

**ENVIRONMENTAL PROTECTION
AGENCY**

40 CFR Part 789

(OFTS-42012A; TSM-FRL 2845-5a)

**Diethylenetriamine; Proposed Test
Rule**

AGENCY: Environmental Protection
Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Under section 4(a) of the Toxic Substances Control Act (TSCA), EPA is proposing that manufacturers and processors of diethylenetriamine (DETA; CAS No. 111-40-9) be required to conduct chronic oncogenicity bioassays of this substance in both rats and mice, if positive test results are obtained for DETA in certain of the mutagenicity assays required for this substance in the final Phase I test rule for DETA, which the Agency is promulgating elsewhere in this issue of the Federal Register. Oncogenicity bioassay testing of DETA is being proposed as a single-phase test rule.

DATE: Comments on this proposed rule must be submitted on or before July 22, 1985.

ADDRESS: Written comments should bear the document control number OFTS-42012A, and should be submitted in triplicate to: TSCA Public Information Office (TS-793), Office of Toxic Substances, Environmental Protection Agency, Room E-106, 401 M St., SW., Washington, D.C. 20460

All written comments filed under this proposal will be available for public inspection in room E-107 at the address given above from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-792), Office of Toxic Substances, Environmental Protection Agency, Rm. E-543, 401 M St., SW., Washington, D.C. 20460. Toll Free: (800-424-8065). In Washington, D.C.: (554-1404). Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: EPA is proposing to amend its final Phase I test rule for DETA, which appears elsewhere in this issue of the Federal Register, to include an automatic requirement for chronic oncogenicity testing, if positive results are obtained for DETA in certain of the mutagenicity assays required in the final test rule for this substance.

I. Background

A. Introduction

Section 4(e) of TSCA (Pub. L. 94-469, 90 Stat. 2003; 15 U.S.C. 2601) established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for testing under section 4(a) of the Act. The ITC may designate substances on the list 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 by publishing in the Federal Register reasons for not initiating rulemaking.

The ITC designated DETA for priority consideration in its Eighth Report, published in the Federal Register of May 22, 1981 (46 FR 29138). The ITC recommended that DETA be tested for the following health effects: Chronic effects, reproductive effects, and teratogenicity.

EPA issued a proposed test rule for DETA, published in the Federal Register of April 29, 1982 (47 FR 18386), in which the testing of DETA in at least two mammalian species for oral subchronic (90-day) health effects, for mutagenicity (both gene mutations and chromosomal aberrations), and for chemical fate under both aerobic and anaerobic conditions was proposed. The proposed test rule for DETA did not include chronic oncogenicity bioassay testing of DETA, either as an absolute requirement or as a result of positive test results in specified mutagenicity assays.

Since the test rule for DETA was proposed, EPA has adopted the general approach of requiring tiered testing sequences for both gene mutation testing and chromosomal aberration testing in its TSCA section 4 test rules for mutagenic effects. These sequences usually include an automatic requirement for chronic oncogenicity bioassays of chemical substances exhibiting positive responses in any of the following mutagenicity tests contained in the tiered testing sequences: (1) The gene mutation assay in mammalian cells, (2) the sex-linked recessive lethal gene mutation assay in *Drosophila melanogaster*, (3) the *in vitro* cytogenetics assay, or (4) the *in vivo* cytogenetics assay. These mutagenicity testing sequences, as well as the assays within these sequences for which positive test results usually automatically trigger a requirement for chronic oncogenicity bioassays of the tested chemical substance, have been previously described in proposed test rules for methyl oxide (48 FR 30899; July 5, 1983), cresols (48 FR 31812; July

11, 1983), and ethyltoluene, trimethylbenzenes, and the C9 aromatic hydrocarbon fraction (48 FR 23088; May 23, 1983). Responses to comments on these mutagenicity testing sequences and the triggers within them for required chronic oncogenicity testing may be found in the final Phase I test rule for the C9 aromatic hydrocarbon fraction (50 FR 20662; May 17, 1985). The Agency believes that there is a high correlation between positive test results in any of the four previously listed mutagenicity assays and positive test results in chronic oncogenicity bioassays for a large number of substances tested in both types of assay systems. Therefore, the Agency believes that chemical substances exhibiting a positive response in any of these four mutagenicity tests should be viewed, under section 4(a)(1)(A) of TSCA, as potentially posing an unreasonable risk of oncogenicity, assuming a potential for human exposure and the lack of substantial scientific evidence to the contrary.

Elsewhere in this issue of the Federal Register, EPA is promulgating a final Phase I test rule for DETA, requiring testing of this chemical substance for oral subchronic (90-day) health effects in at least one mammalian species, for dermal absorption in the same mammalian species used for the subchronic study, for chemical fate under aerobic conditions, and for inducing *in vivo* gene mutations (tiered testing sequence) and *in vitro* and *in vivo* chromosomal aberrations (tiered testing sequences). Consistent with the Agency's approach of requiring oncogenicity bioassay testing under section 4 of TSCA when certain mutagenicity tests are positive, EPA now is proposing under TSCA section 4(a)(1)(A) to require chronic oncogenicity bioassays of DETA in both rats and mice, if this substance exhibits positive test results in any of the following mutagenicity assays in the tiered mutagenicity testing sequences (for *in vivo* gene mutation testing and both *in vitro* and *in vivo* chromosomal aberration testing) required in the final Phase I test rule for DETA: (1) The sex-linked recessive lethal gene mutation assay in *Drosophila melanogaster*, (2) the *in vitro* cytogenetics assay, or (3) the *in vivo* cytogenetics assay.

B. Change in Process for Adopting Test Standards

In the Federal Register of March 26, 1982 (47 FR 13012), EPA announced an approach to adopting test rules that involved two-phase rulemaking. In the first phase of rulemaking, EPA would

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specify the test substance, who would be responsible for testing and the required tests. In the second phase, EPA would establish the test methodologies (test standards) and the deadlines for submission of test data. EPA has used this approach for most of the test rules it has proposed for chemicals recommended in the first through the thirteenth ITC reports.

In December, 1983, the Natural Resources Defense Council (NRDC) and the Industrial Union Department of the American Federation of Labor-Congress of Industrial Organizations (AFL-CIO) filed an action under TSCA section 20, which challenged, among other things, the use of the two-phase process [NRDC and AFL-CIO v. EPA, 565 F. Supp. 1255 (S.D.N.Y., 1984)]. In an August 23, 1984 Opinion and Order, the Court found that utilization of the two-phase rulemaking process was permissible. However, the Court also held that the Agency was subject to a standard of promulgating test rules within a reasonable time frame [NRDC and AFL-CIO v. EPA, 565 F. Supp. 1255, 1267-1270 (S.D.N.Y., 1984)].

Subsequent to the issuance of this Opinion, the Agency submitted papers to the Court which indicated that in order to expedite the test rule development process, EPA would utilize a single-phase rulemaking process for most test rules. The Agency also indicated that EPA would publicly announce this policy in the first test rule proposal to be published in the spring of 1985 (Declaration of Don R. Clay, at 12 (September 24, 1984)). In accordance with this commitment, the Agency has promulgated a rule on Test Rule Development and Exemption Procedures (50 FR 20652; May 17, 1985), which describes in detail the procedures to be utilized in the one-phase rulemaking process. These one-phase rulemaking procedures are, therefore, being utilized in this proposed test rule for DETA.

Section 4(b)(1) of TSCA specifies that test rules shall include standards for the development of test data ("test standards") and deadlines for submission of test data. Under the two-phase process, both test standards and data submission deadlines are established during the second phase of rulemaking. However, in the single-phase approach, EPA will propose the pertinent OTS guideline(s) or other suitable test guideline(s) as the required test standard(s) in the initial notice of proposed rulemaking, and EPA will also propose time frames for the submission of the test data. Industry and other commenters may suggest an alternative methodology or modifications to the

OTS guideline, i.e., the proposed test standard, during the public comment period, and such comments should state why the alternative methodology or modification is more suitable for the chemical substance in question than the EPA-proposed test standard. Comment will also be sought on the proposed data submission deadlines. All such submissions, including alternative test methodologies, will be placed in the rulemaking record and will be available for review by the public. The final rule will promulgate as the test standards either the OTS guideline, or other suitable guideline, a modified version of these guidelines, the alternative methodology submitted by commenters, or a modified version of the alternative methodology. The proposed test standards and data submission deadlines will be open for discussion at any public meeting held pursuant to TSCA section 4(b)(1).

The single-phase approach offers a number of advantages over the two-phase approach. First, the Agency believes that the single-phase approach will shorten rulemaking by as much as 18 months, resulting in the expedited initiation of the required testing. Secondly, by allowing commenters to submit alternative test methodologies during the comment period, it preserves the flexibility of the two-phase process, but at reduced administrative cost. Because of these advantages, the Agency intends to utilize single-phase rulemaking for most rules promulgated under TSCA section 4(a).

II. DETA

A. Data Contained in Final Phase I Test Rule

The final Phase I test rule for DETA, appearing elsewhere in this issue of the Federal Register, contains (1) DETA's profile, (2) EPA's previous findings with respect to DETA, (3) a description of the persons who would be required to conduct the proposed chronic oncogenicity bioassays of DETA, should the substance exhibit positive results in certain mutagenicity assays, and (4) a description of the test substance to be utilized for this bioassay testing. The test standard for the oncogenicity testing of DETA, if required, will be the OTS test guideline for chronic oncogenicity bioassay testing, published by the National Technical Information Service (NTIS) in report number PB 82-232984. The final Phase I test rule for DETA also contains a detailed description of the tiered testing sequences for both *in vivo* gene mutation testing and for *in vitro* and *in*

vivo cytogenetics testing which are required for this chemical substance.

B. Automatic Triggers for Chronic Oncogenicity Bioassays

EPA's approach of using sequences of tiered tests to assess the mutagenic potential (with respect both to gene mutations and chromosomal aberrations) of chemical substances, as well as the use of positive test results in certain assays in these test sequences to trigger a requirement for chronic oncogenicity bioassays, has been previously described in test rules proposed by the Agency for mesityl oxide (48 FR 30699), creosols (48 FR 31812), and ethyltoluenes, trimethylbenzenes, and the C9 aromatic hydrocarbon fraction (48 FR 23066). The Agency's responses to a variety of public comments on this approach, the test sequences, and the assays (and triggers for oncogenicity testing) contained within them, may be found in the final Phase I test rule for the C9 aromatic hydrocarbon fraction (49 FR 20662).

As discussed in the final Phase I test rule for the C9 aromatic hydrocarbon fraction (50 FR 20662), the Agency believes that the use of sequences of tiered tests for mutagenicity testing, and the use of automatic triggers to require chronic oncogenicity bioassays based on the results of certain mutagenicity assays, is consistent with both current scientific knowledge and the regulatory approach to chemical testing established under section 4 of TSCA. Existing data show a strong correlation between positive results in certain mutagenicity tests and positive results in animal chronic oncogenicity bioassays for a large number of substances tested in both types of systems. Thus, positive results in one or more of these mutagenicity assays provide a basis for concluding that the substance may be an oncogen, and, in conjunction with evidence of potential for human exposure to the substance, that such exposure may present an unreasonable risk of oncogenicity. Conversely, negative results in all of the "trigger" mutagenicity tests provide substantial evidence that the tested substance is not likely to be an oncogen. In the absence of chemical-specific evidence of possible non-genotoxic oncogenicity of the substance, or evidence that the screening mutagenicity assays are unsuitable for the substance, EPA would not require chronic oncogenicity bioassays for such a substance.

Because the different mutagenicity assays used to trigger chronic oncogenicity bioassay testing generally

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measure different genotoxic effects, or similar effects under substantially different test conditions (e.g., *in vitro* versus *in vivo* metabolic activation), and because each test has independently shown a strong ability to identify animal carcinogens, EPA believes that it generally is appropriate for positive results in any one of these mutagenicity tests to trigger a requirement to perform chronic oncogenicity bioassays. However, EPA agrees with commenters on the proposed test rules mentioned above that the overall scientific weight-of-evidence as to a substance's potential oncogenicity should be appropriately factored into these testing decisions. Furthermore, EPA believes that the weight-of-evidence should apply differently in the case of substances where testing is required under section 4(a)(1)(A) alone (as in the case of DETA) when compared with substances where the Agency finds that testing is supported only under section 4(a)(1)(B) (as is the case for the C9 aromatic hydrocarbon fraction). Where EPA has made findings of substantial production and significant or substantial exposure under section 4(a)(1)(B), there is a presumption that testing of the substance for oncogenicity is needed and the question before the Agency is whether the weight-of-evidence from the mutagenicity testing shows that oncogenic potential of the substance is sufficiently unlikely that EPA can reasonably predict that the anticipated exposures to the substance will not present an unreasonable risk of oncogenicity. In contrast, where testing is being required under section 4(a)(1)(A) alone, EPA must consider whether all of the relevant data available to the Agency after completion of the required mutagenicity tests provide substantial evidence that the substance may present an unreasonable risk of oncogenicity.

In the case of DETA, where testing is being required under section 4(a)(1)(A) alone, existing mutagenicity data show the chemical to be negative in gene mutation assays using bacteria (*Salmonella typhimurium*), yeast (*Saccharomyces cerevisiae*) and cultured mammalian cells (Chinese hamster ovary). However, DETA did produce positive results in tests for sister chromatid exchange (SCE) in Chinese hamster ovary cells and for unscheduled DNA synthesis (UDS) in cultured rat liver cells. Among these tests, only the gene mutation test in cultured mammalian cells (which was negative for DETA) would be used by EPA to trigger oncogenicity testing directly. However, the positive SCE and

UDS test results provide some basis for suspicion that DETA could be a mutagen and/or oncogen. Thus, EPA is requiring an *in vivo* gene mutation test and both *in vitro* and *in vivo* chromosomal aberration tests for DETA in a final test rule published elsewhere in this Federal Register.

If any of these tests produces a clearly positive result, EPA considers that finding to show sufficient potential of DETA to be an oncogen to warrant required chronic oncogenicity bioassays of this substance, despite the existing evidence that DETA does not cause gene mutations in bacteria, yeast, or cultured mammalian cells.

C. EPA's Findings

The EPA finds that, if DETA elicits positive test results in any of the following mutagenicity assays required for DETA in the final Phase I test rule for this substance (published elsewhere in this issue of the Federal Register), then the manufacture, processing, use, and disposal of DETA may present an unreasonable risk to humans of carcinogenicity: (1) The *in vitro* cytogenetics assay, (2) the *in vivo* cytogenetics assay, or (3) the sex-linked recessive lethal gene mutation assay in *Drosophila melanogaster*. This finding is based on the Agency's belief that there is a high correlation between positive test results in any of these three mutagenicity assays with positive test results in chronic oncogenicity bioassays for a large number of chemical substances tested in both kinds of assay systems.

The EPA also finds that, if the mutagenicity assays indicate DETA to be a potential oncogen, there are insufficient data and experience upon which the potential carcinogenic effects of DETA's manufacture, distribution in commerce, processing, use, or disposal, or any combination of these activities, on human health can be reasonably determined or predicted, and that chronic oncogenicity bioassay testing of DETA is necessary to develop such data.

III. Economic Analysis of Proposed Rule

To assess the economic impact of this proposed rule, EPA has prepared an economic evaluation (Ref. 1) that examines the cost of the required testing and analyzes four market characteristics of DETA: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The economic evaluation for the DETA proposed test rule, which estimates a total testing cost of \$480,700 to \$1,462,200 for chronic oncogenicity bioassays in both rats and mice,

indicates that the potential for adverse economic effects due to the estimated cost of testing is low. The annualized test costs for DETA range from \$124,600 to \$373,650. This conclusion is based on the following observations (Ref. 1):

1. The demand for DETA is relatively inelastic, due to limited potential for substitution in end uses.
2. The market expectations for DETA are relatively favorable.
3. The relative magnitude of the test cost is negligible (i.e., an estimated 1.46 cents per pound in the upper-bound case); this represents 0.86 percent of the sales price of DETA.

IV. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules and test programs negotiated with industry in place of rulemaking. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing," October, 1983, can be obtained through the NTIS under publication number PB85-240773.

On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing required in this proposed rule.

V. Public Record

EPA has established a public record for this rulemaking (docket number OPTS-42012A). This record includes the basic information the Agency considered in developing this proposal and appropriate Federal Register notices. This record includes the following information:

A. Supporting Documentation

- (1) Federal Register notices pertaining to this rule, consisting of:
 - (a) Notice of proposed rule on DETA.
 - (b) Notice of previous proposed rule on DETA (47 FR 18386).
 - (c) Notice of final Phase I rule on DETA.
 - (d) Notice containing the ITC designation of DETA to the Priority List (46 FR 28138).
 - (e) Notice containing EPA's Good Laboratory Practice Standards (48 FR 53922).
 - (f) Notice of final rule on test rule development and exemption procedures for one-phase rulemaking (50 FR 20862).

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(g) Notice of final rule concerning data reimbursement (48 FR 31786).

(2) Support documents, consisting of:

(a) Diethylenetriamine support document.

(b) Economic impact analysis of proposed test rule for DETA.

(3) Communications, consisting of:

(a) Written public comments on previous proposed rule on DETA (47 FR 16386).

(b) Summaries of telephone conversations.

(c) Meeting summaries.

(d) Reports—published and unpublished factual materials, including contractors' reports.

(4) OTS Health Effects Test Guidelines—chronic oncogenicity bioassay testing.

B. References

(1) MATHTECH, Inc. "Economic Impact Analysis of Proposed Test Rule for Diethylenetriamine." Washington D.C.: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Contract No. 68-01-6630, 1985.

The Agency will supplement the record with additional information as it is received. The record is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Room E-107, 401 M Street, SW., Washington, D.C.

VI. Other Statutory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "major" and, therefore, subject to the requirement of a Regulatory Impact Analysis. The regulation for this chemical is not major because it does not meet any of the criteria set forth in section 1(b) of the order. First, the actual cost of the testing prescribed for DETA is less than \$1,442,200 over the testing and reimbursement period. Second, because the costs of the required testing will be distributed over a large production volume, the rule will have only very minor effects on producers' costs or users' prices for this chemical substance. Finally, taking into account the nature of the market for this substance, the level of costs involved, and the expected nature of the mechanisms for sharing the costs of the required testing, EPA concludes that there will be no significant adverse economic impact of any type as a result of this rule.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (15 U.S.C. 601, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have significant impact on a substantial number of small businesses for the following reasons:

1. Based on the Economic Impact Analysis prepared for this rule (Ref. 1), there is only one small manufacturer of DETA that manufactures less than 0.003 percent of the estimated annual domestic production of DETA. Although no figures are available to indicate whether or not there are small businesses which import DETA, the total amount of DETA imported is estimated to represent less than 1 percent of the estimated domestic production of DETA. Thus, the estimated number of small manufacturers (including importers) affected by this rule will be quite small.

2. Small manufacturers and small processors of DETA are not expected to perform testing themselves or to participate in the organization of the testing efforts.

3. Small manufacturers and small processors will experience only minor costs, if any, in securing exemption for testing requirements.

4. Small manufacturers and small processors are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The information collection requirements contained in this rule have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* and have been assigned OMB control number 2070-0033.

List of Subjects in 40 CFR Part 799

Testing, Environmental Protection Agency, Environmental protection, Hazardous material, Chemicals.

Dated: May 18, 1985.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

It is proposed that 40 CFR Part 799 be amended as follows:

1. The authority citation for Part 799 continues to read as follows:

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

2. By adding paragraph (c)(5) to § 799.1575 to read as follows:

§ 799.1575 Diethylenetriamine (DETA).

(c)
(5) *Carcinogenicity*—(i) *Required testing*. A chronic dermal oncogenicity bioassay shall be conducted in both rats and mice with DETA, if this substance yields a positive test result in any one of the following mutagenicity tests: the *in vitro* cytogenetics assay conducted pursuant to paragraph (c)(2)(i)(A) of this section, the *in vivo* cytogenetics assay

conducted pursuant to paragraph (c)(2)(i)(B) of this section, or the sex-linked recessive lethal assay in *Drosophila melanogaster* conducted pursuant to paragraph (c)(1)(i)(A) of this section. Positive test results are those which meet the criteria established for these three mutagenicity assays in the OTS Health Effects Guidelines, published by the National Technical Information Service (NTIS; PB 82-232984).

(ii) *Test Standard*. The OTS Health Effects Test Guidelines for chronic exposure-oncogenicity, published by the National Technical Information Service (NTIS; PB 82-232984), shall be the test standard for the required oncogenicity bioassay testing of DETA. It is U.S. Environmental Protection Agency Publication No. EPA 560/6-82-001 and is for sale from the U.S. Department of Commerce, National Technical Information Service, 5285 Port Royal Rd., Springfield, VA 22161. When ordering, use NTIS Accession No. PB 82-232984. It is also available for inspection at the Office of the Federal Register Information Center, Rm. 8301, 1108 L St., NW., Washington, D.C. 20408. A copy of this publication has also been included in the public record for this rule (docket no. OPTS-42012A) and is available for inspection in the OPTS Reading Rm., E-107, 401 M St., SW., Washington, D.C. 20460, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays. These materials are incorporated as they exist on the date of the approval and a notice of any change in these materials will be published in the Federal Register.

(iii) *Reporting requirements*—(A) *Data contained in reports*. In addition to the reporting requirements as specified in the EPA GLP standards in 40 CFR Part 792, the specific information listed in part III. C. of the test standard identified in paragraph (c)(5)(ii) of this section shall be reported.

(B) *Interim quarterly summary reports*. The interim quarterly summary reports 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 shall be submitted to EPA no later than 48 months following the date the test sponsor(s) are notified by the Agency that EPA has determined that DETA has exhibited a positive test result in one or more of the mutagenicity assays conducted pursuant to paragraph (c)(1)(i)(A), (2)(i)(A) or (B) of this section.