ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42043C; FRL-3273-3]

Testing Requirement; Final Test Standards and Reporting Requirements; 1,2-Dichloropropane

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is issuing a final rule under section 4(a) of the Toxic Substances Control Act (TSCA) that requires manufacturers and processors of 1,2-dichloropropane (DCP; CAS Number 78-87-5) to: (1) Conduct pharmacokinetic (absorption, distribution, metabolism, and excretion) testing with this chemical substance, (2) utilize certain TSCA test guidelines as the test standards for previously and currently required studies for DCP, and (3) submit test data within specified timeframes.

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 October 19, 1987.

This rule shall become effective on November 18, 1987.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Room E-543, 401 M Street SW., Washington, DC 20460, (202-554-1404).

SUPPLEMENTARY INFORMATION: This document promulgates a final single-phase test requirement for pharmacokinetic testing of DCP, and a final Phase II rule specifying the test standards and reporting requirements for the testing required in the September 9, 1986 (51 FR 32079) final Phase I test rule.

I. Background

On September 9, 1986 (51 FR 32079), EPA issued a final Phase I rule under TSCA section 4 that established testing requirements for manufacturers and processors of DCP. This Phase I rule specified the following testing requirements for DCP: (1) Neurotoxicity, (2) mutagenicity (chromosomal aberrations), (3) reproductive effects, (4) developmental toxicity, (5) acute toxicity to marine and freshwater algal and mysid shrimp, and (6) chronic toxicity to mysid shrimp and *Daphnia magna*.

Also on September 9, 1986 (51 FR 32107), EPA proposed applicable TSCA guidelines as test standards. Since TSCA test guidelines were available for all the testing requirements included in the final Phase I rule, they were proposed as the test standards. A 45-day comment period was provided to allow the public, including the manufacturers and processors subject to the Phase I rule, to comment on the use of the TSCA guidelines.

As discussed in the September 9, 1986 proposal, under the two-phase process, persons subject to a final Phase I rule are normally required to submit proposed study plans after the effective date of the Phase I rule. However, because EPA proposed applicable TSCA test guidelines as the test standards for the studies required by the final DCP Phase I rule, persons subject to the rule, i.e., manufacturers and processors of DCP, were exempted from this requirement. Persons subject to the rule, however, were still required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.45. For the DCP Phase I rule, Dow Chemical Company notified EPA of its intent to sponsor all the required testing (Ref. 6). The responsibilities of manufacturers and processors of DCP for testing or requesting exemption from testing responsibilities were discussed in the DCP Phase I final rule (51 FR 32079).

After review of the public comments, EPA is now promulgating a final Phase II rule requiring the manufacturers and processors of DCP to conduct the health and environmental effects studies contained in the final Phase I test rule in

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accordance with the test standards for DCP proposed in 51 FR 32107. Persons who notified EPA of their intent to test must now submit study plans (which adhere to the promulgated test standards) no later than 45 days before the initiation of each required test.

Also proposed in 51 FR 32107 was a single-phase test rule for pharmacokinetic (absorption, distribution, metabolism, and excretion) testing with DCP, including test standards and reporting requirements. After review of public comments, EPA is now promulgating a final single-phase rule requiring the manufacturers and processors of DCP to conduct the pharmacokinetic testing. As stated in Unit IV.D. of this preamble, manufacturers and processors of DCP are now required to submit notices of intent to conduct pharmacokinetic testing or exemption applications in accordance with 40 CFR 790.45.

II. Proposed Rule

A. Proposed Pharmacokinetic Testing

In the September 9, 1986 proposed rule, EPA proposed oral-inhalation comparative pharmacokinetic testing for DCP based on the authority of section 4(a)(1)(B) of TSCA. EPA found that DCP is produced and released to the environment in substantial quantities, and that its manufacture, processing, and use may result in substantial human exposure to this substance. The detailed basis for this finding is found in Unit IV.A. of the final Phase I test rule for DCP (51 FR 32079).

EPA also found that there are insufficient data to reasonably predict and compare the distribution and metabolism of DCP in the body as a result of oral or inhalation exposure due to DCP's manufacture, processing, and use, and that an oral-inhalation comparative pharmacokinetic study of DCP is necessary to develop such data.

B. Proposed Test Standards

In the final Phase I test rule for DCP, the required testing included neurotoxicity, mutagenic effects (chromosomal aberrations), developmental effects, reproductive effects, mysid shrimp acute toxicity, algal acute toxicity, and daphnid and mysid chronic toxicity.

In the September 9, 1986 proposed rule, EPA proposed that: (1) The tests for neurotoxicity, i.e., neuropathology, motor activity, and functional observational battery, be conducted according to 40 CFR 798.6400, 798.6200, and 798.6050, respectively; (2) the dominant lethal assay be conducted according to 40 CFR 798.5450; (3) the developmental toxicity study be conducted according to 40 CFR 798.4900; (4) the reproductive effects test be conducted according to 40 CFR 798.4700; and (5) the oral-inhalation comparative pharmacokinetic test (absorption, distribution, metabolism, and excretion) be conducted according to the guideline proposed in the **Federal Register** of November 6, 1985 (50 FR 46104) as § 798.7475 (codified as § 795.230 in this final rule).

With regard to environmental effects testing, EPA proposed that: (1) The algal acute tests with marine and freshwater algae be conducted according to 40 CFR 797.1050 using systems that control for DCP evaporation; (2) the acute toxicity test with mysid shrimp be conducted according to 40 CFR 797.1930 using flow-through systems and measured concentrations; and (3) the chronic toxicity tests with *Daphnia magna* and mysid shrimp be conducted according to 40 CFR 797.1330 and 797.1950, respectively, using flow-through systems and measured concentrations.

C. Proposed Reporting Requirements

The Agency proposed the following specific reporting requirements:

1. The pharmacokinetic, neurotoxicity, dominant lethal assay, and all environmental effects tests would be completed and the final reports submitted to the Agency within 1 year of the effective date of the final Phase II test rule. A progress report on each study would be provided 6 months after the effective date of the final single-phase test rule or final Phase II test rule, whichever is applicable.

2. The developmental toxicity test would be completed and the final report submitted to the Agency within 18 months of the effective date of the final Phase II test rule. Interim progress reports would be provided every 6 months.

3. The two-generation reproductive effects test would be completed and the final report submitted to the Agency within 29 months of the effective date of the final Phase II test rule. Interim progress reports would be provided every 6 months.

III. Response to Public Comments

In the September 9, 1986 proposed rule, EPA invited comments on the following topics:

1. The proposed testing requirement for an oral-inhalation comparative pharmacokinetic study with DCP.

2. Requiring the oral, rather than inhalation, route of administration in conducting health effects tests with DCP.

3. The proposed use of the TSCA test guidelines as the test standards for the required testing of DCP.

4. The proposed schedule for the required testing.

The Agency received written comments (Ref. 1) from Dow Chemical Company (also referred to in this document as "Dow"). A public meeting was not requested. Dow Incorporated by appendix their previous comments on all of the guidelines proposed as standards for the DCP required testing: (1) Comments submitted on October 12, 1979, and March 11, 1981, when the guidelines were first proposed, and (2) comments submitted on March 20, 1986, in response to revisions of some of the guidelines proposed in the **Federal Register** of January 14, 1986 (51 FR 1522). The revisions have been modified and finalized (52 FR 19056; May 20, 1987) after careful consideration of all industry comments, including those of Dow. The Agency believes that all of the revisions to the test standards required in this document are appropriate as test standards for DCP. The remainder of Dow's comments are discussed below.

A. Pharmacokinetic Testing

1. *General comments.* Dow agrees that pharmacokinetic studies can be useful in hazard evaluation, but only when these studies are designed to answer specific questions posed by data generated from toxicity tests. Dow maintains that pharmacokinetic data that cannot be related to specific aspects of toxicity are difficult to interpret and have little value. Since pharmacokinetic data should answer specific questions related to toxicity, Dow believes that these studies are not suited for standard protocols and should be custom-designed for each chemical substance. Dow further commented that if the Agency mandates the use of standard protocols, these protocols should be highly flexible. This flexibility is needed to allow the use of new approaches and to make appropriate chemical-specific adaptations where necessary.

EPA does not agree with Dow that pharmacokinetic data have little value unless they are related to a specific toxicity question. Some aspects of the pharmacokinetic test, such as absorption kinetics, produce data that will help the regulatory toxicologist perform route-to-route extrapolations. Other aspects, such as tissue distribution, may indicate the need for further toxicity testing as a result of the sequestering of the chemical substance or the detection of high levels in non-target tissues. The Agency agrees with Dow that, at times, these data will be

difficult to interpret, as in the hypothetical case proposed by Dow in which sex-related differences in metabolism are observed but no sex-related differences in toxicity are detected. The Agency does not believe that the potential for generating data that is difficult to interpret is a sound rationale for determining that a given test should not be conducted. In the above example, the results of the pharmacokinetic study would have raised concern about the adequacy of the available data to support an evaluation of potential human risk from exposure.

EPA also believes that standard protocols are advantageous from a regulatory standpoint. The use of standard protocols provides a consistent body of data from which regulatory decisions can be made. Because this data set is consistent, comparisons between chemical substances can be made more easily and the historical results of regulatory decisions on substances that have been determined to be similar can be used to provide confidence in present and future decisionmaking processes.

Moreover, the Agency considers the standard protocols as used by the Agency to be highly flexible. As has occurred with many test rules, the standard protocol may be modified as a result of the chemical-specific needs of testing. This ability to modify a standard protocol provides the flexibility needed to address the special characteristics of a substance, or in the absence of such characteristics, allows the Agency to invoke the standard protocol.

2. *Specific comments.* Dow submitted specific written comments on several aspects of the proposed pharmacokinetic test procedure: Animal selection (required species, weight ranges, animal care, and testing of both sexes); administration of test substance (determinations of high dosage and manner of dosing); determination of bioavailability (time intervals for collection of excreta, measuring the concentration of test substance in expired air, and meaning of the term "saturability"); and observation of animals (time intervals for collection of blood). Comments were also submitted on proposed data analysis and reporting requirements, evaluation of results (use of statistics vs. a kinetic model), and the test report (tissue distribution and biotransformation pathways).

The Agency disagrees with some of the points raised by Dow, and a detailed explanation of the Agency's position may be found in the support document (Ref. 2) prepared for EPA by Syracuse Research Corporation (SRC) and a memorandum written by EPA's Health and Environmental Review Division of the Office of Toxic Substances (Ref. 3). Other Dow comments have resulted in guideline modifications and are described below.

a. Dow objected to the designation of specific weight ranges for the Fischer 344 rats to be used in the proposed pharamacokinetic test. In the proposed test guideline, a range of 125 to 175 grams was specified for males while a range of 110 to 150 grams was specified for females. Dow contends that these ranges are needlessly restrictive and will result in the pointless sacrifice of otherwise useful animals. Dow further maintains that the weight ranges are too low, and that the use of such small animals will hinder blood collection from both a technical consideration in obtaining samples and as a result of the relatively small blood volume. Dow recommends that the reference to specific animal weights either be eliminated from the proposed rule or the acceptable weight ranges be increased to 180 to 250 grams for males and 130 to 160 grams for females.

The Agency objective in specifying animal weights was to obtain data on young adult male and female animals. The ages of animals in each group should be close and the range should be comparable from group to group, even when sex differs. Otherwise, age differences may complicate the interpretation of experimental data (Refs. 4 and 5). Consequently, the specified weight ranges have been deleted from 40 CFR 795.230(c)(1)(ii), and instead it is specified that all animals used in the test must be 7 to 9 weeks old. This requirement will ensure that age differences do not affect test results.

b. Dow contended that the specific environmental conditions proposed for animal maintenace are too restrictive and are not consistent with the guidelines in the *Guide for the Care and Use of Laboratory Animals* (Publication No. (NIH)–7–23, 1978). The guide recommends the use of room temperatures between 18 and 26° C and humidity of 40 to 70 percent. In the proposed test guideline, the temperature and humidity are specified as 25 ± 2° C and 50 ± 10 percent, respectively.

EPA believes the range of temperatures and humidity suggested by Dow for animal care is too great because broader ranges of temperature and humidity create more variables in the study and the greater ranges could stress the animals. The NIH guide is a general guide for care of laboratory animals, and not necessarily a standard for changing the temperature requirement of 25 ± 2° C as proposed in §798.7475(c)(1)(iii) (November 6, 1985; 50 FR 46104) to 24 ± 2° C in §795.230(c)(1)(iii) of this final rule to avoid the use of 27° C a temperature above the range recommended in the guide. The Agency believes that a humidity requirement of 50 ± 10 percent is not unduly restrictive and is unchanged in the final test guideline.

c. Dow maintained that methods are not available to distinguish between concentrations of test substance in the inspired and expired air, and stated that the term "saturability" as used in the proposed test guideline is unclear.

The Agency agrees with this comment and has modified § 795.230(c)(2)(iii)(D) to eliminate the measurement of the concentration of test substance in expired air. The concentration of test substance in inspired air does not need to be "measured," since it is equal to the administered dose level (concentration in the test chamber). The calculation of percentage test substance retention, body burden, and "saturability" has also been deleted, along with the test report requirement for these values.

d. Dow objected to the proposed requirement that all results be subjected to statistical analysis. Dow maintains that statistical analysis requires the generation of hypotheses and that the proposed test rule does not provide guidance as to what hypotheses should be tested. Dow contends that there is little value in identifying statistically significant differences, since these differences are usually meaningless for pharmacokinetic studies. Dow recommends that instead of statistical analysis, the data be described using appropriate kinetic models. In addition, the proposed test guideline requires that all results, both quantitative and incidental, shall be analyzed, and Dow is unclear as to what is meant by "incidental results."

The Agency does not agree that statistical analysis is not useful for pharmacokinetic data. Data are statistically analyzed not only to test hypotheses, but also to provide a measure of the amount of variability associated with reported pharmacokinetic parameters. These parameters, such as Km or Vmax, are usually reported along with a standard error or standard deviation that is calculated using the results from a number of experimental determinations. This statistical analysis is needed to ensure that the study has been conducted in a competent manner and that results presented are not meaningless random values. For this reason, the Agency believes that

statistical analysis of pharmacokinetic data does provide useful and necessary information.

The Agency does agree, however, with Dow that pharmacokinetic and metabolism data should be described by an appropriate kinetic model. These models provide descriptions of pharmacokinetic processes and assist in the prediction of such values as body burden and elimination half-life, which are useful in assessing the hazard associated with exposure to a chemical substance. Pharmacokinetic models, however, should be employed in addition to, and not in place of, the statistical analyses of the data. Therefore, the test report section of the pharmacokinetic guideline in § 795.230(d)(3) is modified to ask for any pharmacokinetic model(s) developed from the experimental data.

With regard to Dow's comment on the meaning of the term "incidental" in § 795.230(d)(2), the phrase "quantitative or incidental" has been deleted to reduce any possible confusion. The section now reads, "All observed results shall be evaluated by an appropriate statistical method."

e. The language of proposed § 795.230(c)(2)(iii)(C), (3)(i)(B), (ii), and (iii) have been modified slightly in this final rule for the purpose of clarification. Collection of excreta from 0 to 24 hours and then from 24 to 48 hours is more accurate than "*at* 24 and 48 hours." EPA believes that terminating collection when 90 percent of the dose has been excreted will yield adequate information, and eliminate the possible situation of collecting for additional days only to account for 1 to 2 percent more of the administered dose.

3. Environmental Effects Testing

Dow raised issues concerning the availability of facilities to perform the proposed testing of DCP with mysid shrimp and algae during the proposed time frames.

With regard to algal toxicity testing, Dow believes that stoppering the test vessel, as recommended when testing volatile chemical substances such as DCP, will result in invalid results because decreased CO_2 levels will limit algal growth. Dow recommends that EPA withdraw the proposed test requirement until suitable methodology is developed. The Agency agrees that algal growth will be limited by the decreased CO_2 level in the test vessel; however, the growth will be limited in both control and treatment test vessels, allowing a comparison to be made. Due to this limitation effect, EPA is withdrawing the proposed requirement of § 797.1050(c)(4)(iv) that algal growth in controls reach the logarithmic growth phase by 96 hours.

Dow also raised concern about the availability of suitable cultures to use in conducting the proposed acute and chronic mysid shrimp toxicity tests. Laboratories that have been conducting mysid testing have experienced upsets in the rearing of mysids or have had difficulty in obtaining suitable cultures for testing, e.g., cultures may suffer excessive (greater than 10 percent) mortality. The upsets may be due to poor viability of the young organisms and may be related to nutrient balance.

While EPA acknowledges that some laboratories have had this problem, the Agency believes that it is not insurmountable with regard to the mysid shrimp testing requirements for DCP. The Agency believes that adequate mysid cultures will be available to conduct the acute and chronic toxicity testing within the time alloted by this test rule (1 year).

IV. Final Test Rule

A. Pharmacokinetics

1. Findings

EPA is basing its oral-inhalation comparative pharmacokinetic testing requirement on the authority of section 4(a)(1)(B) of TSCA. EPA finds that DCP is produced and released to the environment in substantial quantities, and that its manufacture, processing, and use may result in substantial human exposure to this chemical substance. The detailed basis for this finding is found in Unit IV.A. of the final Phase I test rule for DCP (51 FR 32079; September 9, 1986).

EPA also finds that there are insufficient data to reasonably predict and compare the absorption, distribution, metabolism, and excretion of DCP in the body as a result of oral or inhalation exposure due to DCP's manufacture, processing, and use, and that an oral-inhalation comparative pharmacokinetic study of DCP is necessary to develop such data. EPA believes that the data resulting from this testing will be relevant to a determination as to whether the manufacture, processing, and use of DCP does or does not present an unreasonable risk of injury to health.

2. Required Testing

EPA is requiring that an oral-inhalation pharmacokinetic study be conducted with DCP.

3. Other Provisions

Test substance specification, persons required to test (as amended in Unit IV.D. of this document), and enforcement provisions presented in the final Phase I rule for DCP (51 FR 32079) are applicable to the pharmacokinetic testing of DCP.

B. Final Test Standards

The TSCA test guidelines (40 CFR Parts 797 and 798) specified in Unit II.B. for neurotoxicity, mutagenicity (chromosomal aberrations), reproductive effects, developmental toxicity, acute toxicity to marine and freshwater algae and mysid shrimp, chronic toxicity to mysid shrimp and *Daphnia magna*, and oral and inhalation pharmacokinetics, as modified in this rule, shall be the test standards for the testing of DCP required under 40 CFR 799.1550. The Agency believes that the conduct of the required studies in accordance with these test standards is necessary to ensure that the results are reliable and adequate.

C. Final Reporting Requirements

EPA requires that all data developed under this rule be reported in accordance with the TSCA Good Laboratory Practice (GLP) Standards, which appear in 40 CFR Part 792.

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.

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 its experience with health and environmental effects testing, EPA is adopting the proposed schedule for the submission of final test results as the final schedule (see Unit II.C.).

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).

D. Persons Required To Test

EPA does not intend for any persons who manufacture or process DCP solely as an impurity to be subject to the DCP Phase I test rule or this rule for pharmacokinetic testing of DCP. The phrase "other than as an impurity" was inadvertently omitted from § 799.1550(b)(1) in the final Phase I rule (51 FR 32079) and from § 799.1550(b)(5) in the proposed rule for pharmacokinetic testing (51 FR 32107). Therefore, those paragraphs are revised in this final rule to reflect the Agency's intention.

E. 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 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 the testing has not been conducted in accordance with the test rule.

Since a sponsor has indicated to EPA by letter of intent (Ref. 6) its agreement to sponsor all of the tests required for DCP in the final Phase I test rule for this substance (51 FR 32079; September 9, 1986) and EPA has adopted test standards and reporting requirements in this final Phase II test rule for DCP, the Agency is hereby granting conditional exemptions to all exemption applicants for all of the testing required for DCP in 40 CFR 799.1550 by the final Phase I test rule. However, manufacturers and processors who are subject to the testing requirements of this rule must comply with the test rule and exemption procedures in 40 CFR Part 790 with regard to pharmacokinetic testing. Manufacturers (including importers) subject to this rule are required to submit either a letter of intent to perform the pharmacokinetic testing or an exemption application on or before 30 days after the effective date of this final test rule. The required procedures for submitting such letters and applications are described in 40 CFR Part 790. A detailed discussion of persons required to test and procedures to be followed are presented in Unit IV.D. of the final Phase I rule for DCP (51 FR 32079).

F. Judicial Review

The promulgation date for the DCP final Phase I rule was established as 1 p.m. eastern standard time on September 23, 1986. To EPA's knowledge, no petitions for judicial review of that final Phase I rule were filed. Any petition for judicial review of this final rule will be limited to a review of the test standards and reporting requirements for the Phase II rule and to the pharmacokinetic test requirement, standards, and reporting requirements established in this rule.

V. Economic Analysis of Final Rule

To assess the economic impact of this final rule, EPA has prepared an economic evaluation (Ref. 7) that examines the cost of the required testing, both for pharmacokinetic testing alone and in conjunction with testing required in the DCP final rule, and analyzes four market characteristics of DCP: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The economic evaluation for the DCP final test rule, which estimates a testing cost of $144,610 to $191,680 for pharmacokinetic testing, and a total testing cost of $470,230 to $608,350 for both the tests required in the final Phase I rule and the pharmacokinetic testing, indicates that the potential for adverse economic effects due to the estimated cost of testing is low. The annualized total test costs for DCP range from $121,855 to $157,648. This conclusion is based on the following observations (Ref. 7):

1. Propylene oxide (PO), the main product in DCP production, is used mainly as a captive intermediate and has a relatively inelastic demand.
2. The market expectations for PO and many of its derivatives are favorable.
3. Dow manufacturers DCP and PO at two highly integrated plants where minor cost increases can be dispersed over numerous end products.
4. The estimated total unit test costs (i.e., the test costs for DCP and PO) are negligible, or less than 0.02 cent per pound or 0.04 percent of PO price in the upper-bound case.

Refer to the economic analysis (Ref. 7) for a complete discussion of test cost estimation and the potential for economic impact resulting from these costs.

VI. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules and test programs negotiated with industry in place of rulemaking. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing," October, 1981, can be obtained through the National Technical Information Service, 5285 Port Royal Road, Springfield, Va., 22161, under publication number PB 82-140773. On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing required in this final rule.

VII. Rulemaking Record

EPA has established a record for this rulemaking, [docket number OPTS-42043C]. 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

The supporting documents for this rulemaking consist of the **Federal Register** documents containing the proposed and final Phase I and proposed Phase II and single-phase test rules on DCP.

B. References

(1) *Dow.* The Dow Chemical Company. Comments on 1,2-dichloropropane proposed test rule and proposed test standards. 51 FR 32107. Submitted to TSCA Public Information Office (TS-793). Office of Pesticides and Toxic Substances, USEPA. Washington, DC. Document Control Number OPTS-42043. (October 24, 1986)

(2) *Syracuse Research Corporation.* Response to general comments on the oral and inhalation pharmacokinetics tests. Prepared for Test Rules Development Branch, Existing Chemical Assessment Division, Office of Toxic Substances, USEPA. (January 22, 1987)

(3) *USEPA.* U.S. Environmental Protection Agency. Response to TRDB request on review of SRC response to comments on pharmacokinetic guidelines. Intraagency memorandum to Gary E. Timm, Existing Chemical Assessment Division, from the Health and Environmental Review Division. (April 10, 1987)

(4) *Calabrese, E.J. "Toxic Susceptibility: Male/Female Differences."* New York: John Wiley & Sons. (1985)

(5) *Calabrese, E.J. "Age and Susceptibility to Toxic Substances."* New York: John Wiley & Sons. (1986)

(6) *Dow.* The Dow Chemical Company. Letter of intent to conduct testing with 1,2-dichloropropane. Submitted to TSCA Public Information Office (TS-793). Office of Pesticides and Toxic Substances, USEPA. Washington, DC. Control Number OPTS 42043. (November 14, 1986)

(7) *EPA.* Economic Impact Analysis of Final Test Rule for 1,2-Dichloropropane. U.S. Environmental Protection Agency, Washington, DC. (1986)

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

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inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Room NE-G004, 401 M Street SW., Washington, DC.

VIII. 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 DCP is discussed in Unit V of this notice.

This rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (5 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this 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 1,2-dichloropropane.

(2) Small processors are not expected to perform testing themselves, or to participate in the organization of the testing efforts.

(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, and any testing costs passed on to small processors through price increases will be small.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this final rule under the provisions of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*, Pub. L. 96-511, December 11, 1980), and has assigned OMB control number 2070-0033.

List of Subjects in 40 CFR Parts 795 and 799

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

Dated: September 25, 1987.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR Chapter I, is amended as follows:

PART 795—[AMENDED]

1. In Part 795:

a. The authority citation for Part 795 is revised to read as follows:

Authority: 15 U.S.C. 2603.

b. Section 795.230 is added, to read as follows:

§ 795.230 Oral and inhalation pharmacokinetic test.

(a) *Purpose.* The purpose of these studies is to determine:

(1) Bioavailability of test substance after oral and inhalation exposure.

(2) Whether or not the biotransformation of the test substance is qualitatively and quantitatively the same after oral and inhalation exposure.

(3) Whether or not the biotransformation of the test substance is changed qualitatively or quantitatively by repeated dosing.

(b) *Definitions.* Bioavailability refers to the rate and extent to which an administered chemical substance compound is absorbed, i.e., reaches the systemic circulation.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species.* The preferred species is the rat for which extensive data on the toxicity and carcinogenicity of numerous chemical substances are available.

(ii) *Animals.* Adult male and female Fischer 344 rats shall be used. The rats shall be 7 to 9 weeks old. Prior to testing, the animals are selected at random for each group. Animals showing signs of ill health shall not be used.

(iii) *Animal care.* Animals shall be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms shall be maintained at a temperature of 24 ±2 °C and humidity 50 ± 10 percent with a 12-hour light/dark cycle per day. The rats shall be isolated for at least 7 days prior to use, and their health status shall then be evaluated. The animals shall be acclimated to the experimental environment for a minimum of 48 hours prior to treatment. Certified feed and water shall be provided *ad libitum.*

(iv) *Numbers.*—(A) At least 8 animals (4 males and 4 females) shall be used at each dose level.

(B) Females shall be nulliparous and nonpregnant.

(2) *Administration of the test substance*—(i) *Test substance.* The test substance shall be at least 99 percent pure. The studies require the use of both nonradioactive and ^{14}C-labeled test substance. Both preparations are needed to investigate the provisions of paragraph (a)(2) of this section. The use of ^{14}C-test substance is recommended for the provisions in paragraphs (a)(1), (a)(2), and (a)(3) of this section in order to facilitate the work, improve the reliability of quantitative determinations, and increase the probability of observing previously unidentified metabolites.

(ii) *Dosage and treatment*—(A) *Oral study.* At least two doses shall be used in the study, a "low" and "high" dose. When administered orally, the "high" dose should induce some overt toxicity such as weight loss. The "low" dose shall not induce observable effects attributable to the test substance. Oral dosing shall be performed by gavage using an appropriate vehicle.

(B) *Inhalation study.* Three concentrations shall be used in the study. Upon exposure, the two higher concentrations should ideally induce some overt symptoms of toxicity, although the intermediate concentration may be excluded from this condition. The lowest concentration shall not induce observable effects attributable to the test substance.

(iii) *Determination of bioavailability*—(A) *Oral studies.* (*1*) Group A (a minimum of 8 animals, 4 males and 4 females) shall be dosed once *per os* with the low dose of ^{14}C-labeled test substance.

(*2*) Group B (a minimum of 8 animals, 4 males and 4 females) shall be dosed once *per os* with the high dose of ^{14}C-labeled test substance.

(B) *Inhalation studies.* (*1*) Group C (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of non-radioactive test substance in air at the prescribed low test substance concentration.

(*2*) Group D (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of non-radioactive test substance in air at the prescribed intermediate test substance concentration.

(*3*) Group E (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of non-radioactive test substance in air at the prescribed high concentration.

(*4*) Group F (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of ^{14}C-labeled test substance in air at the prescribed low test substance concentration.

(*5*) Group G (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of ^{14}C-labeled test substance in air at the prescribed intermediate test substance concentration.

(*6*) Group H (a minimum of 8 animals, 4 males and 4 females) shall be exposed (6 hours) to a mixture of ^{14}C-labeled test

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substance in air at the prescribed high test substance concentration.

(C) *Collection of excreta.* After oral administration (Groups A and B) and inhalation exposure (Groups F through H) the rats shall be placed in individual metabolic cages and excreta (urine, feces and expired air) shall be collected from 0 to 24 hours and then from 24 to 48 hours post-treatment, or until 90 percent of the dose has been excreted, whichever occurs first.

(D) *Kinetic studies.* Groups C through E shall be used to determine the concentration of the test substance in blood at 0, 5, 10, 15, and 30 minutes, and at 1, 2, 4, 8, 16, 24, and 48 hours after initiation of inhalation exposure.

(E) *Repeated dosing study.* Rats (a minimum of 8 animals, 4 males and 4 females) shall receive a series of single daily oral doses of non-radioactive test substance over a period of at least 7 days, followed at 24 hours after the last dose by a single oral dose of ^{14}C-labeled test substance. Each dose shall be at the low-dose level. Urine shall be collected from 0 to 24 hours and then 24 to 48 hours after administering the ^{14}C-labeled test substance.

(3) *Observation of animals*—(i) *Bioavailability*—(A) *Blood levels.* The levels of total ^{14}C-label shall be determined in whole blood, blood plasma, or blood serum of each rat at 0, 4, 8, 16, 24, and 48 hours after dosing rats in Groups A–B and F–H.

(B) *Expired air, urinary and fecal excretion.* The quantities of total ^{14}C-label eliminated in expired air, urine, and feces by each rat in Groups A and B and F through H shall be determined in collections made from 0 to 24 hours and then 24 to 48 hours after dosing and, if necessary, daily thereafter until at least 90 percent of the dose has been excreted or until 7 days after dosing, whichever occurs first.

(C) *Tissue distribution.* The concentration and quantity of ^{14}C-label in tissue and organs shall be determined at the time of sacrifice for each rat in Groups A and B, F through H, and the repeated-dosing group.

(ii) *Biotransformation after oral and inhalation exposure.* Appropriate qualitative and quantitative methods shall be used to assay urine specimens collected from each rat in groups A and B and F through H. Suitable enzymatic steps should be used to distinguish, characterize, and quantify conjugated and unconjugated metabolites of the test substance.

(iii) *Change(s) in biotransformation.* Appropriate qualitative and quantitative assay methodologies shall be used to compare the composition of ^{14}C-labeled components of urine collected from 0 to 24 and then from 24 to 48 hours after dosing rat Group A with those components in the urine collected over the same intervals after administering the radioactive dose in the repeated dosing study.

(d) *Data and reporting*—(1) *Treatment of results.* Data should be summarized in tabular form.

(2) *Evaluation of results.* All observed results shall be evaluated by an appropriate statistical method.

(3) *Test report.* In addition to the reporting requirements as specified in the EPA Good Laboratory Practice Standards (Subpart J, Part 792 of this chapter) the following specific information should be reported:

(i) Labeling site of the test substance.

(ii) A full description of the sensitivity and precision of all procedures used to produce the data.

(iii) Quantity of isotope, together with percent recovery of the administered dose in feces, urine, expired air, and blood for both routes of administration.

(iv) Quantity and distribution of ^{14}C-test substance in bone, brain, fat, gonads, heart, kidney, liver, lung, muscle, spleen, tissue which displayed pathology, and residual carcass.

(v) Biotransformation pathways and quantities of test substance and its metabolites in urine, feces, and expired air collected after oral administration (single low and high doses) and inhalation exposure (low, intermediate, and high concentrations).

(vi) Biotransformation pathways and quantities of the test substance and its metabolites in urine collected after repeated administration of test substance to rats.

(vii) Pharmacokinetic model(s), if any, developed from the experimental data.

(4) *Counting efficiency.* Data should be made available to the Agency upon request.

PART 799—[AMENDED]

2. In Part 799:

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

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

b. Section 799.1550 is amended by revising paragraph (b)(1) and adding paragraphs (b)(5), (c)(1)(ii) and (iii), (2)(ii) and (iii), (3)(ii) and (iii), (4)(ii) and (iii) and (5), and (d)(1)(ii) and (iii), (2)(ii) and (iii), (3)(ii) and (iii), and (4)(ii) and (iii), and (e) to read as follows:

§ 799.1550 1,2-Dichloropropane.

* * * * *

(b) * * *

(1) All persons who manufacture or process 1,2-dichloropropane, other than as an impurity, from October 23, 1986 to the end of the reimbursement period, shall submit letters of intent to conduct testing or exemption applications, conduct tests, and submit data as specified in paragraphs (c)(1), (c)(2), (c)(3), and (c)(4), and (d) of this section, Subpart A of this Part, and Parts 790 and 792 of this chapter for two-phase rulemaking.

* * * * *

(5) All persons who manufacture or process 1,2-dichloropropane, other than as an impurity, from November 18, 1987 to the end of the reimbursement period, shall submit letters of intent to conduct testing or submit exemption applications, conduct tests, and submit data as specified in paragraph (c)(5) of this section, Subpart A of this part, and Parts 790 and 792 of this chapter for single-phase rulemaking.

(c) * * *

(1) * * *

(ii) *Test standards.* The neurotoxicity testing with 1,2-dichloropropane, consisting of a neuropathology test, a motor activity test, and a functional observational battery, shall be conducted in accordance with §§ 798.6400, 798.6200, and 798.6050 of this chapter, respectively, using the oral route of exposure. The animals shall be dosed with DCP for a minimum of 5 days per week, over a period of at least 90 days.

(iii) *Reporting requirements.* (A) The neurotoxicity tests shall be completed and the final reports submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(2) * * *

(ii) *Test standards.* The dominant lethal assay with 1,2-dichloropropane shall be conducted in accordance with § 798.5450 of this chapter

(iii) *Reporting requirements.* (A) The dominant lethal assay shall be completed and the final report submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(3) * * *

(ii) *Test standard.* The developmental toxicity test with 1,2-dichloropropane shall be conducted in accordance with § 798.4900 of this chapter, using the oral route of exposure.

(iii) *Reporting requirements.* (A) The developmental toxicity test shall be completed and the final report submitted to EPA within 18 months of the effective date of the final Phase II rule.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals, beginning 6 months after the effective date of the final Phase II rule and ending with the submission of the Final Test Report.

(4) * * *

(ii) *Test standard.* The two-generation reproductive effects testing with 1,2-dichloropropane shall be conducted in accordance with § 798.4700 of this chapter, using the oral route of exposure.

(iii) *Reporting requirement* (A) The two-generation reproductive effects test shall be completed and the final report submitted to EPA within 29 months of the effective date of the final Phase II rule.

(B) Interim progress reports shall be submitted to EPA at 6-month intervals, beginning 6 months after the effective date of the final Phase II rule and ending with the submission of the Final Test Report.

(5) *Pharmacokinetic studies*—(i) *Required testing.* An oral and inhalation pharmacokinetic test shall be conducted with 1,2-dichloropropane.

(ii) *Test standard.* The oral and inhalation pharmacokinetic testing with 1,2-dichloropropane shall be conducted in accordance with § 795.230 of this chapter.

(iii) *Reporting requirements.* (A) The pharmacokinetic test shall be completed and the final report submitted to EPA within 1 year of the effective date of the final single-phase pharmacokinetics rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final single-phase rule.

(d) * * *

(1) * * *

(ii) *Test standard.* The mysid shrimp acute toxicity test with 1,2-dichloropropane shall be conducted as a flow-through test with measured concentrations using *Mysidopsis bahia* in accordance with § 797.1930 of this chapter.

(iii) *Reporting requirements.* (A) The mysid acute toxicity test shall be completed and the final report submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(2) * * *

(ii) *Test standard.* (A) The algal acute toxicity tests with 1,2-dichloropropane shall be conducted with marine and freshwater algae using systems that control for 1,2-dichloropropane evaporation in accordance with § 797.1050 of this chapter, except for the provisions in § 797.1050(c)(4)(iv).

(B) For the purpose of this section, the following provisions also apply to the algal acute toxicity tests:

(*1*) *Definitive test.* The test begins when algae from 7 to 10-day-old stock cultures are placed in the test chambers containing test solutions having the appropriate concentrations of the test substance. At the end of 96 hours the algal growth response (number or weight of algal cells/ml) in all test containers and controls should be determined by an indirect (spectrophotometry, electronic cell counters, dry weight, etc.) or a direct (actual microscopic cell count) method. Indirect methods should be calibrated by a direct microscopic count. The percentage inhibition or stimulation of growth for each concentration, EC_{10}, EC_{50}, EC_{90}, and the concentration-response curves are determined from these counts.

(*2*) [Reserved]

(iii) *Reporting requirements.* (A) The algal acute toxicity tests shall be completed and the final report submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(3) * * *

(ii) *Test standard.* The daphnid chronic toxicity test with 1,2-dichloropropane shall be conducted as a flowthrough test using *Daphnia magna* in accordance with § 797.1330 of this chapter.

(iii) *Reporting requirements.* (A) The daphnid chronic toxicity test shall be completed and the final report submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(4) * * *

(ii) *Test standard.* The mysid shrimp chronic toxicity test with 1,2-dichloropropane shall be conducted as a flowthrough test using *Mysidopsis bahia* in accordance with § 797.1950 of this chapter.

(iii) *Reporting requirements.* (A) The mysid chronic toxicity test shall be completed and the final report submitted to EPA within 1 year of the effective date of the final Phase II rule.

(B) An interim progress report shall be submitted to EPA 6 months after the effective date of the final Phase II rule.

(e) *Effective date.* The effective date of the final Phase II rule and the final single-phase pharmacokinetics rule for 1,2-dichloropropane is November 18, 1987.

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