

40 CFR Part 799**(OPTS-42030B; FRL-2941-7)****Mesityl Oxide; Proposed Test Standards****AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Proposed rule.

SUMMARY: Elsewhere in this issue of the Federal Register, EPA is issuing a final test rule establishing testing requirements under section 4(a) of the Toxic Substances Control Act (TSCA) for manufacturers and processors of mesityl oxide (MO; CAS No. 141-97-7). In this proposed rule, EPA is proposing that certain TSCA test guidelines be utilized as the test standards for the required studies and that test data be submitted within specified time frames.

DATE: Submit written comments on or before February 3, 1986. If persons request time for oral comment by January 21, 1986, EPA will hold a public meeting on this proposed rule in Washington, DC. For further information on arranging to speak at the meeting, see Unit VI of this preamble.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42030B), in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic

Substances, Environmental Protection Agency, Rm. E-108, 401 M St., SW., Washington, DC 20460.

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

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460. Toll Free: (800-424-9065), In Washington, DC: (554-1404), Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the Federal Register, EPA is issuing a final test rule under section 4(a) of TSCA to require testing of MO for chronic effects, mutagenicity, and oncogenicity (conditional on the mutagenicity test results). The Agency is now proposing the test standards to be used and the time frames for submission of the required test data.

I. Background

Elsewhere in this issue of the Federal Register, EPA is promulgating a Phase I final rule pursuant to TSCA section 4 that establishes testing requirements for manufacturers and processors of MO. This Phase I rule specifies the following testing requirements for MO: (1) Inhalation subchronic (90-day) toxicity; (2) mutagenicity (including tests for both gene mutations and chromosomal aberrations); and (3) oncogenicity (if certain mutagenicity test results are positive).

Once this Phase I test rule becomes effective, manufacturers and processors of MO would normally be required (under the two-phase test rule development process) to submit proposed study plans for each of these required studies and proposed schedules for both the initiation of testing and the submission of study data. (See 40 CFR 790.30, published in the Federal Register of May 17, 1985 (50 FR 20658).) EPA would review the submitted study plans and schedules and would thereafter issue them (with any necessary modifications) in a Phase II test rule proposal. This proposal would request public comment on the ability of the proposed study plans to ensure that the resulting data would be reliable and adequate. After evaluating and responding to public comment, EPA would adopt the study plans, including the reporting schedules, in a Phase II

final rule as the required test standards and data submission deadlines. (See 40 CFR 790.32, published in the Federal Register of May 17, 1985 (50 FR 20659).)

However, in the case of the MO test rule, which was initiated under the two-phase process, EPA has decided to propose the relevant TSCA test guidelines as the test standards (see Unit III below). In addition, EPA is proposing that the data from the required studies be submitted within certain time periods. These time periods will serve as the data submission deadlines required by TSCA section 4(b)(1) (see Unit IV below). The reasons for this change in the test rule development process for mesityl oxide are discussed below.

II. Change in the Test Rule Development Process

A. Test Standards and Data Submission Deadlines

TSCA section 4(b)(1) specifies that test rules shall include standards for the development of test data ("test standards") and deadlines for submission of test data. Under a two-phase test rule development process utilized by EPA since 1982 (47 FR 13012; March 28, 1982) and formally adopted in the fall of 1984 (49 FR 39774; October 10, 1984), test standards and data submission deadlines were to be adopted during the second phase of the rulemaking process. Upon issuance of the Phase I final rule, which established the effects and characteristics for which a given chemical substance must be tested, persons subject to the rule would be required by a specified date to submit proposed study plans detailing the methodologies and protocols they intended to use to perform the required tests. Such study plans were to include proposed schedules for the initiation and completion of testing and submission of test data. (See 40 CFR 790.30 (a) and (c); published in the Federal Register of October 10, 1984 (49 FR 39774).) In the second phase, after consideration of public comment, the Agency would promulgate the Phase II final rule adopting the study plans (with any necessary modifications) as the test standards for the development of test data and deadlines for the submission of test data.

In December 1983, the Natural Resources Defense Council and the Industrial Union Department of the American Federation of Labor-Congress of Industrial Organizations filed an action under TSCA section 20 which challenged, among other things, the use of the two-phase process. 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 v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984).

After issuing that Opinion, the Agency decided that to expedite development of section 4 test rules, it would utilize a single-phase rulemaking process for most test rules. In the document announcing this decision, EPA stated that the single-phase approach offers a number of advantages over the two-phase process (see 50 FR 20652, 20653; May 17, 1985). In this single-phase approach, the Agency proposes (in one document) not only the effects for which testing will be required but also proposes pertinent TSCA or other appropriate guidelines as the test standards and time frames for the submission of test data. After receiving and evaluating public comment on the proposed testing requirements, test guidelines, and data submission deadlines, EPA promulgates a final test rule.

This single-phase approach shortens the rulemaking period and expedites the initiation of required testing that would usually result from use of the two-phase rulemaking process. The single-phase process also eliminates the requirement under the two-phase approach for industry to submit proposed test protocols for approval. Moreover, by allowing commenters to submit alternative testing methodologies during the comment period, the single-phase approach preserves the flexibility of the two-phase process.

These same advantages, i.e., expedited initiation of testing and the elimination of proposed study plan submission requirements for persons subject to a Phase I rule, are factors considered by EPA in deciding to modify the rulemaking process for mesityl oxide. By proposing both pertinent TSCA test guidelines as the test standards and data submission deadlines at the time of issuance of the Phase I rule, EPA expects that the Phase II final rule will be issued 6 months sooner than would occur if the usual two-phase process was followed. Thus, required testing will be initiated on a more expedited basis. In addition, for each of the required tests for mesityl oxide, appropriate TSCA test guidelines are available (see Unit III below). Thus, EPA believes that there is no need for manufacturers and processors of MO to develop study plans for approval independent of these TSCA guidelines.

B. Modifications to Requirements of a Phase I Final Rule for Mesityl Oxide

As indicated above, persons subject to the mesityl oxide Phase I final rule and who have notified EPA of their intent to test would normally be required to submit proposed study plans and proposed data submission deadlines within a specified time of the final rule's effective date (see 40 CFR 790.30 (a) and (c), published in the Federal Register of May 17, 1985 (50 FR 20658)). However, because EPA is proposing certain TSCA guidelines as the test standards and data submission deadlines, persons subject to the Phase I final rule are not required to submit proposed study plans for the required testing or proposed dates for the initiation and completion of that testing.

However, persons subject to the Phase I final rule for mesityl oxide are still required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.25, published in the Federal Register of May 17, 1985 (50 FR 20657). Moreover, once the test standards are promulgated in the Phase II final rule, 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 30 days before the initiation of each required test.

III. Proposed Test Standards

The Phase I rule specifies that MO be tested for inhalation subchronic toxic mutagenicity (including tests for both gene mutations and chromosomal aberrations, and oncogenicity (if certain tests predictive for oncogenicity are positive)). The Agency is now proposing that this testing of MO be conducted using the following TSCA test guidelines (new parts 798.797, 798 of 40 CFR were published in the Federal Register of September 27, 1985 (50 FR 39252)) as the test standards:

1. *Subchronic Exposure: Inhalation Toxicity* which appears at 40 CFR 798.2450.
2. *Mutagenicity: Chromosomal Effects*.
 - i. First Tier:
 - a. *In Vitro: Mammalian Cytogenetics* which appears at 40 CFR 798.5375.
 - b. *In Vivo: Mammalian Bone Marrow Cytogenetics Tests: Chromosomal Analysis* which appears at 40 CFR 798.5385.
 - ii. Second Tier:
 - Rodent Dominant Lethal Assay which appears at 40 CFR 798.5450.
 - iii. Third Tier: Rodent Heritable Translocation Assay which appears at 40 CFR 798.5480.
3. *Mutagenicity: Gene Mutations*.

i. First Tier: *Salmonella typhimurium* which appears at 40 CFR 798.5265. Somatic Cells-in Culture which appears at 40 CFR 798.5300.

ii. Second Tier: Sex Linked Recessive Lethal Test which appears at 40 CFR 798.5275.

iii. Third Tier: Mouse Specific Locus Test which appears at 40 CFR 798.5200.

4. *Chronic Exposure*. Oncogenicity which appears at 40 CFR 798.3300.

EPA believes that the TSCA Health Effects Test Guidelines cited above, if properly followed, should produce adequate and reliable data. These guidelines describe methods for performing testing of chemical substances under TSCA. The methods include the state-of-the-art for evaluating the effects of chemical substances. EPA reviews its TSCA test guidelines annually (see 47 FR 41857; Sept. 22, 1982).

EPA intends to propose shortly in a separate Federal Register notice, certain revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study. In addition, these revisions will avoid repetitive chemical-by-chemical changes to the guidelines in their adoption as test standards for chemical-specific test rules. EPA is proposing that these modifications be adopted in the test standards for MO.

The Agency believes the TSCA subchronic guideline will provide detailed information on toxic effects and target organs, and establish both a no-observed-effect level and appropriate levels for lifetime studies. EPA also uses the data from subchronic studies to predict potential chronic effects. The clinical testing which is required in subchronic studies is more extensive than that normally required in chronic studies. These data will be used in understanding the development of any toxic effects resulting from mesityl oxide exposure.

The Agency is requiring that the subchronic study be conducted by the inhalation route (the major route of human exposure to MO) in the rat. If a second species is chosen for testing it should be the mouse, since the rat and the mouse are the species of choice for oncology studies. Oncology testing for MO will be automatically triggered if select first and second tier mutagenicity test results are positive. The reader is directed to the final rule for MO appearing elsewhere in this issue of the Federal Register for a detailed explanation of EPA's tiered testing approach that automatically triggers both end-point mutagenicity tests and oncology testing. This test standard is proposed under 40 CFR 798.2450.

The Agency believes that the TSCA test guidelines for mutagenicity testing will provide adequate data to assess the potential human hazard resulting from exposure to MO due to interactions of the chemical with genetic material resulting in heritable change (mutation). The Agency is proposing the TSCA guidelines listed above as test standards. The changes made in the guidelines and the justification for these changes are set forth below.

1. *Salmonella typhimurium reverse mutation assay*. The direct plate incorporation method was selected as the choice assay for MO. Strains TA 1535, TA 1537, TA 98 and TA 100 were chosen because they have the largest data base of chemicals tested in this assay. Aroclor 1254 induced rat liver was chosen as the source of metabolic activation because it is the preferred source of activation for this assay, and because of its large historic data base. Both untreated and vehicle controls should be run to ensure that the solvent has no effect upon spontaneous reversion rate. DMSO is the routine solvent of choice for this assay. MO is to be tested over at least five doses up to a maximum of 5 mg/plate (in the absence of toxicity) to ensure an adequate range of test doses for detection of potential activity.

2. *Detection of gene mutation in somatic cells in culture*. L5178Y mouse lymphoma cells were chosen for use in this assay because of the activity of MO's structural analogue, isophorone, in this system. Both untreated and vehicle controls are to be used to ensure that the vehicle has no effect upon cell growth, survival or spontaneous mutation rate. Aroclor 1254 induced rat liver S-9 is the chosen source of metabolic activation because of its historical data base and generally accepted use in this assay. DMSO is the solvent of choice for this system. A 4-hour exposure time was chosen because it is the standard exposure period recommended for this test.

3. *Sex-linked recessive lethal test in Drosophila Melanogaster*. A negative control is to be included regardless of the size of the historical control because the assay is too important to be done without one. This will ensure that any observed effects are the result of chemical treatment and not environmental factors. Exposure is by vapors because it is the route of human exposure.

4. *The mouse visible specific locus test*. EPA is proposing that this assay be done at 2 doses by the inhalation route. EPA believes that dose-response data are essential for risk estimation. The route of administration is by inhalation

because that is the expected route of human exposure. The mouse is the test animal of choice. Strains (C₃H × 101)F₁ or (101 × C₃H)F₁ hybrids are chosen because of the historical data base available for these strains.

IV. Reporting Requirements

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

Test sponsors are required to submit individual study plans at least 30 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. The Agency is proposing specific reporting requirements for each of the proposed test standards as follows:

The subchronic toxicity tests shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final test rule. Interim progress reports shall be provided quarterly.

The mutagenicity studies shall be completed and the final results submitted to the Agency as follows:

First tier gene mutation and chromosomal aberration tests within 1 year.

Second tier gene mutation and chromosomal aberration tests within 2 years.

Third tier gene mutation within 4 years. Interim quarterly reports shall be provided for all tests.

The oncogenicity tests, to be triggered if certain tier I or II mutagenicity tests are positive, shall be completed and the final results submitted to the Agency 53 months after submission of the positive mutagenicity test results. Interim progress reports shall be provided quarterly.

As required by TSCA section 4(d), the Agency 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 persons.

V. Issues for Comment

EPA invites comment on the use of the TSCA test guidelines and the chemical specific modifications to these guidelines as the proposed test standards for the required testing of mesityl oxide. EPA also invites comment on the proposed schedule for the required testing.

VI. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); In Washington, DC: (514-1404); Outside the U.S.A. (Operator—202-554-1404), by January 21, 1986. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

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

VII. Public Record

EPA has established a record for this rulemaking (Docket number (OPTS-42030B)). This record includes basic information considered by the Agency in developing this proposal and appropriate Federal Register notices. The Agency will supplement the record with additional information as it is received.

This record includes the following information:

A. Supporting Documentation

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

(a) Notice containing the ITC designation of mesityl oxide to the Priority List (44 FR 31884; June 1, 1979).

(b) Notice of final rule requiring the submission of unpublished health and safety studies (47 FR 38780; September 2, 1982).

(c) Notice of proposed test rule for mesityl oxide (48 FR 30699; July 5, 1983).

(d) Notice adding mesityl oxide to the list of chemicals subject to the preliminary assessment information rule (49 FR 25859; June 25, 1984).

(e) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (48 FR 53922; November 29, 1983).

(f) Notice of final rule on test rule development and exemption procedures (49 FR 39774; October 10, 1984).

(g) Notice of final rule concerning data reimbursement (48 FR 41786; July 11, 1983).

(h) Notice of interim final rule on test rule development and exemption procedures (50 FR 20652; May 17, 1985).

(i) Notice of final rule on the C₆ Aromatic Hydrocarbon Fraction (50 FR 20662; May 17, 1985).

(j) Final Phase I rule on mesityl oxide.

(2) Support documents consisting of:

(a) Mesityl oxide technical support document for proposed rule.

(b) Economic impact analysis of NPRM for mesityl oxide.

(c) Economic impact analysis of final test rule for mesityl oxide.

(3) Communications consisting of:

(a) Written public comments.

(b) Transcription of public meeting.

(c) Summaries of phone conversations.

(d) Meeting summaries.

(4) Reports—published and unpublished contractor's reports.

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 Rm. E-107, 401 M St., SW., Washington, DC 20460.

VIII. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation 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 mesityl oxide is discussed in the final test rule which appears elsewhere in this issue of the Federal Register.

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

Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs of OMB, marked "Attention, Desk Officer for EPA." The final rule package will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals.

Dated: December 13, 1985.

John A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

Therefore, it is proposed that 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. In § 799.2500 by adding paragraphs (c)(1)(ii) and (iii), (2)(ii) and (iii), (3)(iii) and (iii), and (4)(ii) and (iii) to read as follows:

§ 799.2500 Mesityl oxide (MO)

(c) * * *

(1) * * *

(ii) *Test standard.* (A) Inhalation subchronic toxicity testing shall be conducted with MO in accordance with § 799.2450 of this chapter and modifications specified in paragraph (c)(1)(ii)(B) of this section.

(B) *Test standard modifications.* The requirement under § 799.2450 of this chapter is modified so that the rat is the required species.

(iii) *Reporting requirements.* (A) The subchronic testing shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final test rule.

(B) Interim progress reports shall be provided quarterly beginning 90 days

after the effective date of the final Phase 2 test rule.

(2) * * *

(ii) *Test standard.* (A)(1) The *in vitro* mammalian cytogenetic test shall be conducted with MO in accordance with § 798.5375 of this chapter and modifications specified in paragraph (c)(2)(ii)(A)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5375 of this chapter are required.

(i) The requirement under § 798.5375 of this chapter is modified so that MO shall be tested in established cell lines. The cell line or strain used shall be checked for *Mycoplasma* contamination and for karyotype stability.

(ii) The requirement under § 798.5375 of this chapter is modified so that MO shall be dissolved in DMSO prior to treatment of the cells.

(iii) The requirement under § 798.5375 of this chapter is modified so that at least 3 concentrations of the test substance over a range adequate to define the response shall be tested. The highest test concentration tested with and without metabolic activation shall be 5 mg/ml or that dose which shows evidence of cytotoxicity or reduced mitotic activity.

(B)(1) The *in vivo* mammalian bone marrow cytogenetics test: Chromosomal analysis shall be conducted with MO in accordance with § 798.5385 of this chapter and modifications specified in paragraph (c)(2)(ii)(B)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5385 of this chapter are required.

(i) The requirement under § 798.5385 of this chapter is modified so that the mouse is the required species.

(ii) The requirement under § 798.5385 of this chapter is modified so that three dose levels shall be used. The highest dose tested shall be the maximum tolerated dose or that producing some indication of cytotoxicity (e.g., partial inhibition of mitosis), or shall be the highest dose attainable.

(iii) The requirement under § 798.5385 of this chapter shall be modified so that the animals shall be exposed by inhalation for 6 hours/day for 5 consecutive days.

(C)(1) The rodent dominant lethal assay shall be conducted with MO in accordance with § 798.5450 of this chapter and modifications specified in paragraph (c)(2)(ii)(C)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5450 of this chapter are required.

(i) The requirement under § 798.5450 of this chapter is modified so that the mouse is the required species.

(ii) The requirement under § 798.5450 of this chapter is modified so that exposure shall be by inhalation for 5 days for 6 hours/day. Three dose levels shall be used. The highest dose shall produce signs of toxicity (e.g., slightly reduced fertility) or shall be the highest attainable.

(D)(1) The rodent heritable translocation test shall be conducted with MO in accordance with § 798.5460 of this chapter and modifications specified in paragraph (c)(2)(ii)(D)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5460 of this chapter are required.

(i) The requirement under § 798.5460 of this chapter is modified so that the mouse is the required species.

(ii) The requirement under § 798.5460 of this chapter is modified so that at least two dose levels shall be used. The highest dose shall result in toxic effects (which shall not produce an incidence of fatalities which would prevent a meaningful evaluation), or shall be the highest dose attainable.

(iii) The requirement under § 798.5460 of this chapter is modified so that animals shall be exposed by inhalation.

(iii) *Reporting requirements.* (A) The chromosomal aberration tests shall be completed and the final results submitted to the Agency as follows:

(1) The *in vitro* and *in vivo* (if required) tests within 1 year of the effective date of the final test rule.

(2) The dominant lethal assay (if required) within 2 years of the final test rule.

(3) The heritable translocation assay (if required) within 4 years of the final test rule.

(B) Interim progress reports shall be provided quarterly and beginning 90 days after the effective date of the final Phase 2 test rule.

(3) * * *

(ii) *Test standard.* (A)(1) The *Salmonella typhimurium* mammalian microsomal reverse mutation assay (Ames assay) shall be conducted with MO in accordance with § 798.5285 of this chapter and modifications specified in paragraph (c)(3)(ii)(A)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5285 of this chapter are required.

(i) The requirement under § 798.5285 of this chapter is modified so that the direct plate incorporation method shall be used for this study.

(ii) The requirement under § 798.5285 of this chapter is modified so that strain-specific positive controls shall be

included in the assay. The following controls are examples of those which may be used in the assay without metabolic activation: Strain TA 1535, sodium azide; strain TA 100, nitrofurantoin; TA 98, and TA 1537, 4-nitro-*o*-phenylenediamine.

(iii) The requirement under § 798.5265 of this chapter is modified so that test chemical and positive control reference substances shall be dissolved in DMSO and then further diluted in DMSO for use in the assay.

(iv) The requirement under § 798.5265 of this chapter is modified so that MO shall be tested up to 5 mg/plate or to the limits of solubility or toxicity. A suspected positive response not showing a clear-related response shall be confirmed by testing over a narrow range of concentrations.

(B)(1) The detection of gene mutations in somatic cells in culture shall be conducted with MO in accordance with § 798.5300 of this chapter and modifications specified in paragraph (c)(3)(ii)(B)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5300 of this chapter are required.

(i) The requirement under § 798.5300 of this chapter is modified so that MO shall be tested in LK5178K mouse lymphoma cells.

(ii) The requirement under § 798.5300 of this chapter is modified so that MO shall be dissolved in DMSO prior to treatment of the cells. The final concentration of the vehicle shall not interfere with cell viability or growth rate.

(iii) The requirement under § 798.5300 of this chapter is modified so that the metabolic activation system shall be derived from the postmitochondrial fraction (S-9) of livers from rats pretreated with Aroclor 1254.

(iv) The requirement under § 798.5300 of this chapter is modified so that exposure shall be for 4 hours unless a different exposure time is justified by the investigator.

(C)(1) The sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with MO in accordance with § 798.5275 of this chapter and modifications specified in paragraph (c)(3)(ii)(C)(2) of this section.

(2) Test standard modifications. The requirement under § 798.5275 of this chapter is modified so that exposure shall be by exposure to MO vapors.

(D)(1) The mouse visible specific locus test shall be conducted with MO in accordance with § 798.5200 of this chapter and modifications specified in paragraph (c)(3)(ii)(D)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.5200 of this chapter are required.

(i) The requirement under § 798.5200 of this chapter is modified so that mice shall be used as the test species.

(ii) The requirement under § 798.5200 of this chapter is modified so that a minimum of two dose levels shall be tested.

(iii) The requirement under § 798.5200 of this chapter is modified so that animals shall be exposed to the test substance by inhalation. Exposure shall be for 6 hours a day. Duration of exposure shall be dependent upon accumulated total dose desired for each group.

(iii) Reporting requirements. (A) The gene mutation tests shall be completed and final results submitted to the Agency as follows:

(1) The *Salmonella typhimurium* mammalian microsomal reverse mutation assay and the gene mutation in somatic cells assay (if required) within 1 years of the effective date of the final test rule.

(2) The sex-linked recessive-lethal test in *Drosophila melanogaster* (if required) within 2 years of the effective date of the final test rule.

(3) The mouse specific-locus test (if required) within 4 years of the effective date of the final test rule.

(B) Interim progress reports shall be provided quarterly and beginning 90 days after the effective date of the final Phase 2 test rule.

(4) . . .

(ii) Test standard. (A)(1) An oncogenicity bioassay shall be conducted by inhalation with MO in accordance with § 798.3300 of this chapter and modifications specified in paragraph (c)(4)(ii)(A)(2) of this section.

(2) Test standard modifications. The following modifications to § 798.3300 of this chapter are required.

(i) The requirement under § 798.3300 of this chapter is modified so that MO shall be tested in both rats and mice.

(ii) The requirement under § 798.3300 of this chapter is modified so that the animals shall be exposed to MO by the inhalation route for at least 6 hours per day on a 5-day per week basis.

(iii) Reporting requirements. (A) The oncogenicity tests shall be completed and final results submitted to the Agency 53 months after submission of the positive mutagenicity test results set forth in paragraphs (c)(2)(i) and (3)(i) of this section.

(B) Interim progress reports shall be provided quarterly and beginning 90 days after the submission of the study plan for this test.

(Approved by the Office of Management and Budget under control number 2070-0033.)

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