plans to perform.

—Chromosomal Aberration Testing. EPA believes that the chlorinated benzenes should be further tested for their ability to produce chromosomal aberrations. The tests to be performed on chlorinated benzenes include: *in vitro* cytogenetics, *in vivo* cytogenetics, dominant lethal assay, and the heritable translocation assay.

Chromosomal aberrations may be detected in a variety of animal and plant systems employing both *in vitro* cell culture and whole animal techniques. Because EPA is unaware of tests for chromosomal aberrations having been performed in mammalian systems, the Agency believes that the chlorinated benzenes should be tested for chromosomal aberrations beginning with a test for chromosomal aberrations in mammalian cells in culture. Because it is possible that some agents which are not detected in *in vitro* systems may be detected in whole animal systems, the Agency believes that a negative *in vitro* cytogenetics assay should be followed by a test for chromosomal aberrations *in vivo*. No further testing for chromosomal aberrations will be performed if both the *in vitro* and *in vivo* cytogenetics tests are negative. A positive cytogenetics assay will be followed by a dominant lethal test to demonstrate the effect of the chlorinated benzenes on germinal cell chromosomes. It has been shown that the incidence of chromosome breaks at first cleavage of the fertilized egg is proportional to the number of dominant lethals which occur after treatment and mating. No further testing for chromosomal aberrations will be performed if the dominant lethal test is negative. The heritable translocation test can be used to show the ability of a chemical to induce heritable chromosomal aberrations. Thus, this test can be used not only to detect potential mutagens but also for purposes of assessing risk. Based on its evaluation

of the results of the dominant lethal assay the Agency will decide whether to propose a test rule requiring performance of the final test in the sequence, heritable translocation test, the results of which can be used for hazard assessment.

The test sequence for chromosomal aberrations is the same for all of the chlorinated benzenes and is shown in Figure 7. The figure designates which tests EPA plans to sponsor.

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MONOCHLOROBENZENE
Gene Mutation Testing Scheme

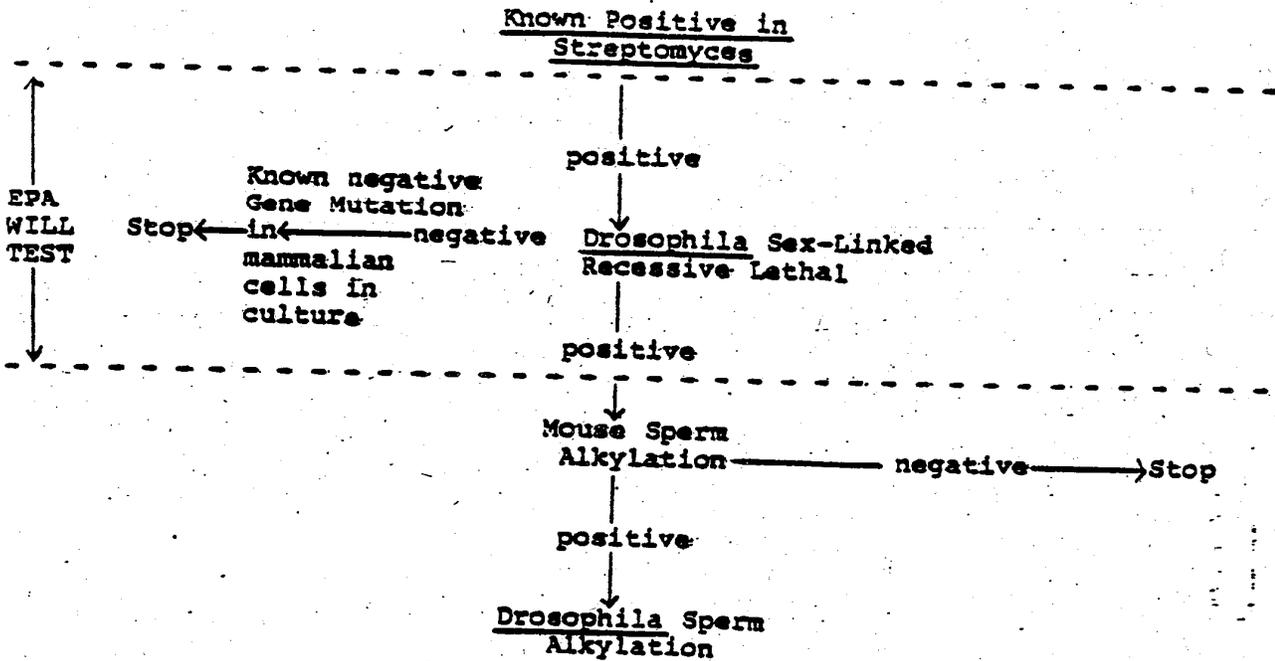


FIGURE 3

o- and p-DICHLOROBENZENE
Gene Mutation Testing Scheme

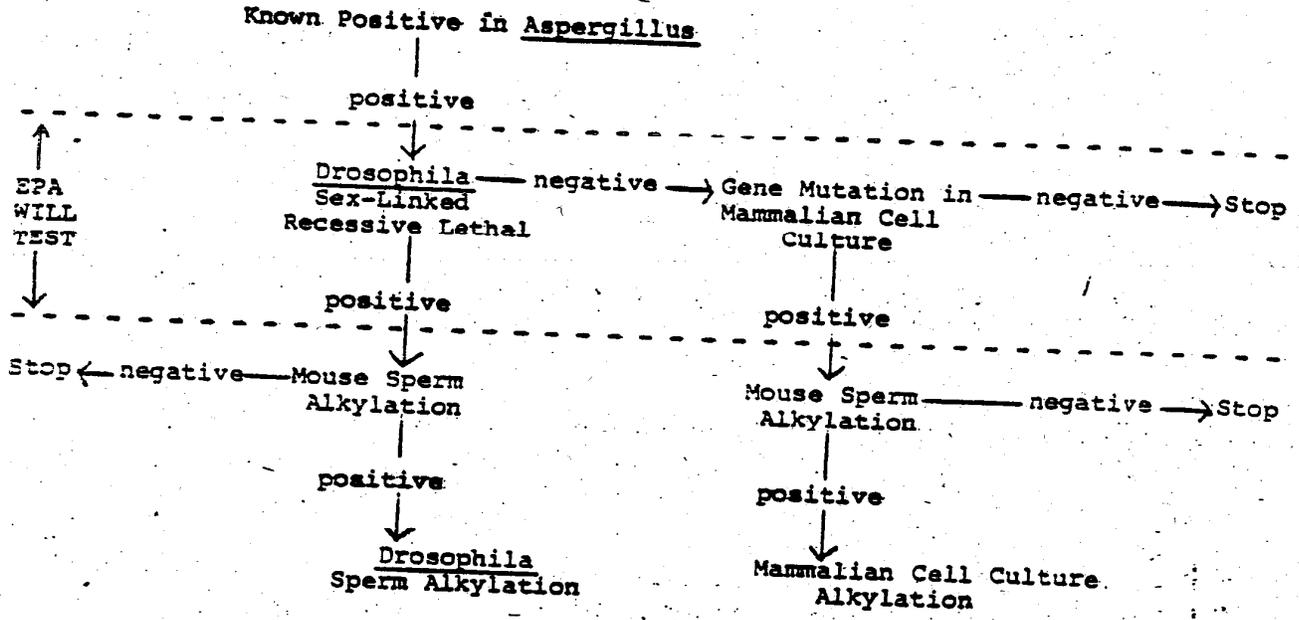


FIGURE 4

TRICHLOROBENZENE AND HIGHER
Gene Mutation Testing Scheme I
(Positive Aspergillus Assay)

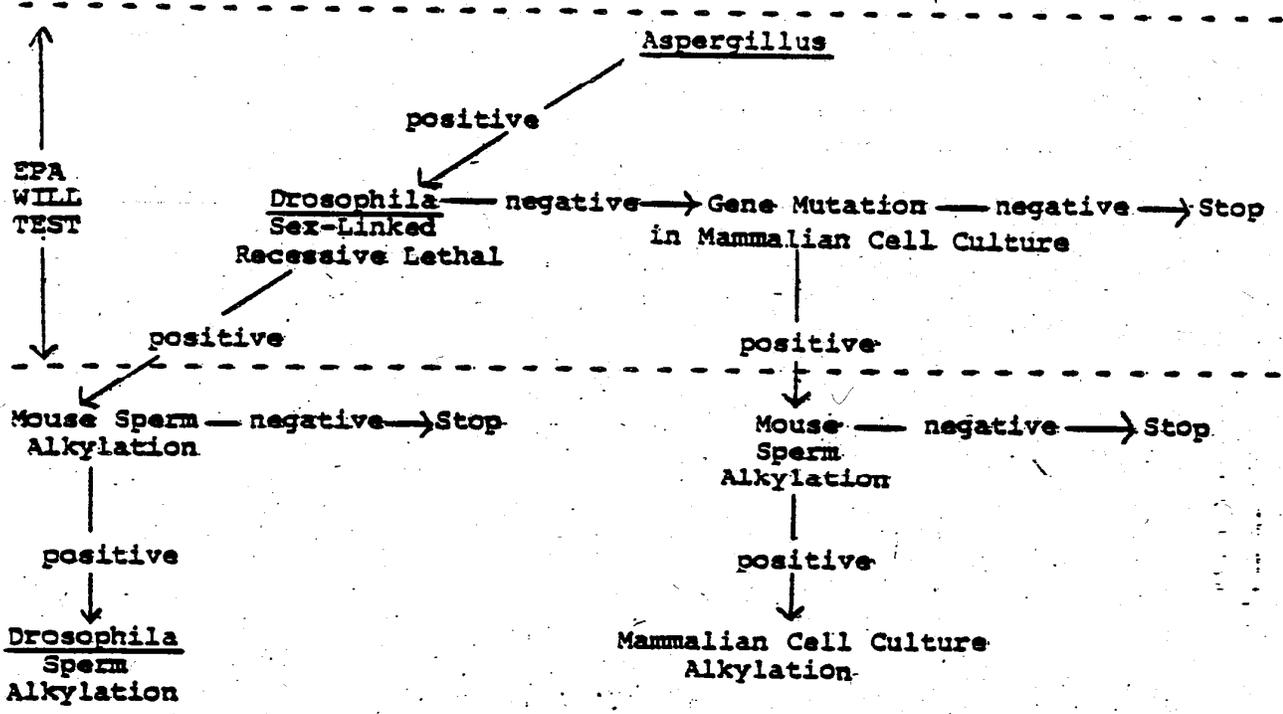


FIGURE 5

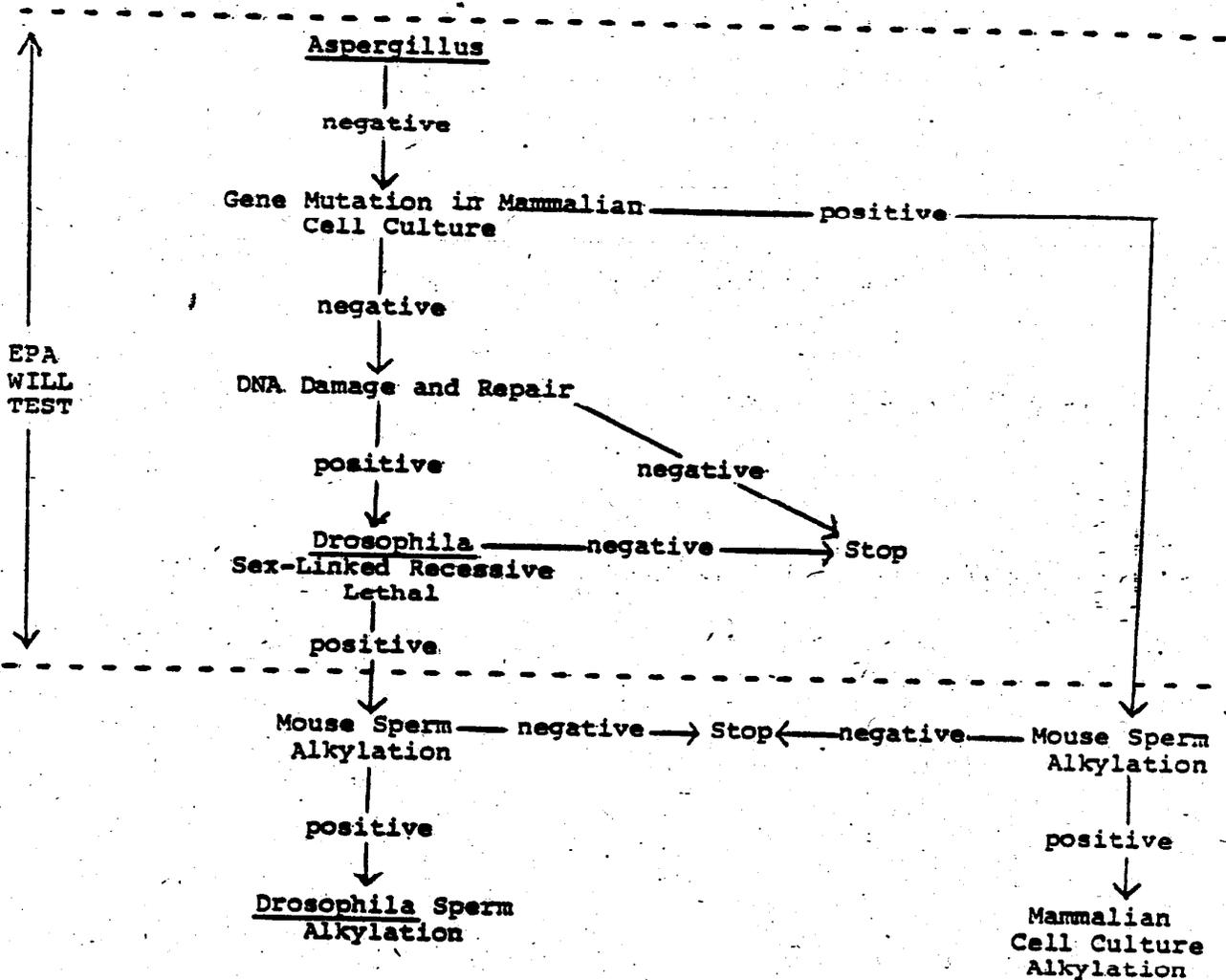


FIGURE 6

CHLORINATED BENZENES

Test Scheme For Chromosomal Aberrations

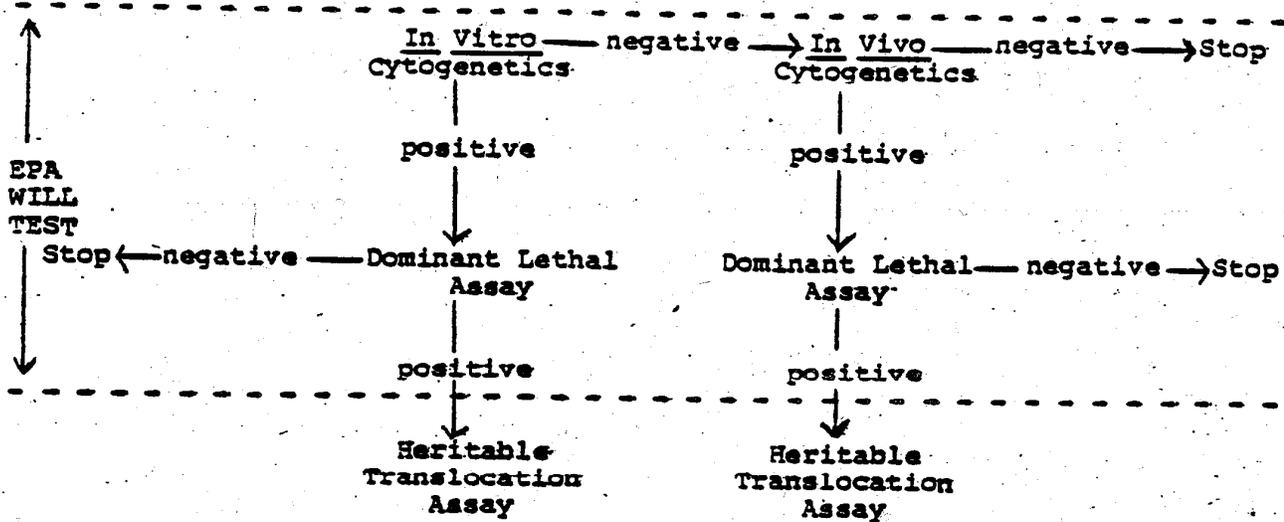


FIGURE 7

4. Metabolism. The metabolism studies discussed in the Chlorinated Benzenes Support Document deal primarily with the products of chlorinated benzene metabolism and provide little information on the pharmacokinetic aspects. The studies lead to the conclusion that the chlorinated benzenes are metabolized at least in part to epoxide (arene oxide) intermediates. Such intermediates may have the ability to react with biological macromolecules, with potentially harmful effects on the target organism. However, more information is desirable on the rates of formation and the reactivity of the intermediate epoxides derived from different chlorobenzenes, as well as on the ability of chlorobenzenes and their metabolites to reach and react with target tissues or molecules. This type of information should contribute to a better understanding of the trends observed in the biological effects of the chlorinated benzenes.

Metabolism studies would provide information on whether or not chlorobenzenes or their metabolites do form covalent compounds with macromolecules, particularly in the brain and gonads and in organs from which excretion is especially slow. If chlorobenzenes do form covalent compounds with macromolecules, experiments could determine whether binding is to DNA, protein, or both. These studies would also provide data on the distribution of chlorobenzene compounds to tissues and organs of the test species and the rates of their clearance from these tissues.

EPA believes that metabolism testing should be performed to help determine the degree of commonality between members of the chlorinated benzenes group with respect to biological effects. EPA is not now proposing metabolism testing because currently proposed test standards for metabolism focus on absorption and excretion studies. EPA is soliciting comment on what other metabolism tests should be included in test standards in order to appropriately characterize these chemicals.

E. Decision Not To Require Testing for Acute Toxicity and Epidemiology

1. Acute toxicity. As discussed in section III.A. of the Chlorinated Benzenes Support Document, EPA believes that available human and animal data are sufficient to evaluate the acute toxicity of the chlorinated benzenes. Therefore, EPA is not proposing further testing for acute toxicity at this time.

2. Epidemiology. EPA believes that an epidemiological study of workers

exposed to the chlorinated benzenes could potentially provide valuable data for evaluating the potential risk from such exposures. However, an epidemiological test requirement is not being proposed today because EPA is currently unable to identify a suitable cohort. The identification of a suitable cohort is a complex process requiring specific information. If EPA obtains information identifying a suitable cohort under Section 8(a) of TSCA, the Agency will evaluate the need for proposing an epidemiologic study on chlorinated benzenes considering in its evaluation test results obtained from the required tests if they are available. In the case of chlorinated benzenes, EPA is soliciting public comment on the feasibility and desirability of an epidemiological study.

VI. Summary of Proposed Rule

A. Chloromethane

1. Effects to be tested.

- **Oncogenicity.** EPA is proposing that a two-year oncogenicity study be conducted in accordance with proposed oncogenicity test standards to be promulgated under 40 CFR 772.113-2. The proposed oncogenicity standard was published in the Federal Register of May 9, 1979 (44 FR 27334). For chloromethane, EPA is proposing modification of the proposed standard to require the use of the hamster instead of the rat because studies have shown that the rat is relatively insensitive to the chronic effects of chloromethane. Thus, the Agency is proposing that mice and hamsters be used in the oncogenicity study and solicits comments on the use of these species.

- **Structural Teratogenicity.** EPA is proposing that a structural teratogenicity study be conducted in accordance with the proposed structural teratogenicity test standard to be promulgated under 40 CFR 772.116-2. The proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054).

EPA is modifying the proposed standard to require use of another species instead of the rat. EPA has inferred that since rats are relatively insensitive to the chronic effects of chloromethane they may also be insensitive to its teratogenic effects (see section III.E. of the Chloromethane Support Document). Thus, EPA is proposing that two of the species recommended in the proposed standard other than the rat be used in the structural teratogenicity test and solicits comment on the exclusion of the rat. This proposal is discussed further in section X, Issues for Comment. EPA does not believe the characteristics of

chloromethane necessitate any other changes to the proposed standard.

2. Test Substance. The EPA is proposing that a grade of chloromethane of 99.95 percent or greater purity be used as the test material in the required tests.

Because chloromethane may contain contaminants which may cause a toxicological effect of concern and are likely to interfere significantly with the outcomes of the proposed tests, EPA believes the proposed higher level of purity should be used. Chloromethane of this purity is available commercially. General considerations for selection of the appropriate form of the substance for testing were discussed earlier in this preamble.

3. Route of administration. Because chloromethane is a gas, the route of administration must be by inhalation.

4. Persons required to test, exemptions. Because chloromethane is used almost exclusively as a chemical intermediate in the production of other products, the maximum potential for exposure exists during its manufacture, processing, and use. In comparison, distribution and disposal activities at present are not of concern. Therefore, in accordance with Section 4(b)(3)(B) of TSCA, the EPA is requiring that testing be performed by both manufacturers and processors of chloromethane.

Because "manufacture" is defined in Section 3(7) of TSCA to include "import", importers of chloromethane are subject to this rule. EPA also proposes to make a Section 12(a)(2) finding requiring persons who manufacture these chemicals solely for export purposes to test in accordance with this rule. Because much of EPA's concern derives from exposure that may occur during domestic manufacturing, EPA believes manufacturing for export purposes may present an unreasonable risk of injury to health within the United States.

EPA's proposed exemption policy and procedures may be found elsewhere in today's Federal Register. Section 771.10(e) as proposed provides that persons subject to the rule who do not test chloromethane or participate in a joint test group to test chloromethane must apply to EPA for an exemption from the test rule. EPA will accept exemption applications from manufacturers and processors of chloromethane after the effective date of this test rule. Persons wishing to comment on EPA's exemption policy and procedure should read the exemption notice. EPA is not proposing to require the submission of equivalence data as a condition for exemptions from the proposed testing because EPA has

designated a relatively pure grade of chloromethane for testing.

5. **Reporting requirements.** This proposal contains additional study plan requirements that will be promulgated as part of the final test standards.

• **Oncogenicity.** The Agency's proposed test standard requires that a Study Plan be submitted to EPA at least 90 days before the initiation date of the test. In addition, Interim Quarterly Summary Reports are required during the 24-30 month test period. The proposed deadline for submission of the Final Report is no later than 53 months after the effective date of the final test rule.

• **Structural Teratogenicity.** The Agency is proposing that a Study Plan be submitted to EPA no later than the initiation date of the test and preferably earlier than this deadline. In addition, it is proposed that no Interim Quarterly Summary Reports be required. The proposed deadline for submission of the Final Report is no later than 11 months after the effective date of the final test rule.

B. Chlorinated Benzenes

1. Effects to be Tested.

• **Oncogenicity.** EPA is proposing that two-year oncogenicity study be conducted on the designated chlorinated benzenes (see B.2.a.), excluding monochlorobenzene and *o*- and *p*-dichlorobenzenes, in accordance with the proposed oncogenicity test standards to be promulgated under 40 CFR 772.113-2. The proposed standard was published in the Federal Register of May 9, 1979 (44 FR 27334). The proposed standard calls for the use of two species of rodents in the study; both the rat and mouse. However, in this case, EPA is specifically proposing that the strain of rat used should be Sprague-Dawley since a recent study has found that this strain is sensitive to production of tumors by benzene (a structurally related compound).

• **Structural Teratogenicity.** EPA is proposing that a structural teratogenicity study be conducted on the designated chlorinated benzenes, excluding pentachlorobenzene, in accordance with the proposed structural teratogenicity test standard to be promulgated under 40 CFR 772.118-2. This proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054). EPA does not believe the characteristics of the chlorinated benzenes necessitate any modifications or additions to the proposed generic teratogenicity standard.

• **Reproductive Effects.** EPA is proposing that a reproductive study be conducted on the designated

chlorobenzenes, except 1, 2, 4-trichlorobenzene, in accordance with the proposed reproductive effects test standard to be promulgated under 40 CFR 772.116-3. This proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054). EPA does not believe the characteristics of the chlorinated benzenes necessitate any modifications or additions to the proposed generic reproductive effects standard.

• **Subchronic/Chronic Effects.** EPA is proposing that a 90-day subchronic toxicity study be conducted on the designated chlorobenzenes excluding pentachlorobenzene, in accordance with the proposed subchronic test standard to be promulgated under 40 CFR 772.112. This proposed standard was published in the Federal Register of July 26, 1979 (44 FR 44054). The oral subchronic standard calls for the use of two species, a rodent and a nonrodent. For the nonrodent species, the proposed standard strongly recommends the use of the dog. However, the dog has been shown to be relatively insensitive to toxic effects from exposure to the chlorinated benzenes (see section III.B. of the Chlorinated Benzenes Support Document). For this reason, EPA is proposing that for both oral and inhalation routes of administration only the rat be tested for subchronic/chronic effects. EPA does not believe the characteristics of the chlorinated benzenes necessitate any other modifications or additions to the proposed generic subchronic effects standard.

2. Test Substances.

(a.) **Representative Sample.** EPA has determined that a representative sample of chemicals in the chlorinated benzenes group be tested. This sample consists of the following chemicals:

Monochlorobenzene
1,2-Dichlorobenzene (*ortho*-
Dichlorobenzene)
1,4-Dichlorobenzene (*para*-
Dichlorobenzene)
1,2,4-Trichlorobenzene
1,2,4,5-tetrachlorobenzene
Pentachlorobenzene

The Agency's decision to propose testing of a representative sample rather than testing of all 11 category members rests in part on the chemical nature of the category and in part on available data on the biological effects of chlorinated benzenes.

As discussed in Section I.A.2. of the Chlorinated Benzenes Support Document, the structural relationships among the chlorinated benzenes lead to the expectation of regular progressive changes in properties going through the

series from mono- to pentachlorinated benzene, with the discontinuities that arise from different isomeric arrangements of chlorine and hydrogen atoms being relatively minor in comparison with the overall trends. This expectation is supported by trends in physiochemical data of which several appear in Table 1, Section I of the Support Document. Thus, in proceeding from monochlorobenzene to pentachlorobenzene, densities, boiling points and partition coefficients show a gradual increase, while water solubility decreases. Since physiochemical properties determine, in a complex fashion, the biological effects of a substance, the observed regularity in these properties of the category provides a basis for expecting that biological data on a well-chosen sample of category members can be used to characterize the biological behavior of the untested members.

In addition, various data reviewed in the Chlorinated Benzenes Support Document support the position that there appear to be certain effects and biological properties associated with the chlorinated benzenes as a group. For example, in animal studies, all of the chlorobenzenes tested have effects on the liver, several have effects on the kidneys, and all those tested lead to changes in the hematopoietic system. Further, the data that are available on the metabolism of chlorobenzenes to support the conclusion that most if not all of the compounds undergo epoxidation, dechlorination, and/or oxidation by none-epoxide mechanisms, with various chlorophenols among the major products. In some cases, different chlorobenzenes are metabolized to a common chlorophenol.

This is not to imply that all category members will necessarily have identical effects or similar potencies for a given effect, but the Agency believes that scientific principles and available data and experience lead to a reasonable presumption that the biological behavior of these 11 chemicals will present a coherent picture of toxicity and that biological data on a well-chosen sample of category members can be used to characterize the biological behavior of the untested members.

In general, EPA has selected the six chlorinated benzenes which comprise the test sample on the basis of spanning the structural spectrum of the category taking into account production and exposure.

In choosing the category test sample, an important factor is that, with increasing chlorination, chlorobenzenes will be more resistant to metabolic attack and more likely to be retained in

body tissues. Thus a sample including only mono- and dichlorobenzenes would be unrepresentative because it would include only the compounds most subject to metabolic attack and least likely to be stored in tissues. EPA is, therefore, proposing a test sample that includes all levels of chlorination. Furthermore, the Agency believes that relative production volume should be an important factor in the sample selection. Applying these two criteria leads to the choice of monochlorobenzene, *o*- or *p*-dichlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,4- or 1,2,4,5-tetrachlorobenzene, and pentachlorobenzene. EPA has decided to include both *o*- or *p*-dichlorobenzene in its test sample for two reasons. First, both have widespread general population exposure. Second, it seems prudent to include more than one isomer for at least one level of chlorination in order to provide information on to what extent the toxic effects of chlorobenzenes may be affected by the distribution of chlorine atoms. The 1,2,4,5-isomer of tetrachlorobenzene was chosen because its production is somewhat higher than that of the 1,2,3,4-isomer, and because there is not a more compelling reason to distinguish between them.

The six sample chemicals thus represent all levels of chlorination, the full range of physicochemical properties, and compounds having the highest commercial production among the chlorinated benzenes. Available data on chlorinated benzenes not included in the testing sample will serve as additional data points for evaluation of chlorobenzene toxicity when the test results become available.

(b.) Purity of the Test Substances. The test material of the six chlorobenzenes used in health effects testing should be substantially free of contaminants that are likely to interfere significantly with the effects to be observed. Since the chlorinated benzenes are often contaminated with benzene and hexachlorobenzene, two related compounds of known toxicity, EPA believes that the tested chlorobenzenes should be of 99.9 percent or greater purity with no more than 0.05 percent benzene and 0.05 percent hexachlorobenzene. The 99.9 percent criterion can be satisfied without excessive difficulty by the purification of commercially available materials. In addition, commercially available chlorinated benzenes have been offered at 99.9 percent level of purity. Sample purity can be checked by currently available analytical methods (e.g., gas chromatography and mass spectrometry).

EPA is aware that monochlorobenzene is available with less than .05 percent benzene, and EPA believes that benzene concentrations below .05 percent are unlikely to significantly affect the results of the tests. Furthermore, other chlorinated benzenes are likely to contain less benzene than mono-chlorobenzene. Thus, EPA believes that .05 percent benzene is a reasonable level to require. The .05 percent level for hexachlorobenzene was selected because the Agency believes that this level is also unlikely to significantly affect test results and because it is probably a relatively easy level to obtain. The Agency is soliciting comment on these levels of purity.

3. *Route of Administration.* The selection of the route of administration of a test substance emphasizes the following considerations:

(a) The physical and chemical constants of the test substance, such as volatility or boiling point, under conditions of probable or actual human exposure;

(b) the predominant portal(s) of entry of the test substance in man, and

(c) the practicability of experimentally approximating the probable conditions of human exposure, given the physical and chemical constants of the test substance and the relative adaptability of the test species to the proposed route of administration.

For subchronic, structural teratogenicity, and reproductive effects testing, EPA is proposing that monochlorobenzene be tested with inhalation as the route of administration. Monochlorobenzene is a volatile liquid, used primarily as a solvent and as an intermediate for synthesis of chloronitrobenzenes. It appears that inhalation would be the most likely exposure route for humans. It is proposed that *ortho*- and *para*-dichlorobenzene be tested with inhalation as the route of administration. Both of these compounds are used in a variety of household products. *para*-Dichlorobenzene, is a solid that sublimates readily; *ortho*-dichlorobenzene, a relatively volatile liquid. Inhalation is the most likely exposure route for humans for the two dichlorobenzenes in both the occupational setting and in the home.

It is proposed that 1,2,4-trichlorobenzene, a liquid, be tested with oral gavage as the route of administration for the structural teratogenicity study. In teratogenicity studies, gavage is the preferred route since addition of test chemical to the feed or water may result in a reduction

of food or water intake, and consequently seriously compromise the value of the study. It shall be administered in the diet for the subchronic, and oncogenicity tests. (Reproductive effects testing is not proposed for 1,2,4-trichlorobenzene). This compound is partly used as a dye carrier. Upon completion of the dyeing process, the carrier is removed from the fabric and discharged as waste. 1,2,4-Trichlorobenzene has also been used in transformers. It has been identified in drinking water, and it appears that the most likely exposure route for humans would be orally through the water supply.

It is proposed that pentachlorobenzene, a crystalline solid, be admixed in the diet for oncogenic and reproductive studies (subchronic studies and structural teratogenicity tests are not proposed for pentachlorobenzene).

It is proposed that 1,2,4,5-tetrachlorobenzene, also a crystalline solid, be admixed in the diet for administration to the animals for the purposes of subchronic, oncogenic, and reproductive studies. The route of administration for the structural teratogenicity study of 1,2,4,5-tetrachlorobenzene should be oral gavage. As stated above, gavage is the preferred route for teratogenicity studies. 1,2,4,5-tetrachlorobenzene has been used in transformers. It has been found in fresh water fish and in herring gull eggs. Pentachlorobenzene is a contaminant in the production of other chlorinated benzenes and is disposed of as waste. It has been found in many foods. Therefore, the most likely exposure route for humans is orally through the food supply.

4. *Persons Required to Test, Exemptions.* On the basis of the use of chlorinated benzenes as chemical intermediates and for other industrial purposes, EPA has determined that exposure may occur to industrial workers and the general population from the manufacture, processing, use, and disposal of chlorinated benzenes. Therefore, EPA is proposing that all manufacturers and processors of any of the eleven chlorinated benzenes defined in § 773.100(a) be required to perform the health effects testing specified in the proposed test rule.

Because "manufacture" is defined in Section 3(7) of TSCA to include "import", importers of the chlorinated benzenes are subject to this rule. EPA also proposes to make a Section 12(a)(2) finding requiring persons who manufacture these chemicals solely for export purposes to test in accordance with this rule. Because much of EPA's

concern derives from exposure that may occur during domestic manufacturing. EPA believes manufacturing for export purposes may present an unreasonable risk of injury to health within the United States.

Two alternatives to EPA's proposal to require all manufacturers and processors of chlorinated benzenes to test the representative sample are being considered: (1) Require all manufacturers and processors of chlorinated benzenes to test the chlorinated benzenes which they manufacture or process but perform the testing in two stages—six chemicals now and, if necessary, the remaining five later, and (2) require only the manufacturers and processors of the six sample chemicals to perform testing of the chemicals which they manufacture or process as individual chemicals. In the second alternative EPA would later issue a separate test rule to require testing on all or some of the remaining five chlorobenzenes if necessary. Discussion of these alternatives may be found below and in the Proposed Statement of Exemption Policy and Procedures in today's Federal Register.

EPA is proposing the "whole category" approach described in Section III.D. In addition, EPA is considering the two other approaches and may adopt one of them in the final rule, depending on the public comments received and EPA's continued evaluation.

EPA is proposing that all manufacturers and processors of the chlorinated benzenes be required to test, or help pay for testing, the sample of six chlorinated benzenes proposed for testing.

An alternative to the proposed (Alternative 1) approach would require all persons who manufacture or process the chlorinated benzenes to test them but to perform the testing in stages. Thus, the present sample of six chemicals would be the first stage tested. Manufacturers and processors of these six chemicals would test now or obtain an exemption as for any individual chemical, whereas persons who manufacture and process the remaining five chemicals (1,3-dichlorobenzene, 1,2,3-trichlorobenzene, 1,3,5-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, and 1,2,3,5-tetrachlorobenzene) would not begin testing these compounds until the results of the tests on the first six were available. If the results of the first six

could characterize the entire category, the manufacturers of the remaining five would obtain exemptions and would reimburse the manufacturers and processors of the six chemicals that were tested.

A second alternative that EPA is considering (Alternative 2) would require that only the six compounds designated be tested as individual chemicals. Thus, manufacturers and processors of 1,3-dichlorobenzene, 1,2,3-trichlorobenzene, et cetera, would not be subject to testing under this rule. The manufacturers and processors of the six chemicals subject to the rule would test or apply for exemptions as they would for any individual chemical.

Because of the specific facts pertinent to the chlorinated benzenes, the same sample would be chosen under all three approaches. In addition, to their potential to act as representative of all chlorinated benzenes, the six chemicals in the sample are those chlorinated benzenes that are produced in relatively higher quantities. Thus, even if EPA decided not to pursue testing of the entire category or not to choose a sample based on structure and physicochemical properties as well as production, EPA would want to test these chemicals as individual chemicals. Under such circumstances, it would not be inequitable to have the manufacturers and processors of monochlorobenzene, *o* and *p*-dichlorobenzenes, 1,2,4-trichlorobenzene, 1,2,4,5-tetrachlorobenzene, and pentachlorobenzene bear the entire cost of testing their respective chemicals.

The economic implications of these options are discussed in Section VII.

5. Reporting Requirements. This proposal contains additional study plan requirements that will be promulgated as part of the final Test Standards.

• **Oncogenicity.** The Agency's proposed test standard requires that a Study Plan be submitted to EPA at least 90 days before the initiation date of the test. In addition, Interim Quarterly Summary Reports are required during the 24–30 month test period. The proposed deadline for submission of the Final Report is no later than 53 months after the effective date of the final test rule.

• **Structural Teratogenicity.** The Agency is proposing that a Study Plan be submitted to EPA no later than the initiation date of the test and preferably

earlier than this deadline. In addition, it is proposed that no Interim Quarterly Summary Reports be required. The proposed deadline for submission of the Final Report is no later than 11 months after the effective date of the final test rule.

• **Reproductive Effects.** The Agency's proposed test standard requires that a Study Plan be submitted to EPA at least 90 days prior to the start of the test. In addition, Interim Quarterly Summary Reports are required during the 13-month test period. The proposed deadline for submission of the Final Report is no later than 29 months after the effective date of the final test rule.

• **Subchronic/Chronic Effects.** The Agency proposes that a Study Plan be submitted to EPA no later than the initiation date of the test and preferably earlier than this deadline. It is proposed that no Interim Quarterly Summary Reports be required. The proposed deadline for submission of the Final Report is no later than 12 months after the effective date of the test rule.

VII. Economic Analysis of Proposed Rule and Alternatives

To evaluate the potential economic impact of test rules, EPA has adopted a two-stage approach. All chemicals will go through a Level I analysis; this analysis consists of evaluating each chemical (or group) on four market characteristics, (1) demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis (along with a consideration of the cost for the required tests) will indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for that chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis will be conducted. This Level II analysis attempts to predict more exactly the magnitude of the expected impact.

The methodology, analyses, costs of the test requirements, and conclusions are presented in the Economic Analysis Support Document accompanying this rulemaking package. The following is a summary of the economic impact of this rule.

A. Cost of the Test Requirements for Chloromethane and the Representative Group of Chlorobenzenes

Compound	Total cost (thousands)	Annualized cost (thousands)*
Chloromethane.....	\$700-\$1,300	\$144-\$267
Monochlorobenzene 1,2.....	192-418	39-85
Dichlorobenzene 1,4.....	192-418	39-85
Dichlorobenzene 1,2,4.....	192-418	39-85
Trichlorobenzene 1,2,4,5.....	383-1,148	79-236
Tetrachlorobenzene.....	440-1,319	90-271
Pentachlorobenzene.....	413-1,238	85-254

* 20% cost of capital for 20 years.

B. Chloromethane

The Level I analysis indicated that the proposed test rule will not pose any significant economic impact on chloromethane manufacturers. A Level II analysis was not needed.

This conclusion is based upon the following considerations: first, demand for chloromethane appears to be insensitive to change in price. That is, an increase in price is expected to result in a proportionately smaller decrease in the quantity demanded. The primary use of chloromethane is in the production of silicones, and the demand for silicones is particularly insensitive to price. In addition, the market for silicone products is clearly expanding, indicating that the demand for chloromethane will be increasing.

C. Chlorobenzenes

The result of the Level I analysis indicated the possibility of potential economic impact as a result of these proposed rules. The highest volume chlorobenzene is monochlorobenzene, which is used primarily in industrial solvent applications. The market for monochlorobenzene is characterized by many potential substitutes which suggested that the demand for monochlorobenzene could be price sensitive. The dichlorobenzenes (para and ortho-) appeared to face similar market conditions. Although the higher chlorobenzenes seemed to face less competition from substitutes, their production levels appeared to be significantly lower. This tentative conclusion was based on their weak market performance over the past few years and pessimism regarding the end-uses for chlorobenzenes. Therefore on the basis of competitiveness, potential price sensitivity, and production complementarity, chlorobenzenes were considered a potentially sensitive product group and, thus candidates for a Level II analysis.

However, the Level II analysis concluded that the economic impacts

will be small. This conclusion was based on the following findings:

(1) Annualized testing costs will not be unduly large, either in an absolute or relative sense, particularly if the proposed approach to testing and exemptions is adopted;

(2) The demand for chlorobenzenes (both as a group and for individual members) appears relatively insensitive to price changes;

(3) The growth of export markets may mitigate the effects of fairly static domestic market for chlorobenzenes; and

(4) The small (and perhaps, the most financially marginal) producers have already abandoned the market.

While the Level II analysis indicates that there may be some impacts (most likely on very small processing firms), it is expected that the impacts (if realized) will be less than estimated for two major reasons: (1) the analysis followed a "worst case" approach, and (2) the possibility of reimbursement (cost sharing) will reduce the absolute cost that each firm affected by this proposed rule will have to bear.

D. Economic Analysis of Regulatory Alternatives for Chlorobenzenes

Three separate schemes for testing chlorobenzenes are being considered for this test rule. Using the methodologies developed and discussed in the Economic Analysis Support Document, the differential impacts of each alternative were compared through examination of resultant product price changes.

As discussed in the Economic Analysis Support Document, under the proposed approach and Alternative 2, only six chemicals are proposed for testing. The only difference in the two approaches, in terms of economic impact, is that under the first alternative, all manufacturers and processors of chlorinated benzenes must share the testing costs; whereas, under the second alternative, only manufacturers and processors of mono-, di-, tri-, tetra-, and pentachlorobenzene may be required to pay. However, this difference appears to be insignificant for this rule since the producers of the chlorobenzenes that are not being tested seem, on the whole, to be the same persons who produce the six chlorobenzenes for which testing is being required. Consequently, the greatest difference appears to be between Alternative 1 and the other options since only the former approach is most likely to entail the testing of all 11 chlorobenzenes.

Despite these apparent distinctions, the conclusions with regard to the three options are identical. Little or no economic impact is expected. The impact is particularly modest if the Agency promulgates this rule with the exemption policy being proposed today. In that case, all six of the test substances will face a testing cost equivalent to approximately ¼ cent per pound of production, and the fungicide PCNB (the end-use of tetra- and pentachlorobenzene) will face an increase of about 0.6 cent per pound. Under the two alternative exemption approaches, the upper three chlorinated benzenes would face testing costs equivalent to between 2.8 cents per pound and 25.4 cents per pound, with PCNB facing additional input costs equivalent to between 0.3% and 14.2% of its selling price. However, because of its strong market position, even those increased costs are not expected to affect consumption of that product.

The Agency invites comments on the methodology, analyses, and conclusions. Comments should be accompanied by relevant data.

VIII. Availability of Test Facilities and Personnel

In addition to the requirements discussed previously, Section 4(b)(1) requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule."

Because this is the first test rule under TSCA and covers relatively few chemicals, EPA believes there will be available resources to perform the required testing. The rule initially requires testing of only chloromethane and six of the chlorinated benzenes; at most, testing could be required later for the five other chlorinated benzenes granted contingent exemptions. In addition, it is expected that the many manufacturers and processors subject to the rule will not pursue testing individually, but rather will make use of joint testing arrangements or the exemption and reimbursement provisions of Section 4 to minimize the number of tests that will be performed.

EPA is aware that as more test rules are developed, the cumulative effects of testing requirements under TSCA and the Federal Insecticide, Fungicide, and Rodenticide Act may be significant. Hence, the Office of Regulatory Analysis (ORA) of the Office of Pesticides and Toxic Substances is currently developing the necessary

methodology for assessing the potential resource impact of EPA testing requirements on the testing community.

IX. Compliance and Enforcement

Compliance and enforcement issues have been discussed in the proposed oncogenicity and chronic effects standards published in the Federal Register May 9, 1979 (44 FR 27334). When promulgated, the standards will appear under 40 CFR 770.5.

X. Issues for Comment

The public is encouraged to submit comments on the various matters discussed in the preamble and accompanying support documents. In addition, EPA specifically requests comments on the issues highlighted below. Part A addresses scientific issues relating to the proposed rules on chloromethane and the chlorinated benzenes, and Part B discusses scientific issues pertaining to EPA's plans to propose test rules and standards for neurotoxicity (neurologic and behavioral effects), behavioral teratogenicity, mutagenicity, metabolism, and epidemiology. Part C raises general issues concerning this rulemaking and Section 4 of TSCA.

Review of the various support documents and related Federal Register notices will facilitate comments on the issues listed below. In particular, the Support Documents for chloromethane and the chlorinated benzenes indicate EPA's views on the scientific issues in further detail.

As stated previously, there is no need to repeat comments that were previously submitted to EPA concerning the proposed health effects standards.

A. Scientific Issues Pertaining to Proposed Rule

1. Chloromethane.

(a) Are the species proposed for oncogenicity testing and structural teratogenicity testing appropriate for assessing these risks associated with chloromethane? In addition, should EPA specify which species should be used or should the choice be made by those performing such tests?

The Agency believes that chronic studies have shown that the rat is relatively insensitive to the chronic effects of chloromethane. Therefore, EPA is proposing that the oncogenicity tests be conducted using mice and hamsters instead of rats and that the species selected for the teratogenicity study be in accordance with the proposed test standard except that the rat should not be selected (see sections D and E of the Chloromethane Support Document, respectively). The Agency

solicits comment on the specification that the rat is not to be used for these studies.

(b) Do any additional modifications of the testing procedures or standards need to be made for testing chloromethane?

EPA has tailored this test rule to chloromethane by proposing that all tests be performed with inhalation as the route of exposure. The Agency has not specified any other modifications to the test standards other than the use of a species other than the rat for structural teratogenicity and oncogenicity testing (discussed in a. above).

(c) Should the structural and behavioral teratogenicity studies be combined? If so, what methodology should be used?

EPA is proposing that structural teratogenicity tests be performed on chloromethane. The Agency is interested in comments on whether modifications in the structural teratogenicity tests which would adequately test for behavioral teratogenicity are feasible and/or desirable. Commentors should also consider whether combining these tests would delay obtaining results from the structural teratogenicity tests.

(d) Is the oncogenicity testing being carried out under contract for CIIT adequate to assess chloromethane's oncogenic potential?

CIIT has reported a number of problems associated with the execution of the CIIT sponsored tests. EPA believes these problems potentially preclude their usability by the Agency to assess chloromethane's oncogenic potential (see section III.D. of the Chloromethane Support Document). The Agency solicits comment on this issue.

(e) Are there significant studies which have not come to the attention of EPA which would provide sufficient data and experience for evaluation of chloromethane especially with respect to reproductive effects?

Studies which have been considered by EPA in the course of this rulemaking are listed in the bibliography of the Chloromethane Support Document or are otherwise available in the public record of this proceeding. EPA acquired this information through a comprehensive literature search, information submitted in response to a Section 8(d) rule, and requests for information addressed to other Federal Agencies. EPA was unable to identify any data to support a conclusion that chloromethane may present a risk of reproductive effects and is therefore particularly interested in information on reproductive effects.

2. Chlorinated Benzenes.

(a) Should any additional chlorinated benzenes be incorporated in the sample designated for testing? Should any be deleted? Alternatively, should all chlorinated benzenes that are members of the category, as defined by EPA, be tested?

The options considered in the choice of chemicals to include in the sample designated for testing are discussed in section C which follows on General Issues. EPA's sample of chlorinated benzenes is intended to span the structural spectrum of the category taking into account exposure. EPA expects to be able to extrapolate the results of testing on the sample to the category as a whole. EPA is soliciting comment as to whether it is necessary to include any other chlorinated benzenes in the test sample, whether a lesser number of chemicals would be appropriate, or whether all chlorinated benzenes category members should be tested (i.e., extrapolation of results from the sample is likely to be infeasible), or whether a sample should be selected on another basis.

(b) Do any additional modifications need to be made to the proposed routes of administration for testing particular chlorinated benzenes?

The Agency's proposed routes of administration have been discussed previously in Section VI.B.3 of this preamble. For the most part the routes were selected taking into account the route of human exposure, characteristics of the particular chemical, and effect of concern. EPA also considered recommending the same route for all chemicals tested for a certain effect because this might aid in EPA's extrapolation of results from the tested chemicals to other chlorinated benzenes. If all tests were performed using an oral route of administration instead of inhalation, testing costs for the lower three chlorinated benzenes would be reduced by about \$360,000 to \$450,000. However, EPA believes that despite the benefits to be had from using the same route of administration and the lower economic costs of this approach, it is more desirable to obtain test data from animals exposed to chlorinated benzenes in a manner which mimics the major route by which humans are exposed.

(c) What species and strains are most appropriate to use for assessing the leukemogenic potential of the lower chlorinated benzenes (mono- and di-)?

Because the lower chlorinated benzenes are more closely related to benzene than the higher ones and benzene has been associated with acute myelogenous leukemia in humans, it follows that leukemia is an effect of

concern for the lower chlorinated benzenes. The Sprague-Dawley rat, the species recommended by the Agency for oncogenicity testing of the higher chlorobenzenes, and the Fischer rat used by the National Cancer Institute (NCI) for testing the lower chlorinated benzenes may not be the most sensitive rodent strains for detecting chemically induced acute myelogenous leukemia; and, therefore, these may not be the appropriate species to use to assess leukemogenic potential. EPA has identified three species which are susceptible to chemically induced acute myelogenous leukemia: Rhesus monkey, Cynomolgus monkey, and Donryu rat. The Agency solicits comments on the desirability and feasibility of proposing additional oncogenicity testing of the lower chlorinated benzenes using one of these species.

(d) Is the Agency's requirement that the chlorinated benzene test chemicals be 99.9 percent pure with no more than .05 percent benzene and .05 percent hexachlorobenzene appropriate? Also, what additional costs would be incurred if the level of these two contaminants were specified at .01 percent instead of .05 percent?

EPA believes that chlorinated benzenes of 99.9 percent purity are readily available for use in the proposed tests either by direct use of commercial materials offered at this purity or by purification of other chlorobenzene materials. In addition, the Agency is aware that monochlorobenzene with no more than .05 percent benzene contamination is available and that it is likely that the other chlorobenzenes contain even less benzene than monochlorobenzene. Furthermore, EPA believes that hexachlorobenzene contamination can be limited to .05 percent level. EPA solicits comment on the belief that these purity requirements can be relatively easily met and on the costs of meeting .01 percent benzene and .01 percent hexachlorobenzene contamination levels.

(e) Should the structural and behavioral teratogenicity studies be combined? If so, what methodology should be used? EPA is proposing that structural teratogenicity tests be performed on the chlorinated benzenes. The Agency is interested in comments on whether modifications in the structural teratogenicity tests which would adequately assess for behavioral teratogenicity are feasible and/or desirable. Commentors should also consider whether combining these tests would delay obtaining results from the structural teratogenicity tests.

(f) Are there significant studies that have not come to the attention of EPA

which would provide sufficient data and experience for evaluation of the chlorinated benzenes?

Studies which have been considered by EPA in the course of this rulemaking are listed in the bibliography of the Chlorinated Benzenes Support Document or are otherwise contained in the public record of this proceeding. EPA acquired this information through a comprehensive literature search, through information submitted in response to a Section 8(d) rule on the lower chlorinated benzenes, and through requests for information addressed to other Federal Agencies.

(g) Are data from 90-day subchronic studies adequate for assessing the potential chronic effects of the chlorinated benzenes?

Several studies discussed in the Chlorinated Benzenes Support Document provide the basis for proposing 90-day subchronic toxicity studies as predictive for more long-term chronic effects with the exception of those related to oncogenicity, delayed hormonal or neurotoxic effects. The advantage of requiring 90-day subchronic studies are that test results would be available earlier and at substantially lower cost than would be the case if the Agency required chronic studies. EPA believes that 90-day studies will be sufficient to predict long-term effects from the chlorinated benzenes. Some studies on such compounds as benzene, bromobenzene, and hexachlorobenzene have shown that these chemicals exhibit toxic manifestations within 90 days. However, the Agency is concerned that factors such as accumulation potential of the chlorinated benzenes and the equilibrium concentration between free and tissue/fat compartments might complicate extrapolation from subchronic studies to potential chronic effects. The Agency requests comment on the risks and benefits associated with the use of 90-day subchronic studies for evaluation of chronic effects of the chlorinated benzenes.

(h) What strain(s) of rat is (are) most appropriate for assessing the oncogenic effects and subchronic/chronic effects of the chlorinated benzenes?

EPA is proposing the use of the Sprague-Dawley rat for oncogenicity testing of the designated higher chlorinated benzenes (tri-, tetra-, and pentachlorobenzene) because this species has shown sensitivity to the tumor-producing effects of benzene. However, NCI is performing oncogenicity studies on the lower chlorinated benzenes (monochlorobenzene and *o*- and *p*-dichlorobenzenes) using the Fischer rat.

Comment is solicited on the selection of the appropriate strain of rat for the proposed oncogenicity and subchronic effects testing taking into consideration the following factors: (1) The benefits of recommending that the Agency's proposed oncogenicity testing use the same strain as NCI, i.e., Fischer, for extrapolation of results from the test sample to the category versus the benefits of using the Sprague-Dawley strain. (2) The Agency prefers that the subchronic studies use the same species and strain with which oncogenicity studies will be performed since the subchronic studies are used as range finding tests for the oncogenicity studies. (3) For the sake of extrapolation of test results to the various chlorinated benzenes, the Agency prefers that all six chlorinated benzenes for which subchronic studies are proposed be performed using the same species and strain. (Although it might be interesting if the subchronic studies on the lower chlorinated benzenes were performed in the Fischer rat since this would result in a comparison between inhalation and gavage administration of these substances.) (4) The historical data base on these strains.

(i) Are the present oncogenicity studies as cited in the Chlorinated Benzenes Support Document sufficient positive controls to determine the sensitivity of the rodent to the oncogenic effects of the chlorinated benzenes?

The Agency's oncogenicity test standard published in the Federal Register of May 9, 1979 discusses the usefulness of positive controls to establish the inherent sensitivity of the test animal to the test substance. The Agency is considering requiring a positive control(s) such as benzene and/or hexachlorobenzene as a model for the sensitivity of the test animal to the class of chlorinated benzenes. Comment is requested on the sufficiency of existing studies cited in the Chlorinated Benzenes Support Document for use as positive controls.

(j) Will oral subchronic tests on the chlorinated benzenes using only the rat (i.e., only one species) be sufficient to characterize the risk of subchronic/chronic effects?

Section III.B. of the Chlorinated Benzenes Support Document discusses the rationale for the use of the rat for the oral subchronic testing of certain chlorinated benzenes. EPA's proposed oral subchronic test standards and this proposal specify the use of two species; one rodent and one nonrodent (usually the dog), but EPA solicits comments as to whether oral subchronic studies performed using only the rat will be sufficient.

(k) Are there additional studies that should be performed to further characterize the teratogenic potential of pentachlorobenzene?

Section III.E. of the Chlorinated Benzenes Support Document discusses two teratogenic studies performed on pentachlorobenzene. In one there were no significant effects in mice whereas the other showed extra ribs in rats. EPA believes that this evidence indicates that pentachlorobenzene is a potential teratogen in animals but that these data do not provide evidence sufficient to determine that pentachlorobenzene is an animal teratogen. EPA solicits comment on the relationship of pentachlorobenzene's ability to produce extra ribs in rats and the determination that pentachlorobenzene is a teratogen in rats as well as the implication of these results on the teratogenic potential of pentachlorobenzene in humans.

B. Scientific Issues Pertaining to Deferred Rules

1. Chloromethane.

(a) In general, are the neurotoxicity tests under consideration by EPA appropriate for assessing the neurologic and behavioral effects associated with chloromethane?

Section IV.D. of this preamble discusses EPA's views of test methods for assessing the neurotoxicity (neurologic and behavioral effects) of chloromethane. The Agency is specifically interested in comment on the following issues:

(1) What methodology is most appropriate for establishing adequate levels for control of neurotoxic effects due to chronic exposure to chloromethane?

(2) In light of the previous animal studies on chloromethane discussed in section IV.D., what species would be most appropriate for neurotoxicity testing for chronic effects?

(3) Should EPA require testing of chloromethane for delayed neurological effects? If so, what period of observation and what means should be used to assess the severity and persistence of these effects in test species?

(4) Should EPA require testing of chloromethane for abuse potential? If so, what test procedure should be required?

(5) Should EPA require an ethanol interaction component in any chronic neurotoxicity studies which are required for chloromethane? If so, what methods for including this component are appropriate?

(6) Is there a need for assessing neurotoxicity due to mixed exposure hazards such as high acute exposures coupled with low chronic exposure to

chloromethane? If so, what methods can be used for such testing?

(b) In general, are the mutagenicity test sequences under consideration by EPA appropriate for assessing the mutagenic risk associated with chloromethane?

Section IV.D. of this preamble discusses mutagenicity sequences to assess the risk of gene mutation and chromosomal aberration from exposure to chloromethane. It is the Agency's view that a sequential approach which first requires screening tests on a chemical and then requires confirmatory tests which are used for risk assessment purposes, is appropriate for testing chloromethane. The alternative of requiring only upper level tests whose results can be used for risk assessment was considered. However, the Agency favors the sequential approach to this alternative in an effort to minimize costs.

(c) Should EPA require behavioral teratogenicity testing of chloromethane? If so, what test methodologies for assessing behavioral teratogenic endpoints are appropriate for chloromethane?

Section IV.D. of this preamble discusses the rationale for requiring that chloromethane be tested for behavioral teratogenicity. EPA has also set forth the endpoints of concern for such testing of chloromethane. The Agency solicits comment on these endpoints and the use of the suggested reference, which describes tests for evaluation of behavioral and neurological development in offspring of exposed pregnant animals, for determining the behavioral teratogenic potential of chloromethane.

(d) Should an epidemiology study be proposed for chloromethane if a suitable cohort can be found?

EPA has decided not to propose an epidemiologic study on chloromethane for reasons stated in Section IV.E. in this preamble. However, EPA will consider proposing an epidemiology study on chloromethane, if a suitable cohort can be located. Given the chloromethane production and exposure situation, is it likely that a suitable cohort can be found? Comment also is solicited as to whether an epidemiology study should be conducted if a cohort can be located.

(e) Should EPA propose further subchronic/chronic effects testing of chloromethane?

Section IV.E. of the preamble discusses the Agency's rationale for deciding not to propose further subchronic/chronic effects testing of chloromethane. The Agency is interested in receiving comment on this decision.

2. Chlorinated Benzenes.

a. In general, are the neurotoxicity tests under consideration by EPA appropriate for assessing the neurologic and behavioral effects associated with the chlorinated benzenes?

Section V.D. of this preamble discusses EPA's views on test methods for assessing the neurotoxicity of the chlorinated benzenes. The Agency is specifically interested in comment on the following issues:

(1) Are the suggested motor function tests appropriate for measuring the neurologic and behavioral effects from chlorinated benzenes?

(2) Is use of rodents in the first tests of a neurotoxicity sequence and use of primates in confirmatory tests appropriate?

(3) Should neurotoxicity studies be longer than 90 days in order to adequately assess the potential of chlorinated benzenes for causing neurologic and behavioral effects?

(4) Are the methodologies presented in the suggested references appropriate for neurotoxicity testing of chlorinated benzenes?

(b) Should EPA propose measurement of behavioral and neurological development of offspring of pregnant animals exposed to the chlorinated benzenes?

Section V.D. of this preamble discusses the rationale for requiring behavioral teratogenicity testing of the chlorinated benzenes. EPA solicits comment on the necessity for such testing and the usefulness of the suggested reference which describes potentially appropriate tests.

(c) In general, are the mutagenicity test sequences under consideration by EPA appropriate for assessing the mutagenic risk associated with chlorinated benzenes?

Section V.D.3 of this preamble discusses the mutagenicity sequences to assess the risk of gene mutation and chromosomal aberration from exposure to chlorinated benzenes. In addition, the appendix of the support document discusses in further detail the rationale for the proposed sequences. It is the Agency's view that a sequential approach, which first requires screening tests on a chemical and then requires confirmatory tests which are used for risk assessment purposes, is appropriate for testing the chlorinated benzenes. The alternative of requiring only those tests whose results can be used for risk assessment was considered. However, the Agency favors the sequential approach to this alternative in an effort to minimize costs.

(d.) Should EPA propose metabolism testing on the chlorinated benzenes? If

so, what test standards should be developed to appropriately characterize these chemicals?

Section V.D.4 of this preamble discusses the rationale for EPA's belief that metabolism testing of the chlorinated benzenes would be useful in determining the degree of commonality between members of the group with respect to biological effects. EPA solicits comment on whether metabolism testing should be proposed and what test standards need to be developed.

(e.) Should an epidemiology study for chlorinated benzenes be proposed if a suitable cohort can be found?

EPA has decided not to propose an epidemiologic study for the chlorinated benzenes for reasons explained in Section V.E.2 of this preamble. However, EPA is considering proposing an epidemiology study on chlorinated benzenes, if a suitable cohort can be located. Is it likely that a suitable cohort can be found for such a study? Comment is solicited as to whether an epidemiology study should be conducted if a cohort can be located.

C. General Issues

1. How much exposure information is pertinent to the unreasonable risk finding under Section 4(a)(1)(A)(i)?

EPA has taken the position that as long as it can be shown that some exposure to a substance exists or that there is a potential for such exposure, and there is the potential for serious health effects, a Section 4(a)(1)(A)(i) finding can be made. Presumably, more widespread exposure would be necessary under Section 4(a)(1)(A)(i) if the potential health effects of concern were less severe. (See Section III.B.)

2. In considering whether an activity causes sufficient current or potential exposure to justify a finding that it may present an unreasonable risk, to what extent should the Agency take into account the possibility of accidental or intermittent exposures, in view of the fact that tighter engineering controls, transportation safeguards, etc., might be adopted as an appropriate control measure?

EPA has not yet made a Section 4(a)(1)(A)(i) or 4(a)(1)(B)(i) finding solely on the basis of possible accidental exposures. However, the Agency believes such possibilities are an important consideration in deciding whether or not to require testing of a chemical. The possibility of adopting appropriate engineering or other controls potentially might make such activities unreasonable risks in the Agency's view, were the effects findings to be confirmed. (See section III.B.)

3. When EPA determines that a chemical is already well-characterized for a serious health (or environmental) effect and that controls for that effect would be likely to prevent harm from other health (or environmental) effects, should the Agency require testing for other effects which are not yet fully characterized and for which Section 4(a) findings might be made? In what circumstances would such a policy choice be appropriate?

Today in a separate notice EPA is publishing its determination that it plans to proceed to a pre-regulatory assessment of acrylamide on the basis that its neurotoxicity is well characterized and that any control adopted for acrylamide based on its neurotoxicity will likely provide reasonable protection from the other effects due to the allowance of reasonable margins of safety. In addition, a long-term study has been initiated by industry which might present additional information concerning other potential effects. Thus, EPA does not believe that it would be in the public interest to spend additional resources to perform a thorough assessment of these other effects nor does the Agency plan to require industry to spend resources to test for these effects. (If valid conclusions cannot be drawn from the industry study, EPA will reconsider this decision.) EPA recognizes that in rejecting the alternative to always require testing for effects which are not fully characterized, it is leaving gaps in the toxicity data base it is trying to create and may in some cases fail to reduce the risk of a health hazard to the extent it could if the effect were fully characterized. However, EPA believes that in such circumstances this approach is warranted to conserve both the Agency's resources and testing resources in order that more pressing testing needs may be addressed (See the notice in today's Federal Register concerning acrylamide.)

4. To what extent should EPA consider ongoing testing in determining whether additional testing should be required for a chemical?

EPA does not believe that it should ignore ongoing tests of which it has knowledge when making findings under Section 4(a). However, the Agency has rejected the alternative of waiting until such testing is completed in favor of examining the test protocols and available interim data and making its findings on the basis of whether such a study is likely to be adequate or inadequate to characterize the chemical. (See, for example, the discussion of the CIIT-

sponsored ongoing testing of chloromethane in the Chloromethane Support Document.)

5. Other than attempting to develop appropriate standards as rapidly as possible, are there other approaches that EPA might take when it believes that a chemical has met all of the Section 4(a) criteria other than the "testing is necessary" finding but there is no appropriate test standard available for the effect under consideration?

EPA considered the possibility of using references from the scientific literature as "standards" for specific chemicals where generic test standards have not yet been proposed. However, EPA has decided to devote more resources to the development of generally applicable test standards rather than the development of methodology for any particular chemical.

6. After a test rule has been made final, under what circumstances and utilizing what procedure should the Agency consider permitting sponsor-requested modifications to the test rules and test standards?

As a general rule, EPA believes that all requests for modifications should be made during the proposal stage for each test rule. Upon a showing of good cause and compelling necessity, however, the Agency may be willing to accept requests made at a later time. Such situations might result from complications arising during the testing procedure. EPA believes that the most desirable procedure in such circumstances would be for the sponsor to address such requests in writing to the Document Control Officer (see Addressess above). Because there may be a need for a quick response from EPA, it would be useful to have an expeditious, relatively informal process for addressing such requests. EPA is also considering the need or desirability of amending the test rule to reflect such post promulgation modifications.

7. EPA is considering a policy of utilizing sequenced testing in which negative results in tests early in the sequence serve as a stop point with respect to further testing. For which effects is this approach adequate to assess the consequences of exposure to chemicals?

EPA is attempting to develop a sequence of tests consisting of screening and confirmatory tests for both health and environmental effects in an effort to minimize the costs of testing and to avoid unnecessarily tying up scarce testing resources. However, to do so requires that there exist one or more relatively inexpensive screening test(s) for a given effect for which a negative

result can be accepted as a final determination that the chemical does not pose an unreasonable risk.

8. Is the Agency's approach to deciding what substance to test the most appropriate one?

EPA considered a totally *ad hoc* approach for determining what to test versus a case-by-case approach within a general policy stating considerations for selecting a test substance considered for purposes of Section 4 of TSCA. EPA decided upon the latter course. This preamble previously discussed some factors which bear upon the choice of test substances. Are there other considerations that the Agency should take into account in its approach for deciding what substance to test?

9. What role should information about exposure play in constructing a structure-based category meeting the finding under Section 4(a)(1)(A)(i) of TSCA?

Typically the production range encompassed by members of a class of chemical compounds (a structure-based category) as to which a finding may be made under Section 4(a)(1)(A)(i) is quite broad. It may range from no commercial production of one substance to hundreds of millions of pounds of another. Although an answer to this issue cannot be given without considering question 10 below, EPA has considered the following alternatives: (1) consider all chemicals of the group that result from commercial production (including, for example, isomers that are never marketed as such but are merely by-products which are impurities in a commercial grade product or which are discharged as a waste), (2) consider only those members that are expressly made as commercial end-products, (3) consider only those members that are produced above a certain threshold level, or (4) consider all chemicals of a group as members of the category when there exists a realistic potential of substitution of substances not commercially produced for those in commercial production due to similarities in physical and chemical properties. Because EPA believes that for such purposes it is the category as to which its findings are made, not the individual members of the category, it believes that the first and fourth alternatives are most appropriate. An additional reason for this approach is EPA's knowledge that high hazard may lead to unreasonable risk even with low exposure.

10. With respect to testing to be required for structure-based categories, should EPA utilize a sampling approach where the sampled members are considered to be representative of all

members of the category, or require full testing of all members? If the former approach is chosen, what approach should EPA use in determining what is an appropriate subset to sample?

EPA has considered four alternatives with respect to the question of sampling within structure-based categories: (1) Do not sample—test every category member. This alternative would treat every chemical as an individual for purposes of testing, but discuss them as a group for convenience. (2) Sample only when there is strong evidence that one or more substances can, in fact, represent the category. (3) Sample on the basis of spanning the structural spectrum of a category taking into account exposure and production information. (4) Test the highest or most critical exposure substances. EPA has chosen option 3 because the Agency believes it is likely that data obtained on the sample members can be extrapolated to other members of the category. However, EPA recognizes that it may be necessary to require further testing of other members of the category should the test data from the sample show that there is not a sufficient basis for extrapolation. EPA believes it is infeasible to generally require the testing of all category members (option 1). The selection of option 2 would mean categories would rarely be used because it requires information ahead of rule promulgation that is generally not available. Option 4 was rejected because a sample chosen on the basis of exposure alone may not be truly representative of the category and, therefore, would not be likely to yield data which could be used to characterize the effects of the category.

11. If EPA adopts an approach of sampling for structure based categories, what approach to exemptions and reimbursement should the Agency take?

EPA has proposed one approach and is considering two alternative approaches for exemptions and reimbursements (See the Proposed Statement of Exemption Policy and Procedures in today's Federal Register and Section IV.B.4. of this preamble). EPA may adopt any one or a combination or minor variation of these approaches in its final rule.

12. How can the Agency assist in insuring a cooperative coordinated response from industry members subject to a test rule in order to minimize duplicative, costly testing?

In Section I. of the preamble which contains a section on the exemptions process, the Agency discusses its support of a coordinated response or joint testing approach of members subject to a test rule. Exactly what the

Agency's role in this process is has not yet been defined.

13. How can EPA encourage voluntary testing of chemicals designated by the ITC while remaining confident that such tests will be carried out expeditiously and in a manner that will generate data acceptable to EPA?

For those chemicals in which there is agreement between EPA and industry that testing is necessary, it is advantageous for EPA and the public for industry to proceed with testing without waiting for EPA to issue a test rule. EPA is interested in working with industry to facilitate such testing and to insure that such data will meet EPA test standards and good laboratory practice requirements.

14. Should EPA adopt a special definition of "processor" for purposes of Section 4 testing responsibility? Should EPA exclude certain categories of "processor" from testing and exemption requirements and how should this be done?

The definition of processor found in the Act is broad and includes many people. If they are all subject to Section 4 test rules, this will likely complicate the exemption and reimbursement process. The options considered by EPA for restricting the number of processors subject to Section 4 are discussed in Section III.E. of this preamble. The Agency would like comment on these options and any suggestions which the Agency has not considered.

15. The Agency solicits comment on the proposed time frame for requiring submission of final reports containing the results of the tests proposed for chloromethane and the chlorinated benzenes.

EPA has proposed deadlines for submission of final reports on the proposed testing as follows:

Test	Months from the effective date of the rule
Oncogenicity.....	53
Structural teratogenicity.....	11
Reproductive effects.....	29
Subchronic/Chronic effects.....	12

These final dates were arrived at through the consideration of 5 major factors:

1. coordination among test sponsors.
2. study plan preparation.
3. ninety-day pre-test reporting requirement.
4. test performance.
5. analysis of test results and preparation of Final Report.

The time frame for each factor for each type of health effect test is shown in Table 2 of Section III F. of this preamble.

16. Because there is a different time frame for submission of data on each effect, should the effective period of the test rule also vary according to each effect?

Section 4(b)(4) of TSCA states that a test rule expires at the end of the reimbursement period for the test data for such substance. The reimbursement period begins when the data (the final reports) are submitted and ends five years after the date. However, depending upon the length of the data development and evaluation period, final reports will be submitted at different times for different effects. EPA requests comments on whether the effective period of the rule and the reimbursement period should vary according to each effect, or whether the periods should end at one specific time, such as five years after the first (or last) final report is received.

XI. Environmental Impact Statement

EPA is not required to prepare environmental impact statements under the National Environmental Policy Act (NEPA), 42 U.S.C. 4321 *et seq.* for test rules and has determined that voluntary preparation of an environmental impact statement is not appropriate for regulations issued under Section 4 of TSCA. See the preamble to the Agency's rules for compliance with NEPA, 44 FR 64174 (Nov. 6, 1979).

XII. Public Participation

During the development of these proposed rules, several meetings and discussions were held with non-EPA scientists, industry officials, trade press, and representatives of environmental groups. A meeting was held on September 25, 1978, during which attendees discussed various issues including:

1. What form of a chemical to test ("pure" vs. technical grade substances),
2. who is a processor in terms of TSCA, and
3. the approach for testing structure-based categories.

A meeting was held on December 5, 1979, during which EPA representatives and officials from the Chemical Manufacturers Association discussed issues numbers 1 and 3 again, with focus on specific chemicals.

In addition, comments have been received in response to the Federal Register publications on October 12, 1977 (42 FR 55026) and October 30, 1978 (43 FR 50630) which discussed the ITC's designation of chloromethane and the chlorinated benzenes to the Priority List.

A meeting was held on February 25, 1980, with representatives of the Synthetic Organic Chemical

Manufacturers Association (SOCMA) to discuss employee exposure to the chlorinated benzenes.

Draft documents contained in the first test rule package were distributed for comment on March 7, 1980, to the representatives of industry, environmental groups and trade press who participated in the September 25, 1979, meeting. A meeting to discuss the draft documents was held with these groups on March 27, 1980.

A meeting of the Administrator's Toxic Substances Advisory Committee (ATSAC) was held on March 20, 1980 to discuss this proposed test rule package.

A meeting of the EPA Science Advisory Board (SAB) was held on March 21, 1980, to discuss this proposed test rule package.

XIII. Public Meetings

EPA will hold a general public meeting on September 24, 1980, in Washington, D.C. to provide the public an opportunity to present comments and questions on these proposed rules as required by Section 4(b)(5) to EPA officials who are directly responsible for developing the rule and supporting analyses. The public meeting will start with a short summary by EPA of the proposed rules and will be followed by oral presentations from the floor. A time limit of 15 minutes per person, company, or organization may be imposed depending upon the number of requests. EPA will allot speaking times in advance of the meeting on a first come basis, although the Agency reserves the right to alter the order depending upon the nature of the particular comments and other relevant factors. For the benefit of all concerned, EPA encourages the elimination of redundant comments. If time permits, following these prepared presentations, EPA will receive any other comments from the floor. Presenters are invited, but not required, to submit copies of their statements on the day of the meeting. All such written materials will become a part of EPA's record for this rulemaking. In addition, the Agency will transcribe each meeting and will include the written transcripts in the public record. The exact location and time of this meeting will be announced later in the Federal Register and the press.

In addition to the general public meeting, EPA personnel responsible for developing these proposals will be available at EPA's discretion to meet in public sessions at EPA in Washington, D.C., during the 105 day comment period, with interested parties from individual companies, trade associations, organized labor and citizen organizations to discuss these proposals.

EPA encourages using special request meetings for discussing technical data and implementation issues. However, persons should plan to present their views at the general meeting to ensure their opportunity for comment since special meetings will be held only when EPA believes that the subject is more appropriately discussed in a special format than in a general meeting. EPA will provide facilities and make other necessary arrangements for such meetings. The Agency will make transcripts or summaries of the meetings for inclusion in the official public record. While these meetings for inclusion in the official public record. While these meetings will be open to the public, active participation will be limited to those requesting the session and designated EPA participants.

Persons who wish to present comments at the September 24, 1980 general meeting should contact EPA no later than September 12, 1980 by calling toll-free 800-424-9065 (in Washington, D.C., call 554-1404), or by writing to the address listed at the beginning of this preamble under "For Further Information Contact". Persons wishing to arrange a special meeting should follow the same procedures.

XIV. Public Record

EPA has established a public record for this rulemaking (docket number 80T-126) which is available for inspection in the OPTS Reading Room from 9:00 a.m. to 5:00 p.m. on working days (Room 47 East Tower, 401 M Street, S.W. Washington, D.C. 20460). This record includes basic information considered by the Agency in developing this proposal. The Agency will supplement the record with additional information as it is received. The record includes the following information.

- (1) Federal Register notices pertaining to this rule:
 - (a) Notice of proposed rule on chloromethane and chlorinated benzenes.
 - (b) Notices containing the ITC designation of chloromethane and chlorinated benzenes to the Priority List (42 FR 55026 and 43 FR 50630).
 - (c) Notice containing EPA's response to the ITC designation of chloromethane and chlorinated benzenes to the Priority List (43 FR 50134).
 - (d) Notices containing EPA's proposed health effects test standards and Good Laboratory Practice Standards (44 FR 27334 and 44 FR 44054).
 - (e) Notice of EPA's proposed action with respect to Acrylamide.
 - (f) Notice of proposed rule on exemption policy and procedures.

(g) Notice containing the Advance Notice of Proposed Rulemaking on reimbursement policy and procedures.

(h) Notice of rule proposed under Section 8(d) of TSCA requiring submission of health and safety information (44 FR 77470).

(i) Notice of rule proposed under Section 8(a) of TSCA requiring submission of production and exposure-related data (44 FR 13646).

(2) Support Documents:

(a) Chloromethane Support Document

(b) Chlorinated Benzenes Support Document

(c) Economic Analysis Support Document

(d) Exposure Support Document

(e) Chronic Health Effects Standards (May, 1979).

(3) Drafts of Proposed Rule and Support Documents Released to Public before Proposal (March 6, 1980).

(4) Minutes of Informal Public Participation Meetings.

(5) Communications Before Proposal:

(a) Written: Public and Intra-agency or Interagency Memoranda and Comments

(b) Telephone conversations

(c) Meetings

(6) Reports—Published and Unpublished Factual materials (including contractor's reports).

Note.—Under Executive Order 12044, EPA is required to judge whether a regulation is "significant" and, therefore, subject to the procedural requirements of the Order or whether it may follow other specialized development procedures which EPA labels "specialized" regulations. I have reviewed this regulation and determined that it is a significant regulation subject to the procedural requirements of Executive Order 12044.

XV. Related Actions

EPA proposed health effects test standards for oncogenicity and other chronic effects in the Federal Register on May 9, 1979 (44 FR 27334) and for acute toxicity, eye and dermal irritation, dermal sensitization, subchronic toxicity, teratology, reproductive effects, certain mutagenicity tests, and metabolism on July 26, 1979 (44 FR 44054). The agency proposed standards for Good Laboratory Practices for Health Effects in the Federal Register on May 9, 1979 (44 FR 27362). Amendment to these standards are proposed in today's discussion of Study Plan requirements in Section III F. of this preamble.

In a separate Federal Register notice appearing today, EPA announces its tentative decision not to require any health effects testing for acrylamide. Acrylamide appeared on the second list of ITC recommendations for testing.

EPA also has published a proposed rule under Section 8(d) of TSCA which would require submission of health and safety studies concerning all chemicals recommended for testing by the Interagency Testing Committee (ITC), 44 FR 77470 (Dec. 31, 1979). A Section 8(a) rule was proposed February 29, 1980 (45 FR 13646) to obtain information from chemical manufacturers on production volume, environmental release, and worker exposure to the same ITC chemicals.

EPA also is proposing a Statement of Exemption Policy and Procedure published in today's Federal Register relating to the granting of exemptions from testing under Section 4(c) of TSCA and approval of joint testing arrangements under Section 4(b)(3)(A).

Dated: July 1, 1980.

Douglas M. Costle,
Administrator.

It is proposed to add a new Part 773 of Chapter I of Title 40 of the CFR to read as follows:

PART 773—IDENTIFICATION OF CHEMICAL SUBSTANCES AND MIXTURES TO BE TESTED

Subpart A—General Provisions

Sec.

773.11 Scope and purpose.

773.12 Applicability.

773.13 Definitions.

773.14 Submission of information.

773.15 Test standards.

Subpart B—Chemical Substances

773.100 Chlorinated Benzenes.

773.130 Chloromethane.

Subpart C—Mixtures [Reserved]

Authority: Section 4, Section 12, and Section 26, Toxic Substances Control Act (TSCA, 90 Stat. 2008, 2033, 2047; 15 U.S.C. 2603, 2611, 2625).

Subpart A—General Provisions

§ 773.11 Scope and purpose.

(a) This part identifies the chemical substances, mixtures, and categories of substances and mixtures for which data are to be developed, specifies the persons required to test (manufacturers, including importers, and/or processors), specifies the test substances(s) in each case, prescribes the tests that are required including the test standards, and provides deadlines for the submission of reports and data to EPA.

(b) This part requires manufacturers and/or processors of chemical substances or mixtures ("chemicals") identified in Subparts B and C to test the chemical in accordance with EPA test standards contained in Part 772 and any modifications to such standards

contained in this part in order to develop data on the health and environmental effects of these chemicals. These data will be used by the Administrator to assess the risk of injury to human health or the environment presented by these chemicals.

§ 773.12 Applicability

This part is applicable to each person who manufactures or intends to manufacture (including import) and/or to each person who processes or intends to process a chemical substance or mixture identified in this part for testing during the period commencing with the effective date of this rule until the end of the reimbursement period. Each set of testing requirements in subparts B and C specifies whether those requirements apply to manufacturers only, to processors only, or to both manufacturers and processors.

§ 773.13 Definitions.

The definitions in section 3 of the Toxic Substances Control Act (TSCA) and the definitions of § 770.2 of this chapter apply to this part.

§ 773.14 Submission of information.

Information (Study Plans, Interim Quarterly Summary Reports, Final Test Reports) submitted to EPA must bear the Code of Federal Regulations (CFR) - section number of the subject chemical (e.g., 773.130 for chloromethane) and must be addressed to the Document Control Officer, Chemical Information Division, Office of Pesticides and Toxic Substances (TS-793), Environmental Protection Agency, Washington, D.C. 20460.

§ 773.15 Test Standards.

The health effects testing required by this part shall be performed according to the test standards and Good Laboratory Practice (GLP) Standards set forth in Part 772 of this chapter unless modified in this Part.

SUBPART B—CHEMICAL SUBSTANCES

§ 773.100 Chlorinated Benzenes

(a) *Definition of chlorinated benzenes category.*

(1) Pursuant to Sections 26 and 4(a)(1)(A) of TSCA, a structure-based category, chlorinated benzenes, is defined as the group of substituted benzene compounds in which one to five hydrogen atoms of benzene are replaced by chlorine atoms, with no substituents present other than chlorine and hydrogen.

(2) The category includes the following substances:

- (i) monochlorobenzene (chlorobenzene, CAS No. 108-90-7),
- (ii) 1, 2-dichlorobenzene (*ortho*-dichlorobenzene, CAS No. 95-50-1),
- (iii) 1, 3-dichlorobenzene (*meta*-dichlorobenzene, CAS No. 541-73-1),
- (iv) 1, 4-dichlorobenzene (*para*-dichlorobenzene, CAS No. 106-46-7),
- (v) 1, 2, 3-trichlorobenzene (CAS No. 87-61-6),
- (vi) 1, 2, 4-trichlorobenzene (CAS No. 120-82-1),
- (vii) 1, 3, 5-trichlorobenzene (CAS No. 108-70-3),
- (viii) 1, 2, 3, 4-trichlorobenzene (CAS No. 634-66-2),
- (ix) 1, 2, 3, 5-tetrachlorobenzene (CAS No. 634-90-2),
- (x) 1, 2, 4, 5-tetrachlorobenzene (CAS No. 95-94-3), and
- (xi) pentachlorobenzene (CAS No. 608-93-5).

(3) Hexachlorobenzene is not included in the category for purposes of this rule.

(b) *Identification of test substances.*

(1) The following substances shall be tested in accordance with this subpart as representatives of the chlorinated benzenes category.

- (i) Monochlorobenzene (CAS No. 108-90-7)
- (ii) 1, 2-Dichlorobenzene (*o*-dichlorobenzene, CAS No. 95-50-1)
- (iii) 1, 4-Dichlorobenzene (*p*-dichlorobenzene, CAS No. 106-46-7)
- (iv) 1, 2, 4-Trichlorobenzene (CAS No. 120-82-1)
- (v) 1, 2, 4, 5-Tetrachlorobenzene (CAS No. 95-94-3)
- (vi) Pentachlorobenzene (CAS No. 608-93-5)

(2) Chemicals of at least 99.9 percent purity containing no more than 0.05 percent benzene and 0.05 percent hexachlorobenzene shall be used as the test substance in all tests required by this section.

(c) *Persons required to test.* (1) All persons who manufacture, intend to manufacture, process or intend to process one or more chlorinated benzenes defined in paragraph (a) of this section from (effective date of the rule) to (5 years from the date the last final report is due) shall conduct tests and submit data as specified by this subpart.

(2) Persons who manufacture, intend to manufacture process, or intend to process one or more chlorinated benzenes defined in paragraph (a) of this section for export from the United States shall conduct tests and submit data as specified by this subpart.

(3) Any person subject to the requirements of this section may apply to EPA for an exemption from testing pursuant to subpart E of Part 770.

(d) *Health effects testing.—(1) Oncogenic effects.—(i) Required testing.*

(A) Testing for oncogenic effects shall be performed on each chlorinated benzene listed in § 773.100(b)(1), excluding monochlorobenzene and 1,2- and 1,4-dichlorobenzenes, in accordance with the proposed test standard in § 772.113-2 of this chapter (44 FR 27334) except that the strain of rat to be used shall be Sprague-Dawley.

(B) The test substance shall be administered in the feed.

(ii) *Reporting requirements.—*

(A) *Study Plans.* The Study Plan required by § 772.113-1(f) of this chapter shall be submitted to EPA at least 90 days prior to the start of oncogenic testing.

(B) *Interim Quarterly Summary Reports.* The Interim Quarterly Summary Reports required by § 772.113-1(j) of this chapter shall be submitted to EPA at least every three months beginning with the start of oncogenic testing and ending with the submission of the Final Report.

(C) *Final Test Report submission date.* The Final Test Report required by § 772.113-1(j) of this chapter shall be submitted to EPA no later than (53 months after the effective date of this rule).

(2) *Structural teratogenic effects.—(i) Required testing.*

(A) Testing for structural teratogenic effects shall be performed on each chlorinated benzene listed in § 773.100(b)(1), except for pentachlorobenzene, in accordance with the proposed test standard in § 772.116-2 of this chapter (44 FR 44054).

(B) The route of administration shall be: (1) inhalation for monochlorobenzene, 1,2-dichlorobenzene and 1,4-dichlorobenzene, and (2) oral gavage for 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene.

(ii) *Reporting requirements.—*

(A) *Study Plans.* The Study Plan required by § 773.116-2 of this chapter shall be submitted to EPA no later than the initiation date of the test.

(B) *Interim Quarterly Summary Reports.* No Interim Quarterly Summary Reports are required.

(C) *Final Test Report submission date.* The Final Test Report required by § 773.116-2(c) of this chapter shall be submitted to EPA no later than (11 months after the effective date of this rule).

(3) *Reproductive effects.—(i) Requiring testing.*

(A) Testing for reproductive effects shall be performed on each chlorinated benzene listed in § 773.100(b)(1), except for 1,2,4-trichlorobenzene, in accordance

with the proposed test standard in § 772.116-3 of this chapter (44 FR 44054).

(B) The route of administration shall be (1) inhalation for monochlorobenzene, 1,2-dichlorobenzene and 1,4-dichlorobenzene, and (2) oral (administration in the feed) for 1,2,4,5-tetrachlorobenzene and pentachlorobenzene.

(ii) *Reporting requirements.—*

(A) *Study Plans.* A Study Plan required by § 773.116-3(c) of this chapter shall be submitted to EPA at least 90 days prior to the start of the test.

(B) *Interim data.* The Interim Quarterly Summary Reports required by § 773.116-3(c) of this chapter shall be submitted to EPA at least every three months beginning with the start of the reproductive tests and ending with the submission of the Final Test Report.

(C) *Final Test Report.* The Final Test Report required by § 773.116-3(c) of this chapter shall be submitted to EPA no later than 29 months after the effective date of this rule.

(4) *Subchronic/chronic effects.—(i) Required testing.—(A)* Testing for chronic effects shall be performed on each chlorinated benzene listed in § 773.100(b)(1) except for pentachlorobenzene. These effects shall be determined in a 90-day subchronic toxicity study conducted in accordance with the proposed test standard in § 772.112-33 (inhalation) and § 772.112-31 (oral) of this chapter except that only testing in the rat is required.

(B) The route of administration shall be (1) inhalation for monochlorobenzene, 1,2-dichlorobenzene and 1,4-dichlorobenzene, and (2) oral (administration in the feed) for 1,2,4-trichlorobenzene, and 1,2,4,5-tetrachlorobenzene.

(ii) *Reporting requirements.*

(A) *Study plans.* The Study Plan required by § 772.112-33 and § 772.112-31 shall be submitted to EPA no later than the initiation date of the test.

(B) *Interim data.* No Interim Quarterly Summary Reports are required.

(C) *Final Test Report submission date.* The Final Test Report shall be submitted to EPA no later than (12 months after the effective date of this rule).

(e) *Environmental effects testing.*

[Reserved]

§ 773.130 Chloromethane.

(a) *Identification of test substance*

(1) Chloromethane (CAS No. 74-87-3, also known as methyl chloride) shall be tested in accordance to this subpart.

(2) Chloromethane of at least 99.95 percent purity shall be used as the test substance in all tests.

(b) Persons required to test.

(1) All persons who manufacture, intend to manufacture, process, or intend to process chloromethane from (effective date of the rule) to (5 years from the date the last final report is due) shall conduct tests and submit data as specified by this Part.

(2) Persons who manufacture, intend to manufacture, process, or intend to process chloromethane for export from the United States shall conduct tests and submit data as specified by this subpart.

(3) Any person subject to the requirements of the section may apply to EPA for an exemption from testing pursuant to Subpart E of Part 770.

(c) Health effects testing.—(1) Oncogenic effects.—(i) Required testing. (A) A 2-year oncogenicity study shall be conducted on chloromethane in accordance with the proposed test standard in § 772.113-2 of this chapter (44 FR 27334) *except* that the species used for testing shall be the hamster and the mouse instead of the rat.

(B) The route of administration shall be inhalation.

(ii) Reporting requirements.—(A) Study Plans. The Study Plan required by § 772.113-1(f) of this chapter shall be submitted to EPA at least 90 days prior to the start of oncogenic testing.

(B) Interim Quarterly Summary Reports. The Interim Quarterly Summary Reports required by § 772.113-1(j) of this chapter shall be submitted to EPA at least every three months beginning with the start of oncogenic testing and ending with submission of the Final Test Report.

(C) Final Test Report Submission Date. The Final Test Report required by § 772.113-1(j) of this chapter shall be submitted to EPA no later than (53 months after the effective date of this rule).

(2) Structural teratogenic effects.

(i) Required testing. (A) A test for structural teratogenicity shall be performed in accordance with the proposed test standards in § 772.116-2 of this chapter (44 FR 44054) *except* that the two species used for testing shall not include the rat.

(B) The route of administration shall be inhalation.

(ii) Reporting requirements.

(A) Study Plans. The Study Plan required by § 772.116-2 of this chapter shall be submitted to EPA no later than the initiation date of the test.

(B) Interim Quarterly Summary Reports. No Interim Quarterly Summary Reports are required.

(C) Final Test Report submission date. The Final Test Report required by § 772.116-2(c) of this chapter shall be

submitted to EPA no later than (11 months after the effective date of this rule).

(d) Environmental effects testing.

[Reserved]

Subpart C—Mixtures [Reserved]

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