

## 40 CFR Part 799

(OPTS-42061E; FRL-3484-7)

**Oleylamine; Final Test Standards and Reporting Requirements**

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

**SUMMARY:** EPA is issuing a final Phase II test rule under section 4(a) of the Toxic Substances Control Act (TSCA) specifying the test standards and reporting requirements to be used by manufacturers and processors of oleylamine (9-octadecanyleamine or ODA; CAS No. 112-99-3). This rule requires that certain TSCA health effects test guidelines be utilized as the test standards for the required studies, and that test data be submitted within specified times.

**DATES:** In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern ["daylight" or "standard" as appropriate] time on December 15, 1988. This rule shall become effective on January 17, 1989.

**FOR FURTHER INFORMATION CONTACT:** Michael M. Stahl, Acting Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. EB-44, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0558.

**SUPPLEMENTARY INFORMATION:** EPA is promulgating a final Phase II test rule specifying test standards and reporting requirements for ODA. The test standards and reporting requirements are added to 40 CFR 799.3175.

Public reporting burden for this collection of information is estimated to average 535 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including

suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503.

**I. Background**

EPA issued a final Phase I rule under section 4(a) of TSCA published in the Federal Register of August 24, 1987 (52 FR 31962), requiring manufacturers and processors to perform developmental toxicity and two-tiered mutagenicity testing of ODA. The need for third tier mutagenicity testing and oncogenicity testing was to be determined by EPA following public program review of all relevant data.

Under the two-phase test rule development process, manufacturers and processors of ODA would normally have been required to submit proposed study plans, including schedules for each of these required tests, in accordance with 40 CFR 799.50. EPA would review the submitted study plans and schedules and issue them, with any necessary modifications, for public comment in a Phase II test rule proposal. After evaluating and responding to public comment, EPA would adopt the study plans in a Phase II final rule as the required test standards and data submission deadlines in accordance with 40 CFR 790.52.

However, in the case of the ODA test rule, which was initiated under the two-phase process, EPA decided to propose the relevant TSCA test guidelines as the test standards for the rule (52 FR 31970; August 24, 1987). EPA also proposed that the data from the required studies be submitted within certain time periods, these time periods serving as the data submission deadlines required by TSCA section 4(b)(1). The reasons for this change in the test rule development process for ODA were discussed in the proposed Phase II rule.

**II. Modifications to the Two-Phase Rulemaking Process**

Because EPA proposed certain TSCA guidelines as the test standards and proposed data submission deadlines, persons subject to the Phase I final rule were not required to submit proposed study plans for the required testing or proposed dates for the initiation and completion of this testing. They were, however, required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.45.

EPA is now promulgating a final Phase II rule requiring manufacturers (including importers) and processors of

ODA who have not been granted exemptions from the rule to conduct testing in accordance with specified test standards and reporting requirements. While EPA has not identified any byproduct manufacturers of ODA, such persons are subject to the requirements of this test rule. These standards and requirements reflect EPA's evaluation of comments received on the proposed rule. Moreover, once this Phase II final rule is promulgated, those persons who have notified EPA of their intent to test must submit study plans (which adhere to the promulgated test standards) no later than 45 days before the initiation of each of the required tests.

**III. Proposed Phase II Test Rule****A. Proposed Test Standards**

EPA proposed that testing of ODA be conducted using the following TSCA test guidelines as test standards:

1. For specific organ/tissue toxicity under 40 CFR 798.4900 *Developmental toxicity study*.
2. For genetic toxicity: Chromosomal effects—*a. First tier under 40 CFR 798.5385 In vivo mammalian bone marrow cytogenetics tests: Chromosomal analysis.*
- b. Second tier under 40 CFR 798.5450 Rodent dominant lethal assay.*
- c. Third tier under 40 CFR 798.5480 Rodent heritable translocation assay.*
3. For genetic toxicity: Gene mutations—*a. First tier under 40 CFR 798.5300 Detection of gene mutations in somatic cells in culture.*
- b. Second tier under 40 CFR 798.5275 Sex-linked recessive lethal test in Drosophila melanogaster.*
- c. Third tier under 40 CFR 798.5200 Mouse visible specific locus test (see Unit V.A.3. of this preamble).*
4. For chronic exposure under 40 CFR 798.3300 *Oncogenicity.*

EPA believes that the TSCA Health Effects Test Guidelines cited in Unit III.A., if properly followed, will produce adequate and reliable data.

**B. Proposed Reporting Requirements**

EPA proposed that all data developed under this rule be conducted and reported in accordance with its TSCA Good Laboratory Practice (GLP) standards which appear at 40 CFR Part 792, and that test sponsors submit individual study plans at least 45 days prior to the initiation of each study.

EPA is required by section 4(b)(1)(c) of TSCA to specify the time period during which persons subject to a test rule must submit test data. EPA proposed that interim progress reports be provided at 6-month intervals

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beginning 6 months after the effective date of the final test rule or notification that testing should be initiated. EPA proposed specific reporting requirements for each of the proposed test standards as follows:

That the developmental toxicity study be conducted and the final results submitted to EPA within 12 months of the effective date of the final test rule.

That the mutagenicity studies be conducted, and the final results submitted to EPA as follows:

1. *In vivo* mammalian bone marrow cytogenetics test and detection of gene mutations in somatic cells in culture within 8 months of the effective date of the final rule.

2. Rodent dominant lethal assay and sex-linked recessive lethal test in *Drosophila melanogaster* within 17 months of the effective date of the final rule.

3. Rodent heritable translocation assays within 24 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

4. Mouse visible specific locus test within 48 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

That oncogenicity testing be conducted and the final results submitted within 53 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

As required by TSCA section 4(d), EPA plans to publish in the Federal Register a notice of the receipt of any test data submitted under this test rule within 15 days of receipt of that data. Except as otherwise provided in TSCA section 14, such data will be made available for examination by any person.

#### IV. Response to Public Comment

EPA received written comments from the Oleylamine Program Panel of the Chemical Manufacturers Association (the Panel) in response to the proposed test standards and reporting requirements for oleylamine on October 8, 1987 (Ref. 1). The Panel was composed of four ODA manufacturers, Akzo Chemie America, Humko Chemicals, Jetco Chemical Company, and Sherex Chemical Company, and one processor, Ethyl Corporation. The Panel also requested a public meeting to give oral comments; the meeting was held on November 16, 1987 (Ref. 2). An additional submission to clarify issues discussed at the EPA public meeting was submitted to EPA by the Panel on January 6, 1988 (Ref. 3). A summary of

the Panel's comments and EPA's responses follows.

#### A. Route of Administration for Developmental Toxicity Study

1. *Comment:* The Panel believes the dietary route should not be used because the Panel found through an animal feed stability study it conducted that only 50 percent of ODA is available in rat chow after 24 hours.

*Response:* EPA agrees with this comment; thus the route of administration shall now be oral by gavage for the developmental toxicity test, the *in vivo* mammalian bone marrow cytogenetic tests—chromosomal analysis, rodent dominant lethal assay, rodent heritable translocation assay, and the oncogenicity test.

2. *Comment:* The gavage route is inappropriate because the bolus effect is different from a mechanics' slow dermal exposure.

*Response:* EPA disagrees. Although gavage gives a bolus dose, it is an accepted method to measure the developmental toxicity of chemicals and will measure the intrinsic capacity of ODA to cause developmental toxicity. Dermal exposure is inappropriate because of the highly corrosive nature of ODA as discussed in the final Phase I rule (52 FR 31982; August 24, 1987).

3. *Comment:* An adequate data base is available to interpret developmental toxicity effects via the dermal route.

*Response:* EPA disagrees because there is a very limited data base on developmental toxicity studies conducted via the dermal route from which background information can be drawn for these studies. Also, those chemicals that have been tested by the dermal route were, for the most part, first tested by the oral route and then tested dermally. Consistent with these tests, EPA would agree to dermal developmental toxicity testing of ODA if an oral developmental toxicity test were done first.

The Panel provided a bibliography of articles to support its contention that there was an adequate data base available to interpret developmental toxicity effects via the dermal route. The Panel's submission included no analysis of this bibliography. In fact, about one-half of the articles were inappropriate to address this question (e.g., frog and chicken embryo studies). The Panel has not provided any analysis or rational argument to support its thesis. Thus, EPA requires that a developmental toxicity study be conducted with ODA via the oral gavage route of exposure.

4. *Comment:* Developmental toxicity effects are different with oral and dermal applications.

*Response:* A developmental toxicity study is designed to ensure that a chemical being tested is administered at a high enough dose to get to the target system. One then determines if the chemical, on the basis of conditions of exposure with consideration of maternal effects, has the potential to produce an adverse effect. Because of the high corrosive nature of ODA, a dermal study may not allow a sufficient dose to reach the target system. Therefore, EPA is requiring that the route of exposure for the developmental toxicity study be oral by gavage.

5. *Comment:* CMA refuted EPA's assertion that a dermal developmental toxicity study on ODA may result in positive effects due solely to stress from the dermal irritating properties of ODA by citing a study in which three dermal irritating chemicals did not cause developmental toxicity. CMA therefore felt that the dermal route of administration of ODA would be acceptable.

*Response:* Although there may be compounds that cause dermal irritation in adult animals but no developmental toxicity whatsoever, EPA believes that ODA's strong dermal irritation properties are likely to stress the test animals and that it is prudent to minimize this confounding factor in a developmental toxicity study. Therefore, EPA is requiring that the route of administration of ODA be oral by gavage in the developmental toxicity study.

6. *Comment:* The Panel believes that sufficient ODA will penetrate to the target organ via the dermal route.

*Response:* EPA disagrees. In the absence of hard data to prove the Panel's point, EPA continues to believe, on the basis of the available data, that because severe irritation will limit the amount of ODA that can be applied to the skin, sufficient ODA will not penetrate the skin to allow for the proper design of the developmental toxicity study, i.e. high dose causing maternal toxicity. In the absence of adequate dermal absorption data (kinetic data), EPA cannot predict what the target organ concentrations of ODA will be.

7. *Comment:* The Panel wants to first conduct the dermal developmental toxicity test with ODA at a level below skin breakdown or obstruction (sic) in rats, and in rabbits whose skin is more permeable than human skin. At this level the maximum tolerated dose (MTD) is expected to approximate maximum use levels in lubricants.

*Response:* EPA disagrees. Available data indicate that ODA is such a strong

dermal irritant that the animal dose will be below the anticipated human exposure level. This will not provide an adequate margin of exposure between animal and human exposure levels.

**B. Oral/Dermal Pharmacokinetics**

*Comment:* EPA stated that it planned to propose an oral/dermal pharmacokinetics study on ODA in its final Phase I rule (52 FR 31962; August 24, 1987). The Panel commented that it felt that such a study would not give reliable comparative results.

*Response:* EPA is reviewing the need for this study. If EPA determines that such a study is necessary, a separate notice of proposed rulemaking for the comparative oral/dermal pharmacokinetics of ODA will be published in the Federal Register.

**C. Oncogenicity Testing**

*Comment:* EPA should specify that oncogenicity testing will not be required until an updated economic impact analysis is completed and considered as part of the program review for such testing.

*Response:* EPA will consider the need for an updated economic impact analysis at the time of the public program review.

**D. Reporting Requirements**

*Comment:* The time for testing is inadequate, and moreover should begin on the effective date of the final Phase II rule, rather than the final Phase I rule published on August 24, 1987.

*Response:* EPA agrees that the time for testing shall be based on the effective date of the final Phase II rule. EPA also believes that the proposed reporting deadlines finalized in this final Phase II rule provide adequate time for completing the testing and submitting final reports for the developmental toxicity and oncogenicity tests. EPA notes that it has extended the reporting deadlines originally proposed for the mutagenicity tests.

**V. Final Phase II Test Rule**

**A. Test Standards**

The first, second, and third tier mutagenicity, developmental toxicity, and oncogenicity test guidelines and chemical-specific modifications proposed for ODA (52 FR 31890; August 24, 1987) shall be the test standards for the testing of ODA under 40 CFR 799.3175 with the following exceptions:

1. *Developmental toxicity study.* EPA is requiring the oral route of administration by gavage for developmental toxicity testing of ODA.

2. *In vivo mammalian bone marrow cytogenetics test, rodent dominant*

*lethal assay, and rodent heritable translocation assays.* The oral route by gavage shall be used to maintain consistency among the tests for ODA test rules and provides an opportunity for public comment. If EPA concludes that third tier mutagenicity testing is still appropriate for ODA, EPA would amend the final test rule for ODA to add this requirement with any appropriate modifications.

3. *Mouse visible specific locus test.* EPA proposed a tiered testing approach to evaluate whether ODA elicits heritable gene mutations. Positive results in certain lower-tier tests would trigger the requirement for conducting a mouse visible specific locus (MVSL) test. EPA believes that the MVSL is necessary, when certain lower-tier tests are positive, to establish definitively whether a substance is capable of eliciting heritable gene mutations. Under the proposed approach, EPA would consider any positive lower-tier test results in a public program review, together with other relevant information, during which interested persons would be able to give their views to EPA. If, after the review, EPA determined that the MVSL was still appropriate, EPA would notify the test sponsors by letter or Federal Register notice that they must conduct the test. If EPA determines that the test is no longer necessary, EPA would propose to amend the rule to delete the test requirement.

The final test rule for ODA includes requirements to conduct the lower-tier tests for gene mutations. However, EPA is not promulgating the Phase II requirement for the MVSL for ODA at this time. EPA has based its proposal to require the MVSL, in part, on certain information and assumptions about the cost of conducting the test and the availability of laboratories able to perform the test. The information and assumptions have since proven to be incorrect. Accordingly, EPA is reexamining this information as it applies to the MVSL requirement for this test rule as well as those for other chemical substances. In particular, EPA is reviewing whether any laboratories are available to perform the MVSL for industry in accordance with the TSCA GLP Standards at 40 CFR Part 792, and the cost of such testing. EPA is also reviewing possible alternative tests to the MVSL as well as modifications of the MVSL for which costs may be lower or laboratory availability may be more certain.

Once EPA completes its evaluation of this additional information, EPA will publish a notice in the Federal Register concerning the MVSL for ODA and other substances subject to TSCA

section 4 test rules. This notice would provide up-to-date information on the cost of MVSL testing, availability of laboratories to perform the MVSL, and possible alternative tests to the MVSL or modifications of the MVSL together with their costs and laboratory availability. The notice would also address EPA's intentions about how any changes to the MVSL requirements would apply to the various test rules and would provide an opportunity for public comment. If EPA concludes that the MVSL is still appropriate for ODA, EPA will amend the final test rule for ODA to add the MVSL requirements with any appropriate modifications.

4. *Oncogenicity bioassay.* The oral route of administration by gavage is required.

**B. Reporting Requirements**

All data developed under this rule shall be reported in accordance with the TSCA GLP Standards (40 CFR Part 792). In addition, test sponsors shall submit individual study plans at least 45 days prior to the initiation of each study in accordance with 40 CFR Part 790.

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. On the basis of EPA's regulatory experience with the health effects tests required for ODA, as well as in response to public comments, EPA is adapting reporting requirements as follows. Results for the required tests shall be reported as specified in the proposed rule for the developmental toxicity and oncogenicity tests. EPA has extended the reporting deadline as originally proposed for the mutagenicity tests. (See Unit III.B. of this preamble). In addition, the rodent heritable translocation assay and oncogenicity test data shall be submitted within the time specified after notification. The following table shows the reporting requirements for ODA:

TABLE—REPORTING REQUIREMENTS FOR ODA

Test	Reporting deadline for final report (months after the effective date of final phase II rule, except as indicated)	Number of interim (6-month) reports required
Developmental toxicity...	12	1
Gene mutation cells in culture assay.....	10	1

TABLE—REPORTING REQUIREMENTS FOR ODA—Continued

Test	Reporting deadline for final report (months after the effective date of final phase II rule, except as indicated)	Number of interim (6-month) reports required
Sex-linked recessive lethal test in <i>Drosophila melanogaster</i> .....	22	3
<i>In vivo</i> cytogenetics test.....	14	2
Rodent dominant lethal test.....	26	4
Rodent heritable translocation assay.....	25	4
Oncogenicity.....	53	8

<sup>1</sup> Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter Federal Register notice that, following public program review of all of the then existing data for ODA, EPA has determined that the required testing must be performed.

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

#### C. Conditional Exemptions Granted

The test rule development and exemption procedures (40 CFR 790.87) indicate that, when certain conditions are met, exemption applicants will be notified by certified mail or in the final Phase II test rule for a given substance that they have received conditional exemptions from test rule requirements. The exemptions granted are conditional because they are based on the assumption that the test sponsors will complete the required testing according to the test standards and reporting requirements established in the final Phase II test rule for the given substance. TSCA section 4(c)(4)(B) provides that if an exemption is granted prospectively (that is, on the basis that one or more persons are developing test data, rather than on the basis of prior test data submissions), EPA must terminate the exemption if any test sponsor has not complied with the test rule.

Since the Oleylamine Program Panel of the Chemical Manufacturers Association has indicated to EPA by letter of intent (Ref. 5) its agreement to sponsor all of the tests required for ODA in the final Phase I test rule for ODA (52 FR 31962; August 24, 1987) according to the test standards and reporting requirements established in this final

Phase II test rule for ODA, EPA is hereby granting conditional exemptions to all exemption applicants for all of the testing required for ODA in 40 CFR 799.3175.

#### D. Judicial Review

The promulgation date for the ODA Phase I final rule was established as 1 p.m. eastern daylight time on September 7, 1987 (52 FR 31962; August 24, 1987). To EPA's knowledge, no petitions for judicial review were filed. Any petition for review of this final rule will be limited to a review of the test standards and reporting requirements for ODA established in this final Phase II rule.

#### E. Other Provisions

Section 4 findings, required testing, test substance specifications, persons required to test, enforcement provisions, and the economic analysis are presented in the final Phase I rule for ODA (52 FR 31962; August 24, 1987).

#### VI. Rulemaking Record

EPA has established a record for this rulemaking [docket number OPTS-42061E]. In addition to the documentation listed in the final Phase I rule, this record includes basic information considered by EPA in developing this final rule, including:

##### A. Supporting Documentation

(1) Federal Register notices pertaining to this final rule consisting of:

(a) Phase I final rule on ODA (52 FR 31962; August 24, 1987).

(b) Notice of Proposed Phase II rule on ODA (52 FR 31970; August 24, 1987).

(c) TSCA test guidelines final rule (40 CFR Parts 796, 797, and 798; September 27, 1985) and modifications (52 FR 19056; May 20, 1987).

(2) Support documents consisting of the economic impact analysis of the final test rule for ODA.

(3) Communications consisting of:

(a) Written public comments.

(b) Summaries of phone conversations.

##### B. References

(1) CMA. Comments in response to proposed test standards for oleylamine submitted to the Environmental Protection Agency, Washington, DC, by the Oleylamine Program Panel of the Chemical Manufacturers Association, Washington, DC (October 6, 1987).

(2) Transcript of proceedings before the Environmental Protection Agency in the matter of test rule development meeting on oleylamine. Heritage Reporting Corporation, Official Reporters, 1220 L Street NW., Washington, DC (November 18, 1987).

(3) Letter to Robert Sanford, Office of Pesticides and Toxic Substances,

Environmental Protection Agency, Washington, DC, from Has Shah, Chemical Manufacturers Association, Washington, DC. Clarification of issues discussed at EPA public hearing on oleylamine test rule at proposed test standards on November 16, 1987 (January 6, 1988).

(4) CMA. Chemical Manufacturers Association, 2510 M Street NW., Washington, DC 20037. CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation (1985).

(5) Letter to document control officer, TSCA Public Information Office, Office of Pesticides and Toxic Substances, Environmental Protection Agency, Washington, DC, from Geraldine V. Cox, Chemical Manufacturers Association, Washington, DC. Letter of intent to conduct testing of oleylamine by the Oleylamine Program Panel of the Chemical Manufacturers Association (October 26, 1987).

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in the TSCA Public Docket Office, Rm. NE-G004, 401 M Street SW., Washington, DC 20460.

#### VII. Other Regulatory Requirements

##### A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a rule is "major" and therefore subject to the requirements of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. The economic analysis of the testing of ODA is discussed in the Phase I test rule (52 FR 31962; August 24, 1987).

This final Phase II test rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments received from OMB, together with any EPA response to these comments, are included in the public record for this rulemaking.

##### B. Regulatory Flexibility Act

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

1. There are no small manufacturers of this chemical.

2. Small processors are not expected to perform testing themselves, or

participate in the organization of the testing effort.

3. Small processors will experience only very minor costs, if any, in securing exemption from testing requirements.

4. 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 OMB under the provisions of the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.*, and have been assigned OMB control number 2070-0033.

Public reporting burden for this collection of information is estimated to average 535 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M Street SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503, marked "Attention: Desk Officer for EPA."

#### List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals, Reporting and recordkeeping requirements.

Dated: November 18, 1988.

Susan F. Vogt,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR Part 799 is amended as follows:

#### PART 799—[AMENDED]

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

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

b. Section 799.3175 is amended by adding paragraphs (c)(1) (ii) and (iii); (2) (ii) and (iii); (3) (ii) and (iii); and (4) (ii) and (iii), and (d) to read as follows:

#### § 799.3175 Oleylamine.

(c) \* \* \*  
(1) \* \* \*  
(ii) *Test standard.* (A) The developmental toxicity study shall be conducted with ODA in accordance with § 798.4900 of this chapter except

the provisions of paragraphs (e) (1)(i) and (5) of § 798.4900.

(B) For purposes of this section, the following provisions also apply:

(1) *Species and strain.* The rat and rabbit shall be the test species. The strain shall not have low fecundity and shall preferably be characterized for its sensitivity to developmental toxins.

(2) *Administration of the test substance.* The route of administration shall be oral by gavage. The test substance shall be administered at approximately the same time each day.

(iii) *Reporting requirements.* (A) The developmental toxicity testing shall be completed and the final report submitted to EPA within 12 months of the date specified in paragraph (d)(1) of this section.

(B) An interim progress report shall be provided to EPA 6 months after the date specified in paragraph (d)(1) of this section.

(2) \* \* \*  
(ii) *Test standard.* (A)(1) The *in vivo* mammalian bone marrow cytogenetics test: Chromosomal analysis shall be conducted with ODA in accordance with § 798.5385 of this chapter except the provisions of paragraphs (d)(3)(i) and (5)(iii) of § 798.5385.

(2) For purposes of this section, the following provisions also apply.

(i) *Species and strain.* Mice shall be used.  
(ii) *Route of administration.* The route of exposure shall be oral by gavage.

(B)(1) The rodent dominant lethal assay shall be conducted with ODA in accordance with § 798.5450 of this chapter except the provisions of paragraphs (d) (3)(i) and (5)(iii) of § 798.5450.

(2) For purposes of this section, the following provisions also apply:

(i) *Species.* Mice shall be used as the test species. Strains with low background dominant lethality, high pregnancy frequency, and high implant numbers are recommended.

(ii) *Route of administration.* The route of administration shall be oral by gavage.

(C)(1) The rodent heritable translocation assay shall be conducted with ODA in accordance with § 798.5460 of this chapter, except for the provisions of paragraphs (d) (3)(i) and (5)(iii) of § 798.5460.

(2) For purposes of this section, the following provisions also apply.

(i) *Species.* Mice shall be used as the test species.

(ii) *Route of administration.* The route of administration shall be oral by gavage.

(iii) *Reporting requirements.* (A) The chromosomal aberration tests shall be

completed and the final reports submitted to EPA as follows:

(1) The *in vivo* mammalian bone marrow cytogenetics test shall be completed within 14 months of the date specified in paragraph (d)(1) of this section.

(2) The rodent dominant lethal assay (if required) shall be completed within 26 months of the date specified in paragraph (d)(1) of this section.

(3) The rodent heritable translocation assay shall be completed (if required) within 25 months of EPA's notification of the test sponsor by certified letter or Federal Register notice under paragraph (c)(2)(i)(C) of this section that testing should be initiated.

(B) Interim progress reports shall be provided to EPA at 6-month intervals for each test beginning 6 months after the date specified in paragraph (d)(1) of this section or notification that testing should be initiated under paragraph (c)(2)(i)(C) of this section, until submission of the final report.

(3) \* \* \*  
(ii) *Test standard.* (A) (1) The detection of gene mutations in somatic cells in culture shall be conducted with ODA in accordance with § 798.5300 of this chapter, except for the provisions of paragraphs (d)(3) (i), (ii) and (4) of § 798.5300.

(2) For purposes of this section, the following provisions also apply:

(i) *Types of cells used in the assay.* ODA shall be tested in L5178Y mouse lymphoma cells. Cells should be checked for *Mycoplasma* contamination and may be periodically checked for karyotype stability.

(ii) *Cell growth and maintenance.* Alternative dosing procedures consisting of suspension cultures or roller-bottle incubation shall be used. Appropriate incubation conditions (CO<sub>2</sub> concentrations, temperature, and humidity) shall be used.

(iii) *Metabolic activation.* The metabolic activation system shall be derived from the postmitochondrial fraction (S-9) of livers from rats pretreated with Aroclor 1254. Cells shall be exposed to test substance both in the presence and absence of an appropriate metabolic activation system.

(B) (1) The sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with ODA in accordance with § 798.5275 of this chapter except for the provisions of paragraph (d)(5)(iii) of § 798.5275.

(2) For purposes of this section, the following provisions also apply:

(i) *Route of administration.* The route of administration shall be oral.

(ii) Reserved.

(iii) *Reporting requirements* (A) Gene mutation tests shall be completed and the final reports submitted to EPA as follows:

(1) The detection of gene mutations in somatic cells in culture shall be completed within 10 months of the date specified in paragraph (d)(1) of this section.

(2) The sex-linked recessive lethal test in *Drosophila melanogaster* (if required) shall be completed within 22 months of the date specified in paragraph (d)(1) of this section.

(B) Interim progress reports shall be provided to EPA at 6-month intervals for each test beginning 6 months after the date specified in paragraph (d)(1) of this section until submission of the final report.

(4) \* \* \*

(ii) *Test standard.* (A)(1) The oncogenicity bioassay shall be conducted with ODA in accordance with § 798.3300 of this chapter, except for the provisions of paragraphs (b)(1)(i) and (6) of § 798.3300.

(2) For purposes of this section, the following provisions also apply:

(i) *Species and strain.* ODA shall be tested in both rats and mice. Commonly used laboratory strains shall be employed.

(ii) *Administration of the test substance.* The route of administration shall be oral by gavage.

(iii) *Reporting requirements.* (A) The oncogenicity bioassay shall be completed and the final report submitted to EPA within 53 months of EPA's notification of the test sponsor by certified letter or Federal Register notice under paragraph (c)(4)(i) of this section that testing should be initiated.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months after the notification under paragraph (c)(4)(i) of this section until submission of the final report.

(d) *Effective dates.* (1) Section 799.3175 is effective October 7, 1987 except for paragraphs (c)(1) (ii) and (iii); (2) (ii) and (iii); (3) (ii) and (iii); (4) (ii) and (iii), and (d) which are effective on January 17, 1989.

(2) The guidelines and other test methods cited in this section are referenced here as they exist on January 1989.

[Doc. 88-27661 Filed 11-30-88; 8:45 am]

BILLING CODE 6560-50-M

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