

(i) *Cells*—Type of cells used in the assay. L5178Y mouse lymphoma cells shall be used. Cells shall be checked for *Mycoplasma* contamination.

(ii) *Metabolic activation*. The metabolic activation system shall be derived from the postmitochondrial fraction (S-9) of rat livers pretreated with Aroclor 1254.

(iii) *Test chemical—Vehicle*. *Meta*- and *para*-cresols 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.

(iv) *Test performance—Exposure*. Exposure shall be for 4 hours unless a different exposure time is justified by the investigator.

(C) (1) *Sex-linked recessive lethal test in *Drosophila melanogaster**. This test shall be conducted with *meta*-cresols in accordance with § 798.5275 of this chapter, except for the provisions in § 798.5275(d)(5)(iii). This sex-linked recessive lethal test shall be conducted with *meta*-cresol if it produces a positive result in either one of the assays conducted pursuant to paragraphs (c)(2)(i) (A) and (B) of this section.

(2) For the purposes of this section the following provision also applies: *Route of administration*. The oral route of administration shall be used.

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

(1) The unscheduled DNA synthesis in mammalian cells in culture assay within 12 months of the effective date of the final Phase II test rule.

(2) The detection of gene mutations in somatic cells in culture assay within 12 months of the effective date of the final Phase II test rule.

(3) The sex-linked recessive lethal test in *Drosophila melanogaster*, if required, within 24 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the unscheduled DNA synthesis in mammalian cells in culture assay, gene mutation in mammalian cells in culture assay, and the *Drosophila* sex-linked recessive lethal test at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(3) * * *
(ii) *Test standards*. (A) *Morphologic transformation of mammalian cells in culture*. This test shall be conducted individually with *ortho*-, *meta*-, and *para*-cresols in accordance with § 795.285 of this chapter, except for provisions in § 795.285(d)(4).

(B) For the purposes of this section the following provision also applies:

Metabolic activation. *Meta*- and *para*-cresol shall initially be tested in this assay performed without metabolic activation. Only if they produce negative results in the assay performed without activation will *meta*- and *para*-cresol then be tested in the assay with metabolic activation. *Ortho*-cresol shall only be tested in this assay performed with metabolic activation.

(iii) *Reporting requirements*. (A) The morphologic transformation of mammalian cells in culture assay shall be completed and final results submitted to the Agency within 12 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the morphologic transformation assay at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II test rule.

(4) * * *

(ii) *Test standards*. (A) *Developmental toxicity*. This study shall be conducted individually with *ortho*-, *meta*-, and *para*-cresols in accordance with § 798.4900 of this chapter, except for provisions in § 798.4900(e)(5).

(B) For the purposes of this section the following provision also applies: *Administration of test substance*. The test substance shall be administered by oral gavage.

(iii) *Reporting requirements*. (A) The developmental toxicity study shall be completed and final results submitted to the Agency within 12 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the developmental toxicity study at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II test rule.

(5) * * *

(ii) *Test standards*. (A) *Reproduction and fertility effects*. This study shall be conducted individually with *ortho*-, *meta*-, and *para*-cresols in accordance with § 798.4700 of this chapter, except for provisions in § 798.4700(c)(5)(i)(A).

(B) For the purposes of this section the following provision also applies: *Administration of the test substance—Oral studies*. The test substance shall be administered by oral gavage.

(iii) *Reporting requirements*. (A) The reproduction and fertility effects study shall be completed and final results submitted to the Agency within 29 months of the effective date of the final Phase II test rule.

(B) Progress reports shall be submitted to the Agency for the reproduction and fertility effects study at 6-month intervals, the first of which is due within

6 months of the effective date of the final Phase II rule.

(d) *Effective date*. The effective date of the final Phase II rule for cresols is July 6, 1987.

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40 CFR Part 799

[OFTS-42030D; FRL 3202-2]

Mesityl Oxide; Final Test Standards and Reporting Requirements

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: On December 20, 1985, EPA issued a final Phase I 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). At that time, EPA also proposed 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 time frames. EPA has reviewed public comments on the proposal and has modified the test guidelines and time frames as appropriate. This final rule specifies these TSCA guidelines as the test standards and the reporting requirements for the testing of MO.

DATES: In accordance with 40 CFR 23.5 (50 FR 7271; February 21, 1985), this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern ["daylight" or "standard" as appropriate] time on June 3, 1987. This rule shall become effective on July 8, 1987.

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 (202-554-1404).

SUPPLEMENTARY INFORMATION: On December 20, 1985 EPA issued a final Phase I 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 promulgating a final Phase II rule specifying the test standards and reporting requirements for this testing. This test rule for MO is being promulgated under 40 CFR 799.2500.

I. Background

The Phase I final test rule for MO specifies the following testing requirements: (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 became effective, manufacturers and processors of MO would normally have been 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 decided to propose the relevant TSCA test guidelines as the test standards (50 FR 51888; December 20, 1985). In addition, EPA 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 MO were discussed in the proposed 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 that testing. They were, however, still required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.25.

On March 3, 1986, the Ketones Program Panel (the Panel) of the Chemical Manufacturers Association

(CMA) notified EPA of its intent to conduct the testing required in the Phase I test rule for MO (Ref. 1). The Panel is composed of Exxon Chemical Americas, Eastman Kodak Co., Shell Chemical Co., and Union Carbide Corp. In addition, Aldrich Chemical Co., Inc., a processor, requested an exemption (Ref. 5). EPA is now promulgating a final Phase II rule requiring manufacturers and processors of MO who have not been granted exemptions from the rule to conduct testing in accordance with specified test standards and reporting requirements. These standards and requirements reflect the Agency'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. Test Standards

The Agency proposed that testing of MO be conducted using the following TSCA test guidelines as test standards:

1. *Subchronic exposure*: Inhalation toxicity (40 CFR 798.2450).
2. *Mutagenicity*: Chromosomal effects.
 - i. First tier:
 - a. *In vitro* mammalian cytogenetics (40 CFR 798.5375).
 - b. *In vivo* mammalian bone marrow cytogenetics tests: Chromosomal analysis (40 CFR 798.5385).
 - ii. Second tier: Rodent dominant lethal assay (40 CFR 798.5450).
 - iii. Third tier: Rodent heritable translocation assay (40 CFR 798.5460).
3. *Mutagenicity*: Gene mutations.
 - i. First tier:
 - a. *Salmonella typhimurium* (40 CFR 798.5265).
 - b. Somatic cells in culture (40 CFR 798.5300).
 - ii. Second tier: Sex linked recessive lethal test (40 CFR 798.5275).
 - iii. Third tier: Mouse specific locus test (40 CFR 798.5200).
4. *Chronic Exposure*: Oncogenicity (40 CFR 798.3300).

EPA also proposed that the revisions to these guidelines, which were proposed in the *Federal Register* of January 14, 1986 (51 FR 1522), be adopted in the test standards for MO. In addition, EPA proposed several chemical-specific test standard modifications such as requiring inhalation testing, multiple doses, negative controls, specific strains, cell lines and species, and specific activation systems. For additional information on the proposed test

standards and supporting rationale for modifications, consult the proposed Phase II rule on MO (50 FR 51888; December 20, 1985).

B. Reporting Requirements

The Agency proposed the following specific reporting requirements:

The subchronic toxicity tests be completed and the final results submitted to the Agency within 15 months of the effective date of the final Phase II test rule.

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

First tier gene mutation and chromosomal aberration tests be completed within 1 year of the effective date of the final Phase II test rule.

Second tier gene mutation and second tier chromosomal aberration tests be completed within 2 years of the effective date of the final Phase II test rule.

Third tier gene mutation and chromosomal effects tests be completed within 4 years of the effective date of the final Phase II test rule.

The oncogenicity tests, to be triggered if certain tier I or II mutagenicity tests are positive, be completed and the final results submitted to the Agency within 53 months after submission of positive mutagenicity test results from these tests. In addition, quarterly reports were proposed for all tests.

IV. Response to Public Comments

The Agency received comments from the Panel (Ref. 2). A public meeting was not requested. However, an extension of the comment period was requested (Ref. 4) to allow additional time to comment on the proposed revisions to the test guidelines published in the *Federal Register* of January 14, 1986 (51 FR 1522). The request was granted (51 FR 5376; February 13, 1986). The major issues identified during the comment period for the required and conditional tests are discussed below.

A. Subchronic Toxicity Test

The Panel commented that continuous monitoring of air concentrations of the test material would preclude use of gas chromatography and that the term "continuous monitoring" should be clarified. Elsewhere in this issue of the *Federal Register* the Agency has issued a final rule revising the TSCA test guidelines. In response to public comment on this rule, the subchronic toxicity test standard has been modified to clarify "continuous monitoring" to include intermittent sampling dependent on the method of analysis. EPA acknowledges that when using gas

chromatography the recording capacity will depend on the retention time of the sample in the column. The method of analysis should be described in detail and specified in the study plan.

The Panel also commented that three animal bleedings (preexposure, day 30, and day 90) would overly stress the animals and are of questionable value since a concurrent control is being run. The Agency agrees that hematological and clinical biochemistry determinations in blood performed at the end of the test period (day 90) may be adequate in certain circumstances. However, the Agency does not believe that day 90 determinations are sufficient if a chemical, such as MO, is suspected of having hematological effects which mandate interim determinations. In addition, it is preferable to have baseline values for these determinations on the animals prior to their undergoing testing since normal range values can be highly variable. The Agency believes that for MO additional blood sampling will clarify apparent blood dyscrasia reported in the Ito study (Ref. 3) which raises concern for potential blood effects from chronic exposure to MO. Sampling only at day 90 would not detect age-dependent blood effects in the treatment groups. Furthermore, preexposure data are needed to ensure that there are no differences in blood parameters between test and control groups and to establish baseline data for each group. The bleedings at all three of these times are technically feasible and are far enough apart so as not to overly stress the animals. The Agency, therefore, has specified that these three animal bleedings be conducted on both exposed and control animals.

B. In Vitro and In Vivo Cytogenetics Tests

The Panel recommended that the Agency not specify DMSO as the solvent for the *in vitro* cytogenetics test and to allow scientific judgment on the selection of an appropriate solvent for this testing. The Agency specified DMSO since comparable testing of an analogue, isophorone, successfully utilized DMSO. A different solvent may be used as long as the sponsor demonstrates that the chosen solvent does not affect test results. The final test standard has been modified to reflect this recommendation.

The Panel also recommended that rats rather than mice be used in the *in vivo* cytogenetics test because rats are more commonly used in this test and rat chromosomes allow more accurate information to be obtained. The Agency proposed mice for this test so that correlations could be made between the

lower and upper tier mutagenicity tests. Since correlations between mice and rats have not been established for the *in vivo* cytogenetics and rodent dominant lethal tests, the Agency proposed that mice be used. In addition, mice can successfully be used in this test, and their chromosomes can be equally well evaluated. However, since the Agency has accepted rats as the test species for *in vivo* cytogenetics testing required for other section 4 test rule chemicals and since the Agency has no data to suggest that mice are more sensitive than rats in their response to this test or to MO, mice have not been specified, and the test sponsor may select rats.

The Panel identified scheduling problems for conducting both these tests within 1 year of the effective date of the test rule and requested 3 additional months. Since issuing the proposed Phase II test rule for MO, the Agency has reevaluated the time periods it will specify for conducting these tests. The final reporting requirements have been modified, allowing 15 months to conduct these tests.

C. Dominant Lethal Test

The Panel recommended that the dominant lethal test be conducted in rats rather than mice because evaluation of ovarian corpora lutea is technically easier and more accurate in rats. The Agency proposed mice so that correlations can be made between lower and upper tier mutagenicity tests for MO. In addition, evaluation of ovarian corpora lutea to determine preimplantation loss is discretionary. The guideline states that preimplantation loss can be calculated as the difference between the number of corpora lutea and the number of implants or as a reduction in the average number of implants per female in comparison with control matings. The guideline allows for scientific judgment in selecting which evaluation method is most appropriate. As noted by the Panel, mice have successfully been used for this test, and the Agency has no reason to believe they cannot successfully be used for testing MO. However, since the Agency has accepted rats as the test species for the dominant lethal testing required for other section 4 test rule chemicals and since the Agency has no data that suggest mice are more sensitive than rats in their response to this test or to MO, mice have not been specified as the test species.

The Panel commented that the use of "slightly reduced fertility" at the highest exposure level as a study endpoint is impracticable and urged adoption of an alternative endpoint such as decreased body weight or clinical evidence of

toxicity. Slightly reduced fertility is a recommended endpoint for this test. Other endpoints may be more appropriate for a given testing program. The test standard requires only that the highest dose produce signs of toxicity or is the highest dose attainable. Furthermore, the test standard requires that the dosing regimen, doses tested, and rationale for dosage selection be reported (see § 798.5460(f)(5)(iii)). The Agency has left endpoint selection to the scientific judgment of those conducting the test.

D. Salmonella Reverse Mutation Assay

The Panel recommended that the Agency not specify DMSO as the solvent for this assay. The final standard for this test has been modified to accommodate this recommendation. See the above response to the use of DMSO in the *in vitro* cytogenetics test for the rationale for this change.

E. Detection of Gene Mutations in Somatic Cells in Culture

The Panel recommended the forward gene mutation assay at the HGPRT locus in the Chinese hamster ovary cell culture (CHO test) for testing MO instead of the LK5178 mouse lymphoma assay proposed by EPA. The Panel commented that there was no evidence that isophorone (an MO analogue) demonstrated a mutagenic response in the mouse lymphoma assay and that this assay is subject to an inconsistent response. The Agency believes these two assays will be equally sensitive to MO and, as such, accepts the Panel's recommendation. The final test standard reflects this change.

The Panel also recommended that the Agency not specify DMSO as the solvent for this assay. The final test standard has been modified to accommodate this recommendation. See the above response to the use of DMSO in the *in vitro* cytogenetics test for the Agency's rationale for this change.

F. Sex-Linked Recessive Lethal Test

The Panel commented that the inhalation route for this test was inappropriate because arthropods (*Drosophila*) have totally different circulatory and respiratory systems than man. Such differences, they commented, preclude use of the data in risk assessment. Concern over differences in physiology and morphology between mammalian and nonmammalian species can be raised for any of the routes of administration for this test. The scientific community accepts *Drosophila* as an acceptable test species to detect both point mutations and small

deletions on the X chromosome which when expressed cause death to the carrier. Administration of MO via inhalation will ensure accurate quantification of dose. Furthermore, since it is technically feasible to conduct this test via the inhalation route of exposure, and since inhalation is the primary route of exposure to this chemical, the Agency believes conducting this test via inhalation is most appropriate. Therefore, the Agency does not agree with the Panel's suggested modification to allow an alternative route of exposure to be used.

G. Mouse Visible Specific Locus Test

The Panel commented that it was inappropriate for the Agency to establish standards for routes of administration and reporting requirements for this test. They recommended that the Agency should delete specific requirements for this assay until appropriate testing facilities have been identified, additional experience is gained with conducting this test, and there is consensus on the utility of this test.

EPA believes these concerns are appropriate topics to be discussed during EPA's public program review of all of the available mutagenicity data for MO, as described in the final Phase I test rule. Currently, Oak Ridge National Laboratory (ORNL) may be available for direct contracting of this testing (Ref. 7). A detailed discussion of ORNL's availability is provided in the final test rule for diethylenetriamine (52 FR 3230; February 3, 1987). Other laboratories may be available at the time this testing becomes necessary.

Before the third tier mutagenicity testing is to begin, EPA will hold a public review if the results of the previous tier tests are positive. If, after review of public comment, no change in the test sequence is deemed necessary, EPA will provide formal notification to the test sponsor that the next tier tests must be conducted. If, however, EPA believes additional testing is no longer warranted as a result of the earlier test results, public comment, scientific judgment, and/or other appropriate factors, EPA will issue a proposed amendment to rescind these requirements.

H. Oncogenicity Test

The Panel recommended that the final report be submitted 50 to 56 months

after completion of the subchronic inhalation study. This extension, they stated, would accommodate the possible need for additional pathology and other technical or scheduling problems encountered. Based upon the Agency's experience, 53 months (the proposed reporting requirement) after submission of positive mutagenicity test results is sufficient to conduct both the 90-day subchronic study and the 2-year oncogenicity test in two species; prepare and evaluate slides for pathology; and submit the required reports. In the final Phase I rule a chronic bioassay is required if certain specified short term tests produce a positive result. If this occurs, EPA will notify the test sponsors to initiate the chronic study. Final results must then be submitted to the Agency within 53 months of this notification.

V. Final Phase II Test Rule

A. Test Standards

The subchronic toxicity, first, second, and third tier mutagenicity, and oncogenicity test guidelines and chemical specific modifications proposed for MO (see Unit III.A. of this preamble) shall be the test standards for the testing of MO under 40 CFR 799.2500 with the following exceptions:

The subchronic toxicity test to be conducted in accordance with § 798.2450 clarifies the term "continuous monitoring" and the hematological, and clinical biochemistry determinations are required at preexposure, day 30 and day 90.

The *in vitro* cytogenetics test, *Salmonella* reverse mutation assay, and detection of gene mutations in somatic cells in culture test to be conducted in accordance with §§ 798.5375, 798.5285, and 798.5300 do not specify DMSO as the required solvent.

The *in vivo* cytogenetics test, the dominant lethal test, and rodent heritable translocation test to be conducted in accordance with §§ 798.5385, 798.5450, and 798.5460 do not specify mice as the required test species.

The detection of gene mutations in somatic cells in culture test to be conducted in accordance with § 798.5300 shall be conducted using either the HGPRT locus in the Chinese hamster ovary cell culture test or the proposed LK5178 mouse lymphoma assay.

The guideline revisions finalized

elsewhere in this issue of the Federal Register for tests included in this Phase II rule are adopted in the test standards for the testing of MO. FPA has responded to comments concerning these guideline revisions in the record for that rulemaking (Ref. 8).

The Agency believes that the conduct of the required studies in accordance with these test standards is necessary to assure that the results are reliable and adequate.

B. Reporting Requirements

All data developed under this rule must be reported in accordance with the TSCA Good Laboratory Practice (GLP) Standards (40 CFR Part 792). In addition, test sponsors are required to submit individual study plans at least 45 days prior to the initiation of each study in accordance with 40 CFR 790.50(a).

The Agency 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 the Agency's regulatory experience with the health effects tests required for MO, as well as in response to certain public comments, EPA is adopting the reporting requirements specified in Table 1. Accordingly, results for the required tests must be reported as specified in the proposed rule (see Unit III.B. of this preamble) except: The final reports for the *in vitro* and *in vivo* cytogenetics tests must be submitted within 15 months of the effective date of this Phase II test rule instead of the proposed 12 months. In addition, the upper tier mutagenicity and oncogenicity test data must be submitted within the time specified after notification. Furthermore, subsequent to the issuance of the proposed test rule for MO, the Agency decided that interim reports for the testing required for substances under section 4 of TSCA be submitted at 6-month intervals rather than at 3-month intervals. This reporting frequency will be sufficient to keep FPA informed of the current status of required testing and of any difficulties which the testing facility may encounter during testing. This change also lessens the reporting burden of test sponsors. Accordingly, the final reporting requirements for the testing required for MO reflect a requirement for 6-month, rather than 3-month, interim reports.

TABLE 1.—REPORTING REQUIREMENTS FOR MO

| 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 |
|---|---|--|
| Subchronic toxicity..... | 15 | 2 |
| Salmonella reverse mutation assay..... | 12 | 1 |
| Gene mutation cells in culture assay..... | 12 | 1 |
| Sex-linked recessive lethal test in <i>Drosophila</i> | 25 | 3 |
| Mouse specific locus assay..... | 148 | 7 |
| <i>In vitro</i> cytogenetics test..... | 15 | 2 |
| <i>In vivo</i> cytogenetics test..... | 15 | 2 |
| Dominant lethal test..... | 24 | 3 |
| Heritable translocation assay..... | 124 | 3 |
| Oncogenicity..... | 153 | 8 |

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

² Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following submission of positive mutagenicity test results, the Agency has determined that the required testing must be performed.

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

C. Conditional Exemptions Granted

The final rule for test rule development and exemption procedures (49 FR 39774; October 10, 1984) indicates 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 will be given 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), the Agency must terminate the exemption if any test sponsor has not complied with the test rule.

Since sponsors have indicated to EPA by letter of intent (Ref. 1) their agreement to sponsor all of the tests required for MO in the final Phase I test rule for this substance (50 FR 51857; December 20, 1985) according to the test standards and reporting requirements established in this final Phase II test rule for MO, the Agency is hereby granting conditional exemptions to all exemption applicants for all of the testing required for MO in 40 CFR 799.2500.

D. Judicial Review

The promulgation date for the MO Phase I final rule was established as 1 p.m. eastern standard time on January 6, 1986 (50 FR 51857; December 20, 1985). On March 7, 1986, a petition for review of that Phase I final rule was filed in the United States Court of Appeals for the Fifth Circuit (Ref. 6). Any petition for judicial review on this Phase II final rule will be limited to a review of the test standards and reporting requirements for MO established in this 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 MO (50 FR 51857).

VI. Public Record

EPA has established a record for this rulemaking [docket number (OPTS-42030D)]. This record includes basic information considered by the Agency in developing this final rule and appropriate Federal Register notices.

This record includes the following information:

A. Supporting Documentation

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

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

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

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

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

(e) Notice of final Phase I rule on mesityl oxide (50 FR 51857; December 20, 1985).

(f) Notice of Proposed Phase II rule on mesityl oxide (50 FR 51866; December 20, 1985).

(g) Notice of proposed rule on revision of TSCA test guidelines (51 FR 1522; January 14, 1986).

(h) Notice of final rule on revision of TSCA test guidelines (this issue of the Federal Register).

(i) Notice of extension of comment period for mesityl oxide proposed test standards (51 FR 5376; February 13, 1986).

(j) Notice of final rules on Toxic Substances Control Act test guidelines (50 FR 38252; September 27, 1985).

(k) Notice of final rule on diethylenetriamine (52 FR 2230; February 3, 1987).

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

(3) Communications consisting of:

(a) Written public comments.

(b) Summaries of phone conversations.

B. References

(1) CMA. Chemical Manufacturers Association. Letter of intent to conduct testing of MO from Geraldine Cox. Chemical Manufacturers Association, 2501 M St., NW., Washington, DC 20037, to TSCA Public Information Office, U.S. Environmental Protection Agency, Washington, DC 20460. (March 3, 1985).

(2) CMA. Chemical Manufacturers Association. "Comments of the Ketones Panel of the Chemical Manufacturers Association on EPA's proposed test standards for mesityl oxidé." Chemical Manufacturers Association, 2501 M St., NW., Washington, DC 20037 (February 28, 1986).

(3) Ito, S. "Industrial Toxicological Studies on Mesityl Oxide." (translation from Japanese). Yokohama Igaku 20(b):253-269. (1969).

(4) CMA. Chemical Manufacturers Association. Letter requesting extension of comment period from Geraldine Cox. Chemical Manufacturers Association, 2501 M St., NW., Washington, DC to Don R. Clay, Director, Office of Toxic Substances, Environmental Protection Agency, Washington, DC (January 23, 1986).

(5) Aldrich Chemical Co., Inc. Letter requesting exemption from the test rule for mesityl oxide from Irwin L. Klundt, Ph.D. Vice President, Aldrich Chemical

Company, Inc. P.O. Box 355, Milwaukee, WI. (January 27, 1986).

(6) Shell Chemical Co., Exxon Chemicals Americas, Eastman Kodak Co., Union Carbide Corp. and Chemical Manufacturers Association v. *Environmental Protection Agency*. "Petition for Review" filed with the United States Court of Appeals for the Fifth Circuit. (March 7, 1986).

(7) US EPA. US Environmental Protection Agency. Summary of Meeting with US Department of Energy on availability of Oak Ridge National Laboratory to conduct the mouse visible specific locus assay at Industry's expense for chemicals subject to a TSCA section 4 Test Rule requirement. Environmental Protection Agency, Washington, DC (October 1986).

(8) USEPA. "Response to Public Comments, Proposed Revision of TSCA Test Guidelines as published in 51 FR 1522 (January 14, 1986)". Test Rules Development Branch, Existing Chemicals Assessment Division, Office of Toxic Substances, Environmental Protection Agency, Washington, DC (January 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 Rm. NE-G004, 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 Phase I test rule (30 FR 51857; December 20, 1965).

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 final Phase II 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. No public comments on these requirements were submitted to the Office of Information and Regulatory Affairs of OMB.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals, Recordkeeping and reporting requirements.

Dated: May 8, 1987.

John A Moore,
Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

Therefore, Part 799 is amended as follows:

1. The authority citation 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) (ii) and (iii), (4) (ii) and (iii), and (d) to read as follows:

§ 799.2500 Mesityl oxide (MO).

(c) * * *

(1) * * *

(ii) *Test standard.* Inhalation subchronic toxicity testing shall be conducted with MO in accordance with § 799.2450 of this chapter, except for the provisions of § 799.2450 (d)(1)(i) and (d)(11)(i)(A).

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

(A) *Animal Selection—species and strain.* The rat shall be used. Commonly used laboratory strains should be employed. The tester should provide justification/reasoning for its selection.

(B) *Clinical examinations.* Certain hematological determinations shall be carried out at least three times during the test period: just prior to initiation of dosing (base line data), after approximately 30 days on test, and just prior to terminal sacrifice at the end of the test period. Hematology determinations which shall be appropriate to all studies include the

following: Hematocrit, hemoglobin concentration, erythrocyte count, total and differential leucocyte count, and a measure of clotting potential such as clotting time, prothrombin time, thromboplastin time, or platelet count.

(iv) *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 Phase II test rule.

(B) Progress reports shall be provided every 6 months beginning 6 months after the effective date of the final Phase II test rule.

(2) * * *

(ii) *Test standard.* (A) (1) The *in vitro* mammalian cytogenetics test shall be conducted with MO in accordance with § 798.5375 of this chapter except for the provisions in § 798.5375 (d)(3)(i) and (d)(6)(ii).

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

(i) *Type of cells used in the assay.* 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) *Exposure concentrations.* 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 milligrams per milliliter 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 except for the provisions in § 798.5385(d)(5) (ii) and (iii).

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

(i) *Dose levels.* 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.

(ii) *Route of administration.* 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 except for the provisions in § 798.5450(d)(5) (ii) and (iii).

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

(i) *Dose levels.* Three dose levels shall be used. The highest dose shall produce signs of toxicity (e.g., slightly reduced fertility or body weight) or shall be the highest attainable.

(i) *Route of administration.* Exposure shall be by inhalation for 5 days for 6 hours/day.

(D) (1) The rodent heritable translocation test shall be conducted with MO in accordance with § 798.5460 of this chapter except for the provisions in § 798.5460(d)(5) (ii) and (iii).

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

(i) *Dose levels.* 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.

(ii) *Route of administration.* 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* (conditional) tests within 15 months of the effective date of the final Phase II test rule.

(2) The dominant lethal assay (conditional) within 24 months of the effective date of the final Phase II test rule.

(3) The heritable translocation test (conditional) within 24 months of the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing shall be initiated.

(B) Progress reports shall be submitted to the Agency for the *in vitro* and *in vivo* cytogenetics assays and the dominant lethal assay at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(C) Progress reports shall be submitted to the Agency for the heritable translocation assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing shall be initiated.

(3) * * *

(ii) *Test standards.*—(A) (1) The *Salmonella typhimurium* mammalian microsomal reverse mutation assay (Ames assay) shall be conducted with MO in accordance with § 798.5265 of this chapter except for the provisions in § 798.5265 (d)(5)(ii), (d)(6)(ii) (A) and (B), and (e)(1).

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

(i) *Strain specific positive controls.* 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; strains TA 98 and TA 1537, 4-nitro-*o*-phenylenediamine.

(ii) *Exposure concentrations.* The test should initially be performed over a broad range of concentrations. Among the criteria to be taken into consideration for determining the upper limits of test chemical concentration are cytotoxicity and solubility. Cytotoxicity of the test chemical may be altered in the presence of metabolic activation systems. Toxicity may be evidenced by a reduction in the number of spontaneous revertants, a clearing of the background lawn or by the degree of survival of treated cultures. Relatively insoluble compounds should be tested up to the limits of solubility. For freely soluble nontoxic chemicals, the upper test chemical concentration should be determined on a case by case basis. MO shall be tested up to 5 milligrams per plate or to the limits of solubility or toxicity. A suspected positive response not showing a clear dose-related response shall be confirmed by testing over a narrow range of concentrations.

(iii) *Test performance—Direct plate incorporation method.* The direct plate incorporation method shall be used for this test. For this test without metabolic activation, test chemical and 0.1 milliliter of a fresh bacterial culture should be added to 2.0 milliliter of overlay agar.

(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 except for the provisions in § 798.5300 (d)(3)(i), (4), and (6)(i) and (e)(1).

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

(i) *Types of cells used in the assay.* MO shall be tested at the HCPRT locus in the Chinese hamster ovary cell culture test or in LK5178K mouse lymphoma cells.

(ii) *Metabolic activation.* Cells shall be exposed to MO both in the presence and absence of a metabolic activation system derived from the postmitochondrial fraction (S-9) of livers from rats pretreated with Aroclor 1254.

(iii) *Vehicle.* MO may be prepared in culture media or dissolved or suspended in appropriate vehicles prior to treatment of the cells. The final concentration of the vehicle shall not interfere with cell viability or growth rate.

(iv) *Test performance.* Cells shall be exposed to MO both with and without exogenous activation. 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 except for the provisions in paragraph (d)(5)(iii).

(2) For the purposes of this section the following provisions also apply: *Route of administration.* 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 except for the provisions in § 798.5200(d) (5) (ii) and (iii).

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

(i) *Dose levels.* A minimum of 2 dose levels shall be tested. Exposure shall be for 6 hours a day. Duration of exposure shall be dependent upon accumulated total dose desired for each group.

(ii) *Route of administration.* Animals shall be exposed to MO by inhalation.

(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 (conditional) within 12 months of the effective date of the final Phase II test rule.

(2) The sex-linked recessive-lethal test in *Drosophila melanogaster* (conditional) within 25 months of the effective date of the final Phase II test rule.

(3) The mouse specific-locus test (conditional) within 48 months of the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing shall be initiated.

(B) Progress reports shall be submitted to the Agency for the *Salmonella typhimurium* mammalian reverse mutation microsomal assay, gene mutation in mammalian cells in culture assays, and *Drosophila* sex-linked recessive lethal test at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(C) Progress reports shall be submitted to the Agency for the mouse specific locus assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing shall be initiated.

(4) * * *

(ii) *Test standard.* (A) (1) An oncogenicity bioassay shall be conducted by inhalation with MO in accordance with § 798.3300 of this chapter except for the provisions in § 798.3300(b) (1)(i), (4), and (6).

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

(i) *Species and strain.* MO shall be tested in both rats and mice. Commonly used laboratory strains should be employed. The tester should provide justification/reasoning for their selection.

(ii) *Exposure conditions.* Animals shall be exposed to MO for at least 6 hours per day on a 5-day per week basis over a period of at least 24 months for rats and 18 months for mice.

(iii) *Administration of the test substance.* Animals shall be exposed to MO by the inhalation route.

(B) [Reserved]

(iii) *Reporting requirements.* (A) The oncogenicity tests shall be completed and final results submitted to the Agency 53 months after the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing shall be initiated.

(B) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which is due within 6 months after the date of EPA's notification of the test sponsor that testing shall be initiated.

(d) *Effective date.* The effective date of this final Phase II rule for mesityl oxide is July 6, 1987.

* * * * *

[FR Doc. 87-11126 Filed 5-19-87; 8:45 am]
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