

**ENVIRONMENTAL PROTECTION  
AGENCY**

**40 CFR Parts 795 and 799**

**[OPTS-42065D; FRL 3659-1]**

**Diethylene Glycol Butyl Ether and  
Diethylene Glycol Butyl Ether Acetate;  
Amendments to Pharmacokinetics  
Test Standard and Reporting  
Requirements**

**AGENCY:** Environmental Protection  
Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** EPA is amending the  
pharmacokinetics test standard in 40  
CFR 795.225 by revising the dose  
occlusion requirements for diethylene  
glycol butyl ether (DGBE) and  
diethylene glycol butyl ether acetate

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(DGBA) in the conduct of the study, reducing the dermal exposure time of the test animals to DGBA and DGBE from 96 to 24 hours, and adding a requirement to administer a neat low dose of DGBE to an additional group of animals. EPA is also amending the associated test rule in 40 CFR 799.1560 by modifying the submission of the progress and final pharmacokinetics test reports to EPA. These amendments are in response to the test sponsor's request to amend the rules because of documented difficulties encountered in attempting to perform the pharmacokinetics test.

**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 26, 1989. This amendment to the final rule shall become effective on November 27, 1989.

**FOR FURTHER INFORMATION CONTACT:** Michael M. Stahl, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. EB-44, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

**SUPPLEMENTARY INFORMATION:** EPA is amending the dermal pharmacokinetics test standard and final rule for DGBE and DGBA by reducing the exposure time to the test substance in the pharmacokinetics test and extending the reporting deadlines.

#### I. Background

EPA issued a final rule under TSCA section 4(a)(1)(A) and (B), published in the Federal Register of February 28, 1988 (53 FR 5932), that established health effects testing requirements for DGBE and DGBA. The rule required dermal pharmacokinetics testing in rats to determine the absorption and biotransformation of DGBE administered dermally, and the dermal absorption of DGBA. The test standard, in 40 CFR 795.225(b)(2)(iv)(E), required that rats be dosed once dermally, that the dosed area be occluded with an aluminum patch, and that the dose be kept on the skin for the duration of the study (96 hours). After dosing, the animals were to be placed in metabolism cages for excreta collection for at least 96 hours and, if necessary, daily thereafter until at least 90 percent of the dose had been excreted, or until 7 days after dosing. The final rule required completion of this test and submission of a final report by April 11, 1989, 12 months after the effective date of the final rule, 40 CFR 799.156(c)(4)(ii).

Shortly after initiation of the pharmacokinetics test, the test sponsor, Eastman Kodak, notified EPA via its

representative, the Chemical Manufacturers Association (CMA) of technical difficulties encountered in trying to perform the test as required (Refs. 1 through 3, and 5). Specifically, Eastman Kodak could not prevent leakage from the dosed area by using the required aluminum patch, and a glass cell occlusion device developed by Eastman Kodak to remedy the problem could not be kept on the animals' backs for longer than 24 to 48 hours. Despite several pilot studies to find an occlusion method which could be maintained for 96 hours, none was found (Refs. 2, 4, 6, and 7 through 10). Therefore, on behalf of Eastman Kodak, CMA requested modifications of the pharmacokinetics test requirement which would delete the requirement to use the aluminum patch, reduce the dose occlusion time from 96 hours to 24 hours, and extend the reporting deadline for the pharmacokinetics test to 10 months after EPA notified industry of its decision (Ref. 2). CMA also notified EPA that Eastman Kodak would add an extra group of animals to the study so that the absorption of a neat, low dose of DGBE could be compared with the required absorption study of an aqueous low dose and a neat, high dose of DGBE (Ref. 2).

EPA believed that the requested modifications were reasonable, however, it considered a 10-month extension excessive to complete the test and submit results due to the considerable prior experience of the laboratory in attempting to perform the test.

Therefore, EPA proposed to modify the pharmacokinetics test for DGBA and DGBE and to grant an 8-month extension in the Federal Register of March 31, 1989 (54 FR 13202).

#### II. Public Comments

Comments on the proposed modifications were submitted by CMA (Ref. 11). CMA clarified their intention, stated in a protocol amendment, to apply DGBA neat (undiluted) to the low dose group and not an aqueous solution as EPA thought. EPA agrees that this approach will allow better comparability with the high dose group and stated this in the proposed rule.

CMA also repeated its request to have 10 months to complete the test and submit results because an additional dose group has been added. EPA still believes that even with the additional dose group 8 months is sufficient time because certain study phases can be run concurrently and Eastman Kodak has had considerable experience in attempting to perform this test.

#### III. Modifications

Based on the difficulties encountered and documented by Eastman Kodak in attempting to perform the pharmacokinetics test of DGBE and DGBA as required by the section 4 test rule, EPA is modifying the pharmacokinetics test standard as follows:

Section 795.225(b)(2)(iv)(E) will require that the test substance be kept on the animal for 24 hours instead of 96 hours. After 24 hours, any test material remaining on the skin will be washed off and the containment cell removed. Radiolabeled material in the wash will be accounted for in the total recovery. Urine and feces will be collected at 8, 24, 48, 72, and 96 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.

Under § 795.225(b)(2)(ii)(B), EPA is eliminating the requirement to occlude the dosed area with an aluminum foil patch secured in place with adhesive tape.

To produce better data, CMA has volunteered to test two, low doses of DGBE, one neat and one a 10 percent aqueous solution. EPA, therefore, is modifying § 795.225(b)(2)(ii)(A) accordingly.

#### IV. Extensions

Due to the need to suspend pharmacokinetics testing because of technical problems, EPA is modifying the reporting deadlines under § 799.1560(c)(4)(ii)(A) and (B) to allow 8 months from the effective date of this amendment for the completion of the test and submission of final results. One progress report will be due 6 months after the effective date of the amendment.

#### V. Economic Analysis

The modifications granted in this amendment will not significantly alter the cost of testing. Thus, the economic analysis for the final test rule for DGBE and DGBA is unchanged.

#### VI. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42085D). This record includes information considered by EPA in developing this proposed amendment and appropriate Federal Register notices.

This record includes the following information:

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**A. Supporting Documentation**

(1) Federal Register notices consisting of:

(a) Notice of proposed test rule for DGBE and DGBA (51 FR 27880, August 4, 1986).

(b) Notice of final test rule for DGBE and DGBA (53 FR 5932, February 26, 1988).

(c) Notice of proposed amendments to the pharmacokinetics test standard and reporting requirements (54 FR 13202, March 31, 1989).

(2) Communications consisting of:

(a) Letters.

(b) Contact reports of telephone conversations and meetings.

**B. References**

(1) USEPA. Contact report of phone conversation between Fred DiCarlo, Health and Environmental Review Division, Office of Toxic Substance (OTS), and Dr. Carol Stack, Chemical Manufacturers Assoc. (CMA), Washington, DC (July 25, 1988).

(2) CMA. Letter from Dr. Geraldine Cox, CMA, to the Director, Office of Compliance Monitoring, Office of Pesticides and Toxic Substances, USEPA, (September 8, 1988).

(3) USEPA. Contact report of phone conversation between Catherine Roman, Test Rules Development Branch (TRDB), and Dr. Carol Stack, CMA (August 3, 1988).

(4) USEPA. Contact report of phone conversation between Catherine Roman, TRDB, and Dr. Carol Stack (CMA), (August 29, 1988).

(5) USEPA. Contact report of phone conversation between Catherine Roman, TRDB, and Dr. Carol Stack, CMA, (August 5, 1988).

(6) USEPA. Contact report of meeting between EPA officials and Dr. Carol Stack, CMA, and Dr. Derek Guest, Eastman Kodak, (August 23, 1988).

(7) Notice of final test rule for 2-Ethylhexanoic Acid (51 FR 40318, November 8, 1986).

(8) Southern Research Institute, Birmingham, Alabama 35255-5305. "Absorption and Disposition of 2-mercapto-benzothiazole-Ring-UL-<sup>14</sup>C and 2-Mercapto-benzothiazole Disulfide-Ring-UL-<sup>14</sup>C in Fischer 344 Male and Female Rats and Female Guinea Pigs Dosed Topically." SoRI-86-1200, Report 5973-V, Contract RA-4.0-SRI PHARM. Contracted by CMA, Washington, DC (May 27, 1987).

(9) USEPA. Letter from Richard Troast, TRDB, to Dr. Carol Stack, CMA, (October 19, 1988).

(10) CMA. Letter and attachments from Dr. Carol Stack, CMA, to the Director, Office of Compliance

Monitoring, Office of Pesticides and Toxic Substances, USEPA (November 16, 1988).

(11) CMA. Letter from Dr. Geraldine Cox, CMA, to TSCA Public Docket Office, Office of Toxic Substances, USEPA (May 1, 1989).

**VII. Other Regulatory Requirements****A. Executive Order 12291**

EPA judged that the final test rule was not subject to the requirement of a Regulatory Impact Analysis under Executive Order 12291. EPA has determined that the modifications to the rule do not alter this determination.

This amendment 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 certified that the final test rule would not have a significant impact on a substantial number of small businesses. The modifications to the final rule made in this rule do not change this determination.

**C. Paperwork Reduction Act**

The information collection requirements associated with this rule have been approved by OMB under the provisions of the Paperwork Reduction Act, 44 U.S.C. 3501 et seq. and have been assigned OMB control number 2070-0033.

EPA has determined that this rule does not change existing recordkeeping or reporting requirements nor does it impose any additional recordkeeping or reporting requirements on the public.

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

**List of Subjects in 40 CFR Parts 795 and 799**

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

Dated: September 22, 1989.

Linda F. Fisher,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR chapter I, subchapter R, is amended as follows:

**PART 795—[AMENDED]**

1. In part 795:

a. The authority citation for part 795 continues to read as follows:

Authority: 15 U.S.C. 2603.

b. By revising § 795.225 (b)(2)(ii)(A), (B), and (iv)(E) to read as follows:

§ 795.225 Dermal pharmacokinetics of DGBE and DGBA.

(b) \* \* \*

(2) \* \* \*

(ii) \* \* \*

(A) Two doses of DGBA shall be used in the study, a "low" dose and a "high" dose. Three doses of DGBE shall be used in the study, a neat "low" dose, an aqueous "low" dose, and neat "high" dose. When administered dermally, the "high" dose level should ideally induce some overt toxicity such as weight loss. The "low" dose level should correspond to a no observed effect level.

(B) For dermal treatment, the doses shall be applied in a volume adequate to deliver the prescribed doses. The backs of the rats should be lightly shaved with an electric clipper shortly before treatment. The dose shall be applied with a micropipette on a specific area (for example, 2 cm<sup>2</sup>) on the freshly shaven skin.

(iv) \* \* \*

(E) The high and low doses of <sup>14</sup>C-DGBE and <sup>14</sup>C-DGBA shall be kept on the skin for 24 hours. After application, the animals shall be placed in metabolism cages for excreta collection. After 24 hours, any test material remaining on the skin will be washed off and the containment cell removed. Radiolabeled material in the wash will be accounted for in the total recovery. Urine and feces shall be collected at 8, 24, 48, 72, and 96 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.

**PART 799—[AMENDED]**

2. In part 799:

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

Authority: 15 U.S.C. 2683, 2611, 2625.

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b. By revising § 799.1560 (c)(4)(ii)(A) and (B), and (e) to read as follows:

§ 799.1560 Diethylene glycol butyl ether and diethylene glycol butyl ether acetate.

(c) \* \* \*  
(4) \* \* \*  
(ii) \* \* \*

(A) The pharmacokinetics tests shall be completed and the final reports submitted to EPA within 8 months of the effective date of the final amendment.

(B) A progress report shall be submitted to EPA 6 months from the effective date of the final amendment.

(e) *Effective dates.* (1) 40 CFR 799.1560 is effective on April 11, 1988, except for the provisions of paragraphs (c)(4)(ii)(A) and (B) which are effective on November 27, 1989.

(2) The guidelines and other test methods cited in this section are referenced as they exist on April 11, 1988, except that § 795.225 of this chapter, originally effective April 11, 1988, is referenced to include amendments to paragraph (b)(2)(ii)(A) and (B) and (iv)(E) of that section, effective as they exist on November 27, 1989.

[FR Doc. 89-24036 Filed 10-11-89; 8:45 am]

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