

debated in the legislature before the option for a full I/M program in Nashua and surrounding towns was selected.

3. Air Quality and Emission Data Bases

A special monitoring study in 1978 and 1979 uncovered the nonattainment program in Nashua. The current continuous monitoring site has been operating since 1981 and satisfies EPA's monitoring criteria. The site is located near one of the most congested intersections in Nashua, and is representative of the worst air quality in the area. The input data for the modeling analyses represent a typical weekday during the worst CO season. The assumptions for meteorological conditions and background concentrations are consistent with EPA guidance. The State's original technical analyses for the attainment plan were performed using the MOBILE2 emissions model. At New Hampshire's request, EPA conducted an additional analysis of the proposed control strategy using the MOBILE3 model. That analysis also demonstrated attainment.

4. Modeling/Attainment Demonstration

New Hampshire conducted a two phased, site specific air quality modeling analysis to assess Nashua's CO attainment problems. A preliminary analysis of all signalized intersections in Nashua, using EPA's "Carbon Monoxide Hot Spot Guidelines," indicated that 46 intersections had the potential for CO violations. Next, New Hampshire conducted a detailed modeling study, using CALINE3 and MOBILE2, of the ten worst intersections for 1987. Excess emissions from queuing vehicles were accounted for using procedures approved by EPA. From this analysis, it was evident that Nashua could not meet the 1985 attainment date. For the 1990 attainment analysis, the three intersections with the highest predicted 1985 CO levels were modeled with CALINE3. This analysis demonstrated that the implementation of New Hampshire's SIP would result in Nashua attaining the NAAQS for CO by 1990.

Proposed Action

EPA is proposing to approve the New Hampshire Carbon Monoxide State Implementation Plan revisions for the City of Nashua that were submitted on September 12, 1985, with the understanding that the state will submit the required I/M rules and regulations by September 30, 1986. Upon receipt of the rules, EPA will publish a supplementary notice of proposed rulemaking for public comment. It is anticipated that the proposals will be

consolidated into a single final rulemaking action.

Under 5 U.S.C. 605(b), I certify that this SIP revision will not have a significant economic impact on a substantial number of small entities (See 46 FR 8709).

The Office of Management and Budget has exempted this rule from the requirements of section 3 of Executive Order 12291.

List of Subjects in 40 CFR Part 52

Air pollution control, Carbon monoxide.

Authority: 42 U.S.C. 7401-7642.

Dated: February 14, 1986.

Paul Keough,

Acting Regional Administrator, Region I.

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42085; FRL-3058-8]

Diethylene Glycol Butyl Ether and Diethylene Glycol Butyl Ether Acetate; Proposed Test rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Rule.

SUMMARY: The EPA, under section 4 of the Toxic Substances Control Act (TSCA), is proposing that manufacturers and processors of diethylene glycol butyl ether (DGBE), CAS No. 112-34-5, and manufacturers and processors of diethylene glycol butyl ether acetate (DGBA), CAS No. 124-17-4, (also known as 2-(2-butoxyethoxy)ethylacetate), be required to perform health effects testing of DGBE for subchronic toxicity with particular emphasis on reproductive, hematological, liver and kidney effects; neurotoxicity/ behavioral effects; developmental neurotoxicity; pharmacokinetics; mutagenicity; and oncogenicity. EPA is also proposing dermal absorption testing of DGBA.

This proposed rule follows an Advance Notice of Proposed Rulemaking (ANPR) for DGBA and DGBE, which EPA issued on November 19, 1984 (49 FR 45606).

DATES: Submit written comments on or before October 3, 1986. If persons request an opportunity to submit oral comment by September 18, 1986, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting see Unit IX of this preamble.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42085), in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. NE-G004, 401 M St., SW., Washington, DC 20460.

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

FOR FURTHER INFORMATION CONTACT:

Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460, Toll free: (800-424-9065).

In Washington, DC: (554-1404).

Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: EPA is issuing a proposed test rule under section 4(a) of TSCA to test diethylene glycol butyl ether for health effects and diethylene glycol butyl ether acetate for dermal absorption.

I. Introduction

A. ITC Recommendation

TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.*) established the ITC under section 4(e) to recommend to EPA a list of chemicals to be considered for testing under section 4(a) of the Act.

The ITC designated DGBA (CAS No. 124-17-4) for priority consideration in its 13th Report submitted to EPA on November 8, 1983, and published in the *Federal Register* on December 14, 1983 (49 FR 55674). The ITC recommended that DGBA be considered for health effects testing, including subchronic toxicity, reproductive effects and toxicokinetics.

The bases for these recommendations were as follows: a subchronic toxicity study in another species was recommended to investigate renal effects due to the renal tubular degenerative damage observed in rabbits in a 90-day dermal study at 2,000 to 3,000 mg/kg/day (Ref. 1); a reproductive effects study was recommended due to the possible testicular effects of a probable alkyloxy acetic acid metabolite (Ref. 2) by analogy to a similar metabolite of ethylene glycol butyl ether (EGBE) which produced a slight testicular effect in mice (Ref. 3); and a toxicokinetics study including biochemical disposition was recommended because DGBA may

be absorbed through the skin, the first product of its hydrolysis would probably be a glycol ether, and both worker and consumer exposures are involved.

B. Test Rule Development Under TSCA

Under section 4(a) of TSCA, EPA shall by rule require testing of a chemical substance or mixture to develop appropriate test data if the Agency finds that:

(1)(A) (i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,

(ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture,

(ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight-of-evidence approach in making a section 4(a)(1)(A)(i) finding; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the finding under section 4(a)(1)(B)(i), EPA considers only production, exposure, and release information to determine whether there is or may be substantial production and significant or substantial human exposure or substantial release to the environment. For the findings under sections 4(a)(1)(A)(ii) and (B)(ii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to, or environmental release of, the chemical. In making the finding under section 4(a)(1)(A)(iii) or (B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's process for determining when these findings apply is described in detail in EPA's first and second proposed test rules as published in the Federal Register of July 18, 1980 (45 FR 48524) and June 5, 1981 (46 FR 30300). The section 4(a)(1)(A) findings are discussed at 45 FR 48524 and 46 FR 30300, and the section 4(a)(1)(B) findings are discussed at 46 FR 30300.

In evaluating the ITC's testing recommendations for DGBA, EPA considered all available relevant information including the following: Information presented in the ITC's report recommending testing consideration; production volume, use, exposure, and release information reported by manufacturers of DGBA under the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 716) for DGBA; and published and unpublished data available to the Agency. Based on its evaluation, EPA responded to the ITC designation by publishing in the Federal Register on November 19, 1984 (49 FR 45606), an advance notice of proposed rulemaking (ANPR) for DGBA under section 4(a) of TSCA. This ANPR also informed the public that EPA was expanding the scope of its rulemaking to include DGBE. The ANPR presented a preliminary section 4(a)(1)(B) finding based upon the potential for substantial inhalation exposure to DGBA and DGBE due to their use in latex paint and the potential for dermal absorption of DGBE due to its use in numerous products which involve dermal exposure; presented a preliminary section 4(a)(1)(A) finding for hematological effects based on the ability of the structural analog EGBE to cause erythrocyte fragility with a no-observed-effect level (NOEL) close to the level estimated for consumer exposure to DGBA and DGBE from the use of latex paint (Ref. 23); defined the testing EPA was considering proposing for both chemicals; and sought public comment on EPA's plan to propose a test rule for these chemicals. The testing EPA was considering for DGBA and DGBE included a 90-day subchronic oral study with a complete histopathology of reproductive organs. Effects observed in these organs would trigger a requirement for full reproductive effects testing. Neurotoxicity and behavioral toxicity testing would also be performed on the test animals. As part of the 90-day subchronic study, a satellite group was being considered to evaluate hematological effects. Hematological testing would consist of serial sacrifices

with blood counts, measurements of blood chemistry, and bone marrow studies over the first 2 weeks of dosing. This schedule was being considered because of the transitory blood effects reported for EGBE (Ref. 19). Developmental effects testing by the oral route was being considered in addition to a tiered mutagenicity test sequence. Positive findings in certain mutagenicity tests consistent with testing policy would lead to further mutagenicity testing and, in some cases, to carcinogenicity testing. EPA was also considering requiring comparative pharmacokinetics for the inhalation and oral routes of exposure to allow an evaluation of the effect of the route of exposure upon the effects of DGBA and DGBE. The Agency also requested comments and information on the effect of the route of administration on the toxicology of these chemicals.

In the ANPR, EPA also announced it was considering testing of only DGBE if DGBA could be shown to rapidly metabolize to DGBE and requested comments on this.

The ANPR also sought comments on the need for neurotoxicity testing since DGBE was reported to cause narcosis at doses near its LD₅₀ (Refs. 5 and 31), and another glycol ether had been reported to cause neuropathy in workers (Ref. 14), but DGBE and DGBA have not been reported to cause neurotoxic effects when tested at lower doses for longer periods of time (Refs. 1 and 34).

In response to the ANPR, comments and studies were received from: Eastman Kodak Company, the Procter and Gamble Company, the Dow Chemical Company, and the Chemical Manufacturers Association (CMA). Based on its evaluation of this information as described in this proposed rule, EPA is proposing health effects testing requirements for DGBE and dermal absorption testing of DGBA under section 4(a)(1)(A) and (B) of TSCA.

C. ANPR Comments

1. *Exposure.* The Dow Chemical Company (Ref. 61) and the Chemical Manufacturers Association (CMA) (Ref. 60) commented that there was not substantial exposure to DGBA and DGBE during manufacturing. This was EPA's conclusion in the ANPR, but now the Agency considers that dermal absorption during manufacturing and processing may be substantial. (See Unit II.D.)

CMA (Ref. 60) and Eastman Kodak (Ref. 59) commented that exposure to DGBA from the use of latex paint would present no unreasonable risk based on a

painting study conducted by Kodak in which the airborne concentration of DGBA was measured (Ref. 16). The study estimated that a painter would receive a dose of 5.6 micrograms per kilogram ($\mu\text{g}/\text{kg}$) from inhalation exposure to DGBA while applying latex paint for 1.3 hours. EPA considers this estimate to be low since the peak concentration of DGBA occurs 2 to 6 hours after application (Ref. 16). This study also predicted the painter's dose of DGBA to be 49.9 $\mu\text{g}/\text{kg}$ for 6.3 hours of exposure based on area samples during the 5-hour period after paint application and the personnel samples on the painter during the 1.3 hours of paint application (Ref. 16). EPA also considers this exposure estimate for 6.3 hours to be low since it was based on DGBA concentrations evolved from only 1.3 hours rather than 6.3 hours of painting; also, area samples gave consistently lower values when compared to personnel samples taken during the same time period (i.e., the 1.3 hours of paint application), despite a ventilation arrangement which caused a downward air flow away from the painter's breathing zone; also, the paint used contained 1 percent DGBA rather than the maximum of 3 percent. EPA does not agree with Eastman Kodak's low estimate of potential exposure and is making a section 4(a)(1)(B) finding based on significant exposure to DGBA in latex paint.

CMA (Ref. 60), Eastman Kodak (Ref. 59), and Procter and Gamble (Ref. 18) commented that dermal absorption and inhalation exposure to DGBE from the use of water-based cleaning products would be very low, based on the low vapor pressure of DGBE and the rate of dermal absorption of 0.035 $\text{mg}/\text{cm}^2/\text{hr}$ measured by Procter and Gamble (Ref. 18). Procter and Gamble estimated consumer exposure to DGBE to be 0.06 mg/kg from the use of a hard surface cleaner by measuring inhalation exposure and estimating dermal absorption during 3 minutes using the full strength cleaner and 9 minutes using a diluted cleaner (Ref. 18). EPA considered Procter and Gamble's exposure estimate somewhat low because the total cleaning time was only 12 minutes and no consideration was given to cases where the film of detergent and water would be allowed to dry on the skin, thereby increasing the dermal dose. EPA is using exposure to DGBE in cleaning and other consumer products, in addition to exposure to DGBA in latex paint, as the basis for the section 4(a)(1)(B) finding.

2. *Hematologic effects of EGBE.* The ANPR made a preliminary section

4(a)(1)(A) finding for hematologic effects by analogy to EGBE which caused erythrocyte fragility in rats. CMA submitted a review which assessed the hematologic toxicity of EGBE and concluded that rats are the most susceptible species to erythrocyte fragility caused by EGBE and that this effect should not be extrapolated to humans (Ref. 42). Dow also submitted a study which showed that EGBE, but not DGBE, caused erythrocyte fragility in rats (Ref. 41). (See Unit II.G.4.)

EPA is no longer basing a section 4(a)(1)(A) finding on analogy to EGBE's ability to cause erythrocyte fragility, but rather on the reduced blood cell counts due to DGBE reported in two studies (Refs. 38 and 39). (See Unit II.G.3.)

3. *Testing of DGBE only.* Eastman Kodak submitted a study which demonstrated that DGBA rapidly hydrolyzed to DGBE (Ref. 29) and commented that test data on DGBE was therefore sufficient to evaluate the toxicity of DGBA (Ref. 59).

EPA accepts the Kodak study and believes it adequately demonstrates the rapid hydrolysis of DGBA to DGBE and that the testing of DGBE alone for health effects will be sufficient.

4. *Test program—a. Subchronic toxicity.* CMA, the Dow Chemical Company, and Eastman Kodak commented that sufficient subchronic toxicity testing has been done to characterize the effects of DGBE (Refs. 59, 60, and 61). They commented that three studies in particular (Refs. 36, 37, and 38) adequately demonstrated the subchronic effects of DGBE. EPA reviewed these studies and found them inadequate to fully assess the potential subchronic toxicity of DGBE. (See Unit II.G.3.)

b. *Oral Testing.* CMA commented that oral testing of DGBE was unwarranted in light of the absence of human oral exposures (Ref. 60). EPA originally chose oral testing because it felt inhalation testing would be difficult, but now that dermal absorption appears to be an equally important route of exposure, EPA is proposing testing by the dermal route, except where specific test guidelines require oral administration.

c. *Oral vs. inhalation pharmacokinetics.* CMA commented that oral vs. inhalation pharmacokinetics testing is unwarranted in light of the absence of human oral exposure and minimal human inhalation exposure (Ref. 60).

EPA is now proposing oral vs. dermal pharmacokinetics because testing will be done by these routes of administration and dermal absorption is

an important route of exposure. EPA does not agree that human inhalation exposure is minimal (See Unit II.D.), but is not asking for inhalation pharmacokinetics because of anticipated difficulties in performing this test.

d. *Reproductive and developmental effects.* CMA (Ref. 60), the Dow Chemical Co. (Ref. 61), and Eastman Kodak (Ref. 59) commented that two reproductive effects studies of DGBE in rats and mice (Refs. 45 and 51) and a dermal teratology study of DGBE in rabbits (Ref. 46) as well as other studies on the glycol ether analog, EGBE, (Refs. 44, 53, and 54) adequately demonstrate that DGBE and DGBA are unlikely to produce human reproductive or developmental toxicity. EPA reviewed these studies and found them inadequate to fully assess or predict the potential reproductive effects of DGBE, but adequate to predict the developmental effects of DGBE. (See Units II.G.7 and 8.)

e. *Mutagenicity.* CMA (Ref. 60) commented that the mutagenic potential of DGBE had been extensively reviewed by Thompson (Ref. 47) in a tiered test sequence similar to that proposed by EPA. EPA agrees that all the necessary tests in the gene mutation test sequence have been done with only one positive result. Such a positive result is normally a trigger for oncogenicity testing. However, EPA is proposing a repeat of this test in another cell line to further assess the need for oncogenicity testing because the weight-of-evidence indicates a low potential for DGBE to be oncogenic.

However, the complete mutagenicity test sequence for chromosomal aberrations was not done and EPA considers this necessary to fully assess the potential of DGBE to cause chromosomal effects (See Unit II.G.6) and also to further assess the need of oncogenicity testing.

5. *Neurotoxicity.* CMA commented that the report of narcosis at DGBE doses near the acute LD_{50} is similar to findings at high doses of many other organic solvents and provides no suggestion of neurotoxicity at lower doses (Ref. 60). EPA agrees that effects near the LD_{50} should not raise undue concern for neurotoxicity, but studies by Krotov (Ref. 39) and the Bushy Run Research Center (Ref. 44) showed effects on the nervous system in rats at much lower dose levels. (See Unit II.G.4.) Therefore, EPA has proposed neurotoxicity testing of DGBE. (See Unit IV.A.)

6. *Effect of route of administration.* Since the ANPR called for oral testing,

but exposure is by inhalation and dermal absorption, EPA asked for comments on the effect of the route of administration on the toxicity of DGBA and DGBE. EPA did not receive any comments on this subject; but is now proposing testing by the oral and dermal routes.

II. Review of Available Data

A. Profile

DGBA and DGBE are colorless, relatively nonpolar liquids with faint, sweet odors. A summary of the physical and chemical properties of DGBA and DGBE is presented in the following Table 1:

TABLE 1.—PHYSICAL AND CHEMICAL PROPERTIES OF DGBA AND DGBE¹

Property	DGBA	DGBE
Density (g/ml).....	0.981	0.948
Molecular weight (g/mole).....	204.3	162.3
Freezing point (°C).....	-32	-68.0
Boiling point (°C).....	246.8	230.4
Vapor pressure at 25 °C (mm Hg).....	< 0.01	0.043
Flash point open cup (°C).....	240.0	200.6
Solubility in water (g/l) ²	65.0	(³)
Log K _{ow} ²	1.9	1.0
K _{ow} (estimated) ²	257.0	83.0

¹(Ref. 5).

²(Ref. 6).

³Miscible. The chemicals are excellent solvents and cosolvents for high molecular weight resins (Ref. 4). DGBA and DGBE have low vapor pressures and are soluble in water.

B. Production

DGBE is manufactured by reacting *n*-butyl alcohol with ethylene oxide. DGBA is manufactured by reacting DGBE with acetic anhydride. Due to the pressure requirements of the reactions, the chemicals are produced in closed systems with all waste streams recycled (Ref. 6).

DGBE is produced by six companies, two of which also make DGBA. The annual production of DGBA and DGBE is 4.8 and 66.5 million pounds per year (Ref. 62).

C. Use

DGBE and DGBA are found in a number of industrial and consumer products. Forty percent of the latex paint consumed in the U.S. contains DGBE or DGBA as coalescing agents at concentrations of 0.5 to 3 percent by weight (Refs. 10, 11, 12, and 63). Coalescing agents are compounds added to latex paints to act as plasticizers for the latex polymer. Plasticizers soften the colloidal latex particles and allow them to merge and form a uniform film upon drying. Coalescing agents slowly volatilize from paint over several days following application (Ref. 11).

DGBE and DGBA are also used in inks and industrial coatings as solvents and carriers. Unlike the lower molecular weight glycol ethers which rapidly evaporate, DGBE and DGBA evaporate more slowly (Ref. 7). Inks and coatings containing DGBE and DGBA are usually oven dried (Refs. 6 and 9). DGBE and DGBA also serve as solvents in the electronics industry (Ref. 13).

In addition, DGBE is used as a diluent in brake fluids, and as a component of cutting oils (Ref. 7), and in a number of consumer and industrial products including hard surface cleaners, metal cleaners, paint removers, stamp pad inks, floor cleaners, floor wax strippers, floor finishes, spray cleaners, penetrating oils, and foam fire extinguishers (Ref. 14).

D. Exposure and Release

Based on available data, EPA believes that the highest exposure to DGBA and DGBE occurs from the consumer and occupational use of latex paints. The use of latex paint is widespread, and the exposed population would include most professional painters and a large percentage of the U.S. consumer population. EPA estimates that 4,500 occupational painters and 15 to 20 million consumers are exposed to latex paint containing DGBA or DGBE each year (Refs. 63 and 25).

DGBA and DGBE act as coalescing agents in latex paint and are slowly released from the painted wall to the air over several days following application. Although DGBA and DGBE have low vapor pressures, releases of the glycol ethers from the large surface areas of painted walls are estimated to result in concentrations of 1 to 5 parts per million (ppm) in consumer homes. Consumers exposed to these levels are estimated to receive doses of 1 to 10 milligrams per kilogram body weight per day (mg/kg/day). While consumers would be exposed to these levels for only a few days per year, painters would be exposed each workday (Ref. 15).

The dosage from dermal exposure to DGBE and DGBA in latex paint is believed to be much less than that by inhalation. While painters and consumers may have significant dermal contact with latex paint, dermal absorption of DGBE and DGBA from paint is expected to be minimal during the first two hours that paint is on the skin. Both compounds are reported to partition into the latex polymer particles from the solvent portion of latex paints where they are relatively unavailable for dermal absorption (Ref. 11). However, according to the Eastman Kodak study (Ref. 16) discussed in Unit I.C.1, DGBA is slowly evaporated from

paint, with the peak airborne concentration appearing 2 to 6 hours after application. It appears possible, therefore, for DGBA to be absorbed from paint if allowed to remain on the skin for a period longer than 2 hours.

Exposure to DGBE is expected from its use in a wide variety of commercial and consumer products which involve skin contact, such as cleaners, paint removers, floor products, brake fluid, cutting oils, and penetrating oils. From its use in cleaners alone, EPA estimates that 20 to 41 million consumers and 40,000 janitors could be exposed to DGBE (Refs. 25 and 63). *In vitro* dermal absorption studies have shown DGBE to be readily absorbed through human skin at a mean steady rate of 35 micrograms per square centimeter per hour (ug/cm²hr) with an equivalent rate expected for the acetate (Ref. 17). An *in vitro* dermal absorption study by Procter and Gamble also showed that the rate of absorption in human skin increases with the duration of exposure: at the end of 1 hour, DGBE in a 50 percent dilution of a cleaning product (4 percent DGBE) is absorbed at the rate of 17 ug/cm²/hr, but at the end of 6 hours it is absorbed at the rate of 66 ug/cm²/hr (Ref. 18). This result implies that increased exposure time results in a greater than linear increase in dose by dermal absorption.

Using airborne concentrations and dermal absorption rates over time determined by the Procter and Gamble study (Ref. 18), EPA estimated the dose of DGBE a consumer would receive from the use of a cleaning product for 12 minutes and from a full 8 hours use of a cleaning product. If a cleaning product containing 4 percent DGBE were used full strength for 3 minutes and at a diluted concentration for 9 minutes, the consumer's exposure would total 0.55 mg/kg/day if the consumer allowed the films of diluted and full strength cleaner to dry on his hands. By not rinsing the films off immediately, additional dermal absorption is permitted to occur, thereby increasing the total dose (Ref. 20). If a consumer were to use the cleaning solution for 8 hours, which may be the case for a janitor, the following exposure estimates were made: After using the diluted cleaning product for 8 hours and allowing the residual film to dry on his hands, a janitor's dose of DGBE could be as high as 0.22 mg/kg/day. After using the cleaning product full strength on a dampened sponge (50 percent dilution) for 8 hours and allowing the residual film to dry on his hands, the janitor's dose of DGBE could be as high as 8.0 mg/kg/day (Ref. 21).

Inhalation exposure during manufacture is expected to be low since chemical production occurs only in enclosed processes. Dow submitted three monitoring studies which looked at employee exposure to DGBE during production, truck loading and rail car hook-up. Exposure was evaluated by determining 8-hour time-weighted average concentrations; none exceeded the detection limit of 0.2 ppm, which Dow considered acceptable when compared to its standard for DGBE of 35 ppm (Refs. 22, 23, and 24). Inhalation exposure during processing is also expected to be low since DGBA and DGBE have low vapor pressures and are used in low concentrations in various products (Ref. 6). There could be opportunities for dermal exposure, however, in manufacturing and processing during such operations as repair of equipment, sampling the process stream, cleaning equipment, changing filters, spill cleanup, and handling, transfer, and packaging of products.

Environmental releases of DGBA and DGBE during production and processing are expected to be small, since both are synthesized in closed reactor systems and only small amounts are expected to be released during loading into shipping containers. Although DGBA and DGBE are released to the atmosphere through the venting of storage tanks, this release is expected to be negligible. Eastman Kodak reports negligible release of DGBA from its plants to air and virtually no release to water or landfill (Refs. 6 and 8).

In their use in paints and inks, DGBA and DGBE will be released to the atmosphere. In products such as cutting oils and brake fluids, release to the environment could occur by disposal in wastewater. In all cases the level of release is expected to be low and widely dispersed (Ref. 6). No monitoring data were found reporting atmospheric or water concentrations of DGBA or DGBE released to the environment during use (Ref. 6).

E. Chemical Fate

By applying the physical and chemical properties of DGBA and DGBE presented in Unit II.A. to the EPA environmental partitioning (ENPART) model, the environmental distribution of DGBA and DGBE can be estimated. Assuming the initial dispersion to air, water, and soil to be 94, 4, and 2 percent and that half lives in air, water, and soil are 0.5 hours, 14 days, and 28 days, the ENPART model predicts the mass environmental distribution of DGBA and DGBE to be 78 and 80 percent in water,

20 and 18 percent in soil, and 2 percent of each in air (Refs. 27 and 28).

Although no specific information was available on the environmental fate of DGBA or DGBE, they are expected to degrade fairly rapidly in air and at a moderate rate in water and soil (Ref. 6). A biodegradation study of DGBA in activated sludge reported more than 90 percent biodegradation in 2 weeks after a 5-day adaptation period (Ref. 64), while a biodegradation study of DGBE reported 11 percent degradation in 5 days after introduction to the diluted effluent from a biological treatment plant (Ref. 65).

Neither DGBA nor DGBE is expected to bioaccumulate because of calculated bioconcentration factors (BCF) of 16 and 3 (Ref. 6), a BCF below 100 indicates a low potential for bioaccumulation.

F. Ecological Effects

Although there are no available data on the aquatic toxicity of DGBA, several screening studies have been performed to estimate the acute toxicity of DGBE to fish, aquatic invertebrates, and algae. The data presented in the following Table 2 demonstrate that DGBE has low aquatic toxicity. The Agency does not expect DGBA to be substantially more toxic than DGBE.

TABLE 2.—THE ACUTE TOXICITY OF DGBE TO AQUATIC ORGANISMS

Species	Test duration	Effect endpoint	Endpoint (mg/l)	Ref.
<i>Menidia beryllina</i>	96h	LC50	2,000	74
<i>Lepomis macrochirus</i>	96h	LC50	1,300	74
<i>Poecilia reticulata</i>	7d	LC50	1,150	75
<i>Carassius auratus</i>	24h	LC50	2,700	76
<i>Leuciscus idus</i>		LC50	1,805	77
<i>Leuciscus idus</i>		LC50	2,304	77
<i>Alburnus alburnus</i>	96h	LC50	>10,000	78
<i>Nitocra spinipes</i>	96h	LC50	6,600	78
<i>Daphnia magna</i>	24h	LC50	2,850	79
<i>Scenedesmus quadricauda</i>	7d	EC3	1,000	56
<i>Entosiphon sulcatum</i>	72h	^a EC5	73	56
<i>Anacystis aeruginosa</i>	8d	^a Th	53	73

¹Threshold concentration reducing growth by 3 percent.

²Threshold concentration reducing growth by 5 percent.

³Threshold concentration.

G. Health Effects

1. *Pharmacokinetics.* DGBA and DGBE are glycol ethers which differ structurally by only an acetate group. The ANPR requested information concerning the metabolism of DGBA to DGBE to evaluate the necessity of testing both chemicals. Eastman Kodak submitted an *in vitro* study which looked at the rate at which DGBA is hydrolyzed in blood to DGBE. When 5 mM of DGBA was incubated in rat blood, 42 percent was hydrolyzed to DGBE in 2 minutes and 68 percent in 4 minutes. With an apparent half-life of DGBA in blood of 3 minutes, this study

adequately demonstrated a rapid hydrolysis of DGBA to DGBE (Ref. 29). No other data on the pharmacokinetics of DGBE are available comparing absorption, biotransformation, and excretion by the oral and dermal routes. Also, there are no data available on the rate of dermal absorption of DGBA.

2. *Acute toxicity.* Several studies of the acute oral toxicity of DGBA and DGBE have been conducted indicating similar toxicity for both chemicals, but an apparent species variation exists in the LD₅₀ which ranges from approximately 2,000 to 12,000 mg/kg, with the guinea pig and rabbit appearing to be most sensitive. The results of the acute studies are summarized in the following Table 3.

TABLE 3.—Summary of Acute Toxic Effects (LD₅₀) of DGBA and DGBE

Species	Route of administration	LD ₅₀ (mg/kg)		References
		DGBA	DGBE	
Rat (fasted)	Oral	7,000		30
Ratdo	11,920	6,560	31
Rat (fasted)do		7,292	32
Rat (fed)do		9,623	32
Mouse (fasted)do		2,406	32
Mouse (fed)do		5,526	32
Mouse (fed)do	6,480		30
Guinea pig (fasted)do	2,550		30
Guinea pigdo	2,340	2,000	31
Rabbit (fed)do	2,750		30
Rabbit	Dermal	5,400		30
Rabbitdo		2,764	33

In the Eastman Kodak study clinical signs of toxicity in rats and mice following oral administration of DGBE were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration, and death (Ref. 32).

The acute dermal toxicity of DGBE in male New Zealand white rabbits was evaluated following exposure for 24 hours at 4 dose levels: 1,700, 3,400, 6,800, and 13,610 mg/kg. Clinical signs of toxicity noted after treatment were anorexia, depression, tremors, prostration, and death. Gross pathology at autopsy showed evidence for adverse effects on the kidneys at the intermediate dose levels (enlarged, discolored renal pelvis). Edematous and hemorrhagic lesions of the thymus were observed at the three higher dose levels, and dark red fluid was noted in the urinary bladder of three rabbits treated with 3,400 mg/kg (Ref. 33).

The rat oral study by Smyth noted narcosis occurring near the LD₅₀ and kidney damage at unspecified doses (Ref. 31). The chemicals are relatively non-irritating to the skin and eye (Ref. 1).

The studies of acute toxicity are adequate to predict the acute effects of exposure to DGBE and DGBA.

3. *Subchronic toxicity.* A subchronic dermal study by Draize applied DGBA to the clipped intact skin of rabbits for 90 days in daily doses from 490 to 3,920 mg/kg. Observed effects included hematuria, hemolysis in the kidney, and renal tubular degenerative changes (Ref. 1). This study was not adequate to assess the subchronic toxicity of DGBA because the histopathology of the other possible target organs was not done, the observed effects were not correlated with dose, and the sex of the animals was not stated.

A 30-day oral study in rats by Kesten saw 650 mg/kg/day of DGBE cause hydropic degeneration of the kidney tubules (Ref. 34). The same study repeated by Smyth and Carpenter saw histopathologic injury in liver, spleen, and testes as well as kidney at 650 mg/kg/day. The maximum dose of DGBE having no observed effect was 51 mg/kg/day (Ref. 35). Because these studies were only 30 days in duration, they are not adequate to evaluate the subchronic toxicity of DGBE.

A 5-week inhalation study in rats by the Dow Chemical Company resulted in increased hepatocyte vacuolization and increased liver weights at doses of 40 and 120 mg/kg/day of DGBE. These effects were also seen in the controls, but the degree was not stated. The study looked for effects on erythrocyte fragility but found none (Ref. 36). Because this study was only 5 weeks in duration, it is not adequate to evaluate the subchronic toxicity of DGBE.

Eastman Kodak submitted the results of a 6-week oral study in which male rats were administered DGBE by gavage at doses of 891 to 3,564 mg/kg/day. At 1,782 and 3,564 mg/kg the absolute and relative weights of spleen and liver were significantly increased compared to controls. Hematological effects were present at these doses and included decreased hemoglobin and total red cells, and abnormal red cell morphology. There were also kidney effects at these doses including proteinaceous casts and hemosiderin in the proximal convoluted tubules. No effect was seen at the dose of 891 mg/kg/day (Ref. 37). Because no liver histopathology was reported for this study, only male rats were used, and the study was only 6 weeks in duration, it is not adequate to fully evaluate the potential subchronic toxicity of DGBE.

The Huntington Research Centre evaluated the subchronic toxicity of DGBE for the Procter and Gamble Company by dermal exposure of six New Zealand rabbits to 30 mg/kg DGBE

for 28 days. The major effects observed in males were a decrease in eosinophils and monocytes. In females, there was a decrease in red cells, white cells, neutrophils and hemoglobin, cortical scarring in the kidney and vacuolization of the liver (Ref. 38). The study, however, used only 3 animals per sex and cannot adequately evaluate the subchronic toxicity of DGBE.

A rat inhalation study by Krotov administered DGBE at doses of 0.7 to 13 mg/kg/day for 4 months. At 3.4 and 13.0 mg/kg/day there were changes in the differential leukocyte count, urea level, lactic acid, and pyruvic acid in blood. At 0.7 mg/kg/day there were reversible changes in the kidney, liver, and nervous system (Ref. 39). Due to the inadequate description of the study design and results, this study was not adequate to fully evaluate the subchronic toxicity of DGBE.

In a dose-setting study for a reproductive screen, female mice were treated by gavage with DGBE for 8 consecutive days at five dose levels, 10 mice per dose level. At the two highest dose levels, 1,000 and 2,000 mg/kg/day, disorientation and lethargy were noted on day 1 in all animals immediately after administration of the first dose. All surviving mice given 1,000 mg/kg/day were hypoactive 1 hour after administration. With one exception, all animals that survived the treatment period remained normal throughout the post-dosing phase. Based on the mortality data, a dose level of 500 mg/kg/day was identified as the maximum tolerated dose (Ref. 40). Because this study was an 8-day, screening study, it is not adequate to fully evaluate subchronic toxicity of DGBE.

Although the above studies raised concern about the effect of DGBA and DGBE on the blood, liver, kidney, testes, spleen, and nervous system, they are inadequate for the above stated reasons to fully evaluate the subchronic toxicity of DGBA and DGBE and establish NOEL's for various effects.

4. *Erythrocyte fragility.* A study by the Dow Chemical Company looked at the fragility of erythrocytes from rats dosed with ethylene glycol monobutyl ether (EGBE) and DGBE. It was found that blood cells from rats dosed at $\frac{1}{2}$ and $\frac{1}{4}$ the LD₅₀ of EGBE lysed in saline concentrations (0.55 to 0.80 percent saline) in which only fragile erythrocytes will lyse. In contrast, blood from rats dosed with DGBE at its LD₅₀ lysed only in saline concentrations (0.35 to 0.45 percent saline) in which normal erythrocytes will lyse (Ref. 41). This study suggests that erythrocyte fragility as an acute effect is caused by EGBE and not DGBE. The study did not raise

the question of how DGBE has caused the reported decrease in erythrocytes in the subchronic studies (Refs. 37 and 38), but bone marrow effects should probably be considered.

The Chemical Manufacturers Association submitted a review of EGBE's hematologic toxicity which concluded that EGBE causes erythrocyte fragility in only certain species, especially rats, which CMA contends are poor hematologic models for humans (Ref. 42). EPA, however, does not believe that data from rats should be discounted, in that data from a sensitive species will provide a greater margin of safety for sensitive humans.

5. *Neurotoxic effects.* No studies in the available literature attempted to investigate the neurotoxicity of DGBA or DGBE. Observations on the subchronic toxicity of DGBE included disorientation and lethargy following oral administration of 1,000 or 2,000 mg/kg to female mice (Ref. 40). Also, Krotov reported irreversible changes in the functional condition of the nervous system (increase in excitability) of rats exposed continuously by inhalation to 13 or 3.4 mg/kg/day DGBE for 4 months. Similar but reversible changes were observed toward the end of the treatment period in rats exposed to 0.7 mg/kg/day (Ref. 39).

In acute studies, DGBE was reported to cause narcosis at doses near its LD₅₀ (Refs. 5 and 31).

Studies on the analog, EGBE, included observations which may indicate neurotoxicity at high dose levels. Following a 4-hour inhalation exposure of rats to 867 or 523 ppm EGBE (LC₅₀ for females was 450 ppm), observations included loss of coordination, narcosis, and respiratory difficulty (Ref. 30). Also, prompt death following a single oral dose of EGBE is attributed to the narcotic effects of the compound (Ref. 5). At much lower dose levels, pregnant rats were hypoactive after inhalation exposure to 100, 200, or 300 ppm for 6 hours per day (Ref. 44).

Although the available studies suggest a concern for neurotoxicity they are not adequate to fully evaluate the potential for DGBA and DGBE to cause neurotoxic effects.

6. *Developmental neurotoxicity.* There was no information in the available literature on the testing of DGBA or DGBE for developmental neurotoxicity. There were data, however, on two analogs, 2-methoxyethanol and 2-ethoxyethanol in studies by Nelson et al. (Refs. 49 and 50). Neurochemical deviations were observed in rat brains from 21-day-old offspring when either the paternal or maternal groups were

exposed to 25 ppm of 2-methoxyethanol for 6 weeks prior to mating (males) or during gestation (females). In addition, behavioral testing revealed significant differences from controls in avoidance conditioning of offspring of mothers exposed to 25 ppm of 2-methoxyethanol on gestation days 7 to 13 (Ref. 49). With 2-ethoxyethanol, prenatal exposure of pregnant rats to 100 ppm also caused behavioral and neurochemical alterations in offspring (Ref. 50).

Although these analog studies raise concern for the neurotoxic effect of glycol ethers on the developing fetus, they are not adequate to predict the potential developmental neurotoxicity of DGBA and DGBE.

7. Reproductive effects. There was no information in the available literature on the testing of DGBA for reproductive effects. Limited information was available on DGBE, but a considerable body of data was found on glycol ether analogs.

In a 90-day study with the analog diethylene glycol monoethyl ether (DGEE), Hall found 5 percent DGEE in drinking water caused testicular atrophy in rats (Ref. 52). Nagano, however, saw no testicular atrophy in mice after dosing with 2 percent diethylene glycol monomethyl ether (DGME) in drinking water for 25 days, although he did see atrophy from similar administration of ethylene glycol methyl ether (EGME) and ethylene glycol ethyl ether (EGEE) (Ref. 53). Foster saw spermatocyte degeneration in rats after dosing with 100 mg/kg/day of EGME and 500 mg/kg/day of EGEE (Ref. 2). In a review by Hardin, it was observed that the methyl and ethyl derivatives of ethylene glycol clearly cause testicular atrophy, but that the butyl derivative apparently did not have the same effect (Ref. 3).

Although the above reviewed analog studies raise a concern for reproductive effects, they are not sufficient to characterize the full reproductive effects of DGBA and DGBE.

The effects of DGBE on fertility and reproductive performance were evaluated in a study done for Procter and Gamble in which male rats were dosed for 60 days and female rats for 2 weeks prior to mating at 0, 250, 500, or 1,000 mg/kg/day by gavage. At each dose level there were 25 rats/sex mated to undosed rats. Controls received deionized water (5 ml/kg) and were similarly mated. Treatment of either males or females at 250 or 500 mg/kg/day had no effect on fertility or reproductive performance. Females dosed at 1,000 mg/kg/day mated with undosed males produced offspring with reduced body weights from days 4 to 21 of lactation, and may have depressed

the mean number of implantations suggesting a possible effect on ovulation, fertility or implantation. No delay to time of delivery was observed in any dosed group of females. Male rats dosed at 1,000 mg/kg/day and mated with undosed females resulted in a slight reduction in total implantations, indicating a possible effect on spermatogenesis, fertilization, or implantation, but a clear effect was not indicated by the data (Ref. 45). This study is not adequate to fully evaluate the potential for DGBE to cause reproductive effects because dosing was not conducted for the full 10 weeks before mating, which EPA considers necessary for a reliable study; there was an insufficient number of pregnant females per dose sacrificed at or near term; there was no fertility study of the F₁ generation; there was no study of the reversibility of effects on the F₁ generation; and there was no maternally toxic dose administered. However, because the effects observed in this study were minimal, the Agency believes that modifications to the subchronic test to further evaluate reproductive toxicity will adequately characterize the reproductive effects of DGBE and DGBA. If the results raise questions which require additional testing to resolve, that testing will be proposed at a later date.

8. Developmental effects. There was no information in the available literature on the testing of DGBA for developmental effects. Information was available on DGBE and its glycol ether analogs, particularly EGEE.

The available studies on the developmental effects of EGEE (Refs. 44, 54, 57, and 58), ethylene glycol monoethyl ether (EGEE) (Ref. 50), ethylene glycol monomethyl ether (EGME) (Ref. 3), and diethylene glycol monomethyl ether (DGME) (Ref. 55) indicated a potential for embryotoxicity, fetotoxicity and delayed parturition. Although the data from the above reviewed glycol ether analogs indicated developmental effects, the data were not sufficient to characterize the developmental effects of DGBE and DGBA.

In a study conducted by Borriston Laboratories for the National Institute for Occupational Safety and Health, DGBE was tested for reproductive effects in a short-term screening assay in mice (Ref. 40). Treatment of 50 pregnant CD-1 mice with DGBE (500 mg/kg/day) by gavage from gestation day 7 to 14 did not adversely affect the survival or gestational weight gain of the dams, delivery time, birth weight, weight gain, or viability of the F₁ generation through the first 3 postpartum days.

However, the dosage used was judged to be an insufficient challenge since there was no evidence of maternal toxicity. When DGBE was subjected to a similar protocol by Schuler at 2,000 mg/kg/day, a dose at which maternal mortality was 8 percent, it likewise caused no adverse effects on any of the parameters mentioned above, except delivery time which was not discussed, suggesting low-concern for developmental toxicity (Ref. 51). In addition, the reproductive study in rats with a limit dose of 1,000 mg/kg/day did not report a delay in time to delivery (Ref. 45, see Unit II. G.7).

In a study done for Procter and Gamble, the teratogenic effects of dermal exposure to DGBE were evaluated (Ref. 46). Twenty rabbits per group were exposed to doses of 100, 300, and 1,000 mg/kg for 4 hours per day on gestation days (GD) 7 to 18. On GD 29 the fetuses were removed for teratological evaluation. In general, the mean numbers of viable and non-viable fetuses, early and late resorptions, post implantation losses, total implantations, and corpora lutea, as well as the mean fetal body weight (by sex) and fetal sex distribution at all dose levels were comparable to control group values. At the low dose level there was a slight increase in the mean postimplantation loss, which was offset by a slight increase in the mean number of total implantations. The number of fetuses and litters with malformations in the three treated groups did not differ significantly from those of the control group. The greatest incidence of anomalies occurred among control and low-dose litters, with a lesser incidence seen in the intermediate and high-dose groups. The most frequently seen malformations, vertebral anomalies with or without associated rib anomalies and fused sternabrae, reflected this pattern. In addition, interventricular septal defects and other heart and major vessel anomalies were observed primarily in the control group. This study appears to be adequate to assess the developmental effects of DGBE in rabbits. Since studies on other glycol ethers indicate rabbits are the most sensitive species for this endpoint and since the Procter and Gamble study was done to the limit dose and administered DGBE by the preferred route of exposure, the Agency will not propose that testing be performed in a second species.

9. Mutagenic effects. The mutagenic potential of DGBE was examined by Thompson et al. (Ref. 47) with 3 assays for gene mutation (gene mutation in *Salmonella*, somatic cells in culture

using mouse lymphoma cells, and *Drosophila* sex-linked recessive lethal), one test for chromosomal aberration (*in vitro* cytogenetics), and one test for DNA repair capacity (unscheduled DNA synthesis). All the tests were negative except the somatic cells in culture test which was positive in the absence of metabolic activation, but negative with activation.

The Agency believes the weight-of-evidence suggests the potential for DGBE to cause gene mutation is low, but that additional testing in this area is necessary to assess the need for oncogenicity testing. Additional tests are also needed to fully evaluate DGBE's potential to induce chromosomal aberrations and to further assess the need for oncogenicity testing.

10. *Oncogenic effects.* There are no data on the oncogenic potential of DGBA or DGBE.

III. Findings

EPA is basing its proposed health effects testing of DGBA and DGBE on the authority of sections 4(a)(1) (A) and (B) of TSCA. Under section 4(a)(1)(B), EPA finds that DGBA and DGBE are produced in substantial quantities and that there may be substantial human exposure to both chemicals in their use, manufacture, and processing. The annual production of DGBA and DGBE is 4.8 and 66.5 million pounds per year, respectively (Ref. 62). Potentially 15 to 20 million consumers and 4,500 occupational painters are exposed to DGBA and DGBE in latex paint at 1 to 10 milligrams per kilogram per day (mg/kg/day) (Refs. 15, 25 and 63). Also, 20 to 41 million consumers and 40,000 janitors are potentially exposed to DGBE in cleaning products at 0.22 to 8.0 mg/kg/day (Refs. 18, 20, 21, 25 and 65). Additionally, there is a potential for dermal absorption in employees of manufacturers and processors.

EPA finds that there are insufficient data to reasonably predict the subchronic, neurotoxic, developmentally neurotoxic, reproductive, chromosomal, and oncogenic effects and pharmacokinetics of human exposure to DGBE and DGBA.

Under section 4(a)(1)(A) EPA finds that the use of DGBE and DGBA in consumer goods may present an unreasonable risk of hematological, reproductive, developmental, developmentally neurotoxic, neurotoxic/behavioral effects, hepatotoxicity, and renal toxicity.

The Agency finds that the available data are sufficient to predict the developmental effects of DGBE and DGBA, but insufficient to reasonably predict or determine the subchronic,

kidney, liver, hematological, reproductive, neurotoxic/behavioral, developmentally neurotoxic, chromosomal, and oncogenic effects of exposure to DGBE and DGBA from the use of these compounds. In addition, the available data are insufficient to fully evaluate the pharmacokinetics of these compounds, specifically the effect of administration route on absorption, biotransformation and excretion. The EPA finds that testing is necessary to develop such data. EPA is aware that the U.S. Navy is currently conducting a 90-day subchronic oral study of DGBE in rats. This study does not address all of the Agency's concerns for DGBE; specifically it does not evaluate neurotoxic/behavioral effects and kidney and liver function, or hematological effects during the first two weeks of dosing (Ref. 48).

Existing data adequately demonstrate that DGBA is rapidly hydrolyzed to DGBE. Therefore, EPA finds that separate health effects testing of DGBA is not necessary. The only exception to this is a dermal absorption test of DGBA, since DGBA could be used interchangeably with DGBE in consumer products which involve dermal exposure, therefore the dermal absorption of DGBA relative to DGBE should be known. The pharmacokinetics test of DGBE will compare absorption, biotransformation and excretion by each of the two routes of administration, i.e. dermal and oral, to enable comparison with existing data and the oral subchronic study being conducted by the Navy (Ref. 48), which may be helpful in dose-setting.

Testing should be by the dermal route since it is a major route of exposure. Exceptions to this include the tests for *in vivo* cytogenetics, dominant lethal assay, and heritable translocation, if required, where oral administration is recommended. Although inhalation is also a main route of exposure, it was considered too difficult for test purposes due to DGBE's low vapor pressure.

IV. Proposed Rule

A. Proposed Testing and Test Standards

The Agency is proposing that health effects and pharmacokinetics testing of DGBE and dermal absorption testing of DGBA be conducted in accordance with specific guidelines set forth in 40 CFR Part 798 as enumerated below.

This proposed rule is a tiered rule. The following tests will be incorporated in Tier I: Subchronic toxicity with particular emphasis on reproductive, hematological, liver and kidney effects; neurotoxicity; developmental neurotoxicity; lower-tier mutagenicity

(somatic cells in culture using CHO cells, *in vivo* cytogenetics, and dominant lethal test, if triggered); pharmacokinetics and dermal absorption.

The Tier II tests may include the heritable translocation test and the oncogenicity test.

All of the tests will be proposed and finalized at one time. Before Tier II testing is initiated, EPA will hold a public program review if the results of the Tier I tests are positive. A review of all available data will be conducted. Public participation in this program review will be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting will be published in the Federal Register. Should EPA determine, based on the available weight-of-evidence, that proceeding to the heritable translocation test and/or oncogenicity test is no longer warranted, the Agency would propose to repeal the appropriate testing requirements and, after public comment, issue a final amendment to rescind such requirements.

DGBE will be tested for subchronic toxicity (§ 798.2250). In addition to an intermediate and high dose, two low dose levels, 1 and 15 mg/kg/day, have been specified to evaluate whether effects occur at 1 mg/kg/day as reported by Krotov (Ref. 39) and at 15 mg/kg/day, which just exceeds the maximum anticipated human exposure. Exposure will be by the dermal route in the rat. Urinalyses in all animals will be done before the study starts, at day 30 and day 90. There will be a special satellite group dealing with liver dysfunction. The details for the liver dysfunction tests and the special hematologic studies are given in § 799.1560. Subchronic dermal neurotoxicity studies will be performed in the rat: A functional observational battery (§ 798.6350), motor activity (§ 798.6200), and neuropathology (§ 798.6400). These neurotoxicity tests may be combined, using 10 animals for each dose and sex.

Some additional work will be required for the subchronic testing to evaluate reproductive toxicity. Special organs of the reproductive tract to be weighed and evaluated are listed in § 799.1560. The integrity of the various cell stages of spermatogenesis shall be determined with particular attention directed toward achieving optimal quality in the fixation and embedding; preparations of testicular and associated reproductive organ samples for histology should follow the recommendations of Lamb and Chapin (Ref. 66), or an equivalent procedure. This evaluation of the

spermatogenic pattern has been shown by Creasy (Ref. 72) and Foster (Ref. 2) to be the most sensitive indicator of glycol ether-induced testicular injury. Testicular spermatid counts shall be performed; the method described by Johnson et al. (Ref. 67) and Blazak et al. (Ref. 68), or an equivalent method should be used. Epididymal sperm count and sperm morphology shall also be done. Data on female cyclicity shall be obtained by performing vaginal cytology over the last two weeks of dosing; the method of Sadleir (Ref. 69), or an equivalent method should be used. The histopathology of the ovary to evaluate oocyte toxicity shall be performed and should follow the method of Mattison (Ref. 70) and Pederson (Ref. 71), or an equivalent method. A satellite group of animals will be used to evaluate fertility effects at high doses of DGBE in both males and females. If the results of the above testing suggest concern for reproductive effects, the Agency will consider the need for additional reproductive effects testing under section 4(a)(1)(A) of TSCA.

To further assess the need for oncogenicity testing, the Agency is proposing mutagenicity testing in the somatic cells in culture test using Chinese hamster ovary (CHO) cells (§ 798.5300).

To further assess the potential for chromosomal aberrations and the need for oncogenicity testing, DGBE shall be tested in the *in vivo* cytogenetics assay (§ 798.5385) in the rat, mouse, or hamster by oral gavage. If this test is negative, no further testing for chromosomal effects need be done. If the test is non-negative, then a dominant lethal study (§ 798.5450) in the rat or mouse shall be performed by oral gavage. If the dominant lethal test is negative, no further chromosomal aberration studies need be done. If the dominant lethal test is positive, a public program review of the data will be held before the mouse heritable translocation test (§ 798.5460) by oral gavage is performed.

For a more detailed discussion concerning mutagenicity testing and public program review procedures see EPA's final test rule for the C₉ aromatic hydrocarbon fraction published in the *Federal Register* of May 17, 1985 (50 FR 20662).

EPA is requiring developmental neurotoxicity testing in the rat according to § 795.250 published in the *Federal Register* of May 15, 1986 (51 FR 17883) by the dermal route of exposure. The offspring shall be allowed to go to parturition, and those offspring shall be evaluated for behavioral alterations at various stages following birth. The developmental neurotoxicity study shall

be performed at doses lower than those which induce severe teratogenic or fetal effects.

The Agency is also proposing pharmacokinetics testing of DGBE and DGBA in rats and guinea pigs to compare absorption, biotransformation and excretion of DGBE by the dermal and oral routes of administration and to determine dermal absorption of DGBA in accordance with § 795.225.

Oncogenicity studies (§ 798.3300) of DGBE will be required in the mouse and rat by dermal absorption unless negative results are obtained in both the somatic cells in culture test using Chinese hamster ovary cells and the *in vivo* cytogenetics assay. EPA will review the mutagenicity and other available data and hold a public program review before oncogenicity testing is performed.

The Agency is proposing that the above-referenced TSCA health effects test guidelines be employed as the test standards for the purposes of the proposed tests for DGBE and DGBA. The TSCA test guidelines for health effects testing specify generally accepted minimal conditions for determining the health effects for substances like DGBE and DGBA to which humans are expected to be exposed. The Agency's review of the TSCA Test Guidelines, which occurs on a yearly basis according to the process described at 47 FR 41857 (September 22, 1982), has found no reason to conclude that these protocols need to be modified significantly.

EPA published in the *Federal Register* certain proposed revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study (51 FR 1522; January 14, 1986). In addition, these revisions will avoid repetitive chemical-by-chemical changes to the guidelines in their adoption as test standards for chemical-specific test rules. EPA is proposing that these modifications be adopted in the test standards for DGBE and DGBA.

B. Test Substance

The EPA is proposing testing of DGBE and DGBA of at least 95 percent purity. The EPA believes that test materials of this purity are available at reasonable cost (Refs. 29 and 37). The Agency has specified relatively pure substances for testing because the EPA is interested in evaluating the effects attributable to the subject compounds themselves. This requirement would lessen the likelihood that any effects seen are due to impurities. Radiolabeled 14_C-DGBE will be needed for the pharmacokinetics testing

and 14_C-DGBA for the dermal absorption study.

C. Persons Required to Test

Section 4(b)(3)(B) specifies that the activities for which the Agency makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing, which includes production of these chemicals as a byproduct, ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. Both manufacturers and processors are required to test if the exposures giving rise to the potential risk occur during use, distribution, or disposal.

Because the EPA has found that existing data are inadequate to assess the health risks from the use, manufacturing, and processing of these compounds the EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process, DGBA or DGBE at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements contained in this proposed rule. The end of the reimbursement period will be 5 years after the last final report is submitted or an amount of time equal to that which was required to develop data if more than 5 years after the submission of the last final report required under the test rule.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that the EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to the EPA for an exemption from the requirement. The EPA promulgated procedures for applying for TSCA section 4(c) exemptions in 40 CFR Part 790.

When both manufacturers and processors are subject to a test rule, the EPA expects that manufacturers will conduct the testing and that processors will ordinarily be exempted from testing. As described in 40 CFR Part 790, processors will be granted an exemption automatically without filing applications if manufacturers perform all of the required testing. Manufacturers are

required to submit either a letter of intent to perform testing or an exemption application within 30 days after the effective date of the test rule.

The EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for DGBE and DGBA. As noted in Unit IV.B, the EPA is interested in evaluating the effects attributable to the specified compounds and has proposed relatively pure substances for testing.

Manufacturers and processors who are subject to this test rule must comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

D. Reporting Requirements

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

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors are required to submit individual study plans at least 45 days before the start of each study.

The EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. The Agency is proposing specific reporting requirements for each of the proposed tests as follows:

1. The subchronic toxicity and subchronic neurotoxicity/behavioral tests of DGBE shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final test rule.

2. The Tier I mutagenicity studies of DGBE shall be completed and final results submitted to the Agency as follows: The somatic cells in culture assay using CHO cells within 6 months of the effective date of the final rule; the *in vivo* cytogenetics assay within 8 months of the effective date of the final rule; and the dominant lethal test within 18 months of the effective date of the final rule, if triggered.

3. The developmental neurotoxicity study of DGBE shall be completed and final results submitted to the Agency within one year of the effective date of the final test rule.

4. The pharmacokinetics tests of DGBE and the dermal absorption test of DGBA shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final test rule.

5. The Tier II heritable translocation test, if triggered, shall be completed and final results submitted to the Agency

within 45 months of the effective date of a final test rule.

6. The oncogenicity test of DGBE, if triggered, shall be completed and the final results submitted to the Agency within 56 months of the effective date of a final test rule.

Progress reports are required for tests except the somatic cells in culture test. Reports shall be submitted every 6 months, beginning 6 months from the effective date of the final rule or in the case of the dominant lethal assay and Tier II tests, beginning 6 months from the date triggered.

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).

Persons who export a chemical substance or mixture which is subject to a section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) are in 40 CFR Part 707. In brief, as of the effective date of this test rule, an exporter of DGBA or DGBE must report to the EPA the first annual export or intended export of either chemical to any one country. The EPA will notify the foreign country about the test rule for the chemical.

E. Enforcement Provisions

The Agency considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to: (1) Establish or maintain records, (2) submit reports, notices, or other information, or (3) permit access to or copying of records required by the Act or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce . . ." The Agency considers a testing facility to be a place where the chemical is held or stored, and therefore, subject to inspection. Laboratory inspections and data audits will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11

by duly designated representatives of the EPA for the purpose of determining compliance with any final rule for DGBA and DGBE. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, and that reports accurately reflect the underlying raw data and interpretations and evaluations to determine compliance with TSCA GLP standards and the test standards established in the rule.

The EPA's authority to inspect a testing facility also derives from section 4(b)(1) of the TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and such other requirements as are necessary to provide such assurance. The Agency maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to \$25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers or processors that fail to submit a letter of intent or an exemption request and that continue manufacturing or processing after the deadlines for such submissions. This provision would also apply to processors that fail to submit a letter of intent or an exemption application and continue processing after the Agency has notified them of their obligation to submit such documents (see 40 CFR 790.28(b)). Intentional violations could lead to the imposition of criminal penalties of up to \$25,000 for each day of violation and imprisonment for up to 1 year. In determining the amount of penalty, the EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in section 16. Other remedies are available to the EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to

"any person" who violates various provisions of TSCA. The EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular, this includes individuals who report false information or who cause it to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

V. Issues for Comment

1. Although the rabbit may be a more sensitive species for some effects and was proposed as the test species for the triethylene glycol ethers proposed test rule, the rat is proposed as the test species due to the greater experience with this animal in the tests proposed in this rule. Use of the rat should produce better data and facilitate interpretation of results. Also, the ITC recommended that subchronic testing be done for renal effects in another species besides rabbit. Should the Agency require rabbit as the test species since it is more sensitive to DGBE for some effects than the rat?

2. The proposed sample size of 10 animals/sex/dose for adult neurotoxicity evaluations may be too small given the degree of variability associated with some of the tasks (e.g. locomotor activity). Would fifteen to twenty animals/sex/dose be more appropriate?

VI. Economic Analysis of Proposed Rule

To assess the potential economic impact of this rule, EPA has prepared an economic analysis (Ref. 62) that evaluates the potential for significant economic impacts on industry as a result of the required testing. The economic analysis estimates the costs of conducting the required testing and evaluates the potential for significant adverse economic impact as a result of these test costs by examining four market characteristics of DGBA and DGBA:

1. Price sensitivity of demand,
2. Industry cost characteristics,
3. Industry structure, and
4. Market expectations.

If these indications are negative, no further economic analysis is performed; however, if the first level of analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted which more precisely predicts the magnitude and distribution of the expected impact.

Total direct testing costs for the proposed rule for DGBE are projected to range from \$1.2 million to \$1.6 million. This estimate includes the costs for both the required minimum series of tests as well as the conditional tests. The

annualized test costs (using a cost of capital of 25 percent over a period of 15 years) range from \$323,000 to \$424,000. Based on the reported 1984 production volume of 66.5 million pounds, the unit test costs range from 0.49 to 0.64 cents per pound. In relation to a unit sales value of 41 cents per pound for DGBE, these costs represent 1.20 to 1.56 percent of unit sales value.

Total direct testing costs for the proposed testing for DGBA are estimated to range from \$78,000 to \$103,000. The annualized test costs range from \$20,000 to \$27,000. Based on 1984 production of 4.8 million pounds and adjusting for upstream testing costs, because DGBA is manufactured from DGBE, the unit test costs range from 0.83 to 1.09 cents per pound. In relation to the current sale price of 72 cents per pound for DGBA, these costs are equivalent to 1.15 to 1.51 percent of price.

Based on these costs and the uses of the chemicals, the economic analysis indicates that the potential for significant adverse economic impact as a result of this test rule is low.

This conclusion is based upon the following observations:

1. The estimated unit test costs are low;
 2. Technical performance tends to offset relatively high product price and contributes to overall price inelasticity of demand;
 3. Market expectations appear favorable for DGBE and DGBA; and
 4. Producers of DGBE and DGBA also produce the likely substitutes for these chemicals, some of which can be produced in the same production equipment.
- Refer to the economic analysis for a complete discussion of test cost estimation and the potential for economic impact resulting from these costs.

VII. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires the EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, the 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. Copies of the study, Chemical Testing Industry: Profile of Toxicological Testing, can be obtained through the NTIS (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 in this proposed rule.

VIII. Public Meetings

If persons indicate to the EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, the EPA will hold a public meeting subsequent to the close of the public comment period in Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); In Washington, DC: (554-1404); Outside the U.S.A. (Operator—202-554-1404), by September 18, 1986. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

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

IX. Public Record

The EPA has established a record for this rulemaking, (docket number OPTS-42085). This record contains the basic information considered by the Agency in developing this proposal and appropriate Federal Register notices.

This record includes the following information:

A. Supporting Documentation

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

(a) Notice containing the ITC designation of 2-(2-butoxyethoxy)ethyl acetate or DGBA (48 FR 55674; December 14, 1983).

(b) Rules requiring TSCA section 8(a) and 8(d) reporting on 2-(2-butoxyethoxy)ethyl acetate or DGBA (48 FR 55685 and 55686; December 14, 1983).

(c) Advance Notice of Proposed Rulemaking (ANPR) for 2-(2-Butoxyethoxy) Ethyl Acetate; Response to the Interagency Testing Committee (49 FR 45606; November 19, 1984).

(d) Notice of final rule on EPA's TSCA good laboratory practice standards (48 FR 53922; November 29, 1983).

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

(f) Notice of final rule on data reimbursement policy and procedures (48 FR 31786; July 11, 1983).

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

(2) Support document consisting of DGBA and DGBE's economic analysis.

(3) TSCA test guidelines and other test methodologies cited as test standards for this rule.

(4) Communications before proposal consisting of:

(a) Written public comments and letters.

(b) Contact reports of telephone conversations.

(c) Meeting summaries.

(5) Reports—published and unpublished factual materials.

B. References

(1) Draize, J.H., Alvarez, E., Whitesell, M.F., Woodard, G., Hagan, E.C., and Nelson, A.A. "Toxicological investigations of compounds proposed for use as insect repellants." *Journal of Pharmacology and Experimental Therapeutics*, 98:26-39, (1948).

(2) Foster, P.M.D., Creasy, D.M., Foster, J.R., Thomas, L.V., Cook, M.W., and Gangolli, S.D. "Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat." *Toxicology and Applied Pharmacology*, 69:385-399, (1983).

(3) Hardin, B.D. "Reproductive toxicity of the glycol ethers." *Toxicology*, 27:91-102, (1983).

(4) SRI, Stanford Research Institute International. Glycol Ethers. In *Chemical Economics Handbook*, Menlo Park, CA, p. 663.5022H, Online update (April 1984).

(5) *Patty's Industrial Hygiene and Toxicology*, 3rd rev. ed., Vol. 2 C, New York: Wiley-Interscience pp. 3909-4052 (1982).

(6) Capital Systems Group, Inc., Kensington, MD 20895 and Dynamac Corp., Enviro Control Division, Rockville, MD 20852. "2-(2-Butoxyethoxy)ethyl acetate and 2-(2-Butoxyethoxy) ethanol. Draft Technical Support Document." Prepared for U.S. Environmental Protection Agency, Test Rules Development Branch, Existing Chemical Assessment Division, Office of Toxic Substances, Washington, DC. Contract No. 68-01-6530. (January 3, 1985).

(7) SRI, Stanford Research Institute International. Glycol Ethers. In *Chemical Economics Handbook*, Menlo Park, CA. Sections 663.5021A-663.5022Z. (1979).

(8) Eastman Kodak Company, Eastman Chemicals Division, Kingsport, TN 37662. Letter from D.W. Kreh to TSCA Public Information Office. U.S. Environmental Protection Agency, Washington, DC 20460. (January 1984).

(9) Volpe, P. National Association of Printing Ink Manufacturers, Harrison, NY. Personal communication with A. Engelkemeir, Dynamac Corp., 11140 Rockville Pike, Rockville, MD 20852. (November 18, 1983).

(10) NIOSH. National Institute for Occupational Safety and Health. Cincinnati, OH. Computer Printout: NIOSH Trade-name Ingredient Data Base—National Occupational Hazard Survey. (Retrieved November 15, 1983).

(11) Sullivan, D.A. "Water and solvent evaporation from latex and latex paint films." *Journal of Paint Technology*, 47(610): 60-67. (1975).

(12) Woebkenberg, J. SCM Glidden Corp., 6151 Sprague Rd., Strongsville, OH 44136. Personal Communication with A. Engelkemeir, Dynamac Corp., 11140 Rockville Pike, Rockville, MD 20852. (December 8, 1983).

(13) Engelhard Industries. Engelhard Industries Specialty Chemicals Division. 1 West Central Ave. East Newark, NJ 07029. Letter from W.J. Stimpfel to Paul Price, U.S. Environmental Protection Agency, Washington, DC 20460 (March 27, 1984).

(14) NIOSH. National Institute for Occupational Safety and Health. Cincinnati, OH. Computer Printout: NIOSH Trade-name Ingredient Data Base—National Occupational Hazard Survey. (Retrieved April 3, 1984).

(15) Platz, R. Dynamac Corp., 11140 Rockville Pike, Rockville, MD 20852. Exposure to DGBE and DGBA in latex paint. Memorandum to Paul Price, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460. (August 20, 1984).

(16) Eastman Kodak Company, Health and Environmental Laboratories. Estimation of the atmospheric concentration of diethylene glycol monobutyl ether acetate resulting from the application of latex paint. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1985).

(17) Dugard, P.H., Walker, M., Mawdsley, S.J., and Scott, R.C. "Absorption of some glycol ethers through human skin in vitro." *Environmental Health Perspectives*, 57:193-197, (1984).

(18) The Procter and Gamble Company. Sharon Woods Technical Center, 11520 Reed Hartman Highway, Cincinnati, Ohio 45241. Letter from D.W. Briggs to Frank Benenati, U.S. Environmental Protection Agency, Washington, DC 20460. Re: Diethylene glycol monobutyl ether: Exposure assessment. (January 28, 1985).

(19) Bushy Run Research Center, R.D. 4, Mellon Rd. Export, PA 15632. (February 27, 1984). "A teratologic evaluation of ethylene glycol monobutyl ether in Fisher 344 rats and New Zealand white rabbits following inhalation exposure." Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1984)

(20) USEPA. U.S. Environmental Protection Agency. "Procter and Gamble exposure assessment for DGBE." Intra-agency memo from Karen Hammerstrom, EED, to Catherine Roman, Test Rules Development Branch (TRDB). (June 26, 1985).

(21) USEPA. U.S. Environmental Protection Agency. "Estimated janitorial exposure to DGBE from 8-hour use of Procter and Gamble cleaning product." Letter to the DGBA/DGBE file from Catherine Roman, TRDB. (December 30, 1985).

(22) Dow Chemical Company, Midland, Michigan 48640. Industrial hygiene surveys during 1983 at the Eastern Division Marine Terminal at Joliet, Illinois. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (May 1985).

(23) Dow Chemical Company, Midland, Michigan 48640. Employees' exposures to Dowanol DB glycol ethers at the * * * plant, * * * building, November and December,

1976. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington DC (May 1985).

(24) Dow Chemical Company, Midland, Michigan 48640. Evaluation of personnel exposures to Dowanol glycol ethers, butylene oxide, ethylene oxide, and propylene oxide at the * * * plant, * * * building, organic chemicals production. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (May 1985).

(25) USEPA. U.S. Environmental Protection Agency. "Consumer exposure to DGBE and DGBA." Intra-agency memo from Karen Hammerstrom, Exposure Assessment Branch, to Catherine Roman, Test Rules Development Branch, Office of Toxic Substance, Washington, DC 20460. (April 29, 1986).

(26) Tyler, T.R. "Acute and subchronic toxicity of ethylene glycol monobutyl ether." Union Carbide Corporation. Corporate Applied Toxicology, P.O. Box 8361, South Charleston, WV 25303. (1983).

(27) USEPA. U.S. Environmental Protection Agency. Thirteenth report of the TSCA Interagency Testing Committee. ENPART analyses of DGBA, TGD, and oleylamine. Intra-agency memorandum to Test Rules Development Branch, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460. (January 12, 1984).

(28) USEPA. U.S. Environmental Protection Agency. Behavior/distribution of diethylene glycol butyl ether in the environment. Intra-agency memorandum from R. Kinerson to P. Price, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC 20460. (July 13, 1984).

(29) Eastman Kodak Company. The *in vitro* hydrolysis of diethylene glycol monobutyl ether acetate in rat blood. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (January 1985).

(30) Dodd, D.E., Snellings, W.M., Maronpot, R.R., Ballantyne, B. "Ethylene glycol monobutyl ether: acute, 9-day, and 90-day vapor inhalation studies in Fischer 344 rats." *Toxicology and Applied Pharmacology* 68:405-414. (1983).

(31) Smyth, H.F. Jr., Seaton, J. and Fischer, L. "The single dose toxicity of some glycols and derivatives." *Journal of Industrial Hygiene and Toxicology*, 23:259-268. (1941).

(32) Eastman Kodak Company. Toxicity studies with diethylene glycol monobutyl ether. I. Acute oral LD₅₀. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (April 1984).

(33) Eastman Kodak Company. Toxicity Studies with diethylene glycol monobutyl ether. II. Acute dermal LD₅₀. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (April 1984).

(34) Kesten, H.D., Mulinos, M.G., Pomerantz, L. "Pathologic effects of certain glycols and related compounds." *Archives of Pathology*, 27:447-465. (1939).

(35) Smyth, H.F. Jr. and Carpenter, C.P. "Further experience with the range finding test in the industrial toxicology laboratory."

- Journal of Industrial Hygiene and Toxicology*, 30: 63-68. (1948).
- (36) Dow Chemical Company. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical USA, Midland, MI 48640. Dowanol®DB: A 5-week repeated vapor inhalation study in rats. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (October 1984).
- (37) Eastman Kodak Company. Rochester, New York. Toxicity studies with diethylene glycol monobutyl ether. III. Six weeks repeat dose study. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (April 1984).
- (38) Huntington Research Centre. Huntington, England. 28-day subchronic percutaneous study of diethylene glycol butyl ether in rabbits. Project ECM-BTS 753. (1982). For Procter and Gamble Company, Cincinnati, Ohio. P&G 995/82956/58. Submitted to Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1984).
- (39) Krotov, Yu. A., Lykova, A.S., Skachkov, M.A. et al. "The toxicological properties of diethyleneglycol ethers (carbitols) in relation to ensuring clean air." *Gig. Sanit.* 2:14-17. (1981) (In Russian; English translation).
- (40) Borriston Laboratories, Inc. 5050 Beech Place, Temple Hills, MD 20748. (1983). Screening of Priority chemicals for reproductive hazards. For National Institute for Occupational Safety and Health, Experimental Toxicology Branch, Division of Biomedical and Behavioral Science, Cincinnati, OH. Contract No. 210-81-6010. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1984).
- (41) Dow Chemical Company. Midland, Michigan 48640. (March 1976). Red blood cell fragility studies on Dowanol DB. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (May 1984).
- (42) Chemical Manufacturers Association. Washington, DC (April 11, 1985). Assessment of hematologic toxicity of ethylene glycol monobutyl ether (EGBE). Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency. (April 23, 1985).
- (43) Nagano, K., Nakayama, E., Koyano, M., Oobayashi, H., Adachi, H., Yamada, T. "Mouse testicular atrophy induced by ethylene glycol mono alkyl ethers." *Japan Journal of Industrial Health*, 21:29-35. (1979).
- (44) Bushy Run Research Center, Export, PA 15632. (November 30, 1983). Inhalation teratological potential of ethylene glycol monobutyl ether in the rat. (February 27, 1984) A teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. For the Chemical Manufacturers Association, Washington, DC. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (March 2, 1984).
- (45) International Research and Development Corporation, Mattawan, Michigan 49071. (January 10, 1984). Study of fertility and general reproductive performance in rats. Test article (TSIN): B0547-01. DRD No. BSBTS-796S2. For Procter and Gamble Company, Cincinnati, OH. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1984).
- (46) International Research and Development Corporation, Mattawan, Michigan 49071. (October 4, 1983). Dermal teratology study in rabbits. Test article (TSIN): B0547-01. DRD No. BSBTS 796. For Procter and Gamble Company, Cincinnati, OH. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC (1984).
- (47) Thompson, E.D., Coppinger, W.J., Valencia, R. and Iavicoli, J. "Mutagenicity testing of diethylene glycol monobutyl ether." *Environmental Health Perspectives*, 57:105-112. (1984).
- (48) Naval Medical Research Institute, Toxicology Detachment, Wright-Patterson Air Force Base, Ohio 45433-6503. Diethylene glycol monobutyl ether, 90-day oral dosing study using F-344 rats. Letter from D.E. Uddin to Catherine Roman, U.S. Environmental Protection Agency, Washington, DC 20460. (September 17, 1985).
- (49) Nelson, B.K., Brightwell, W.S., Setzer, J.V., and O'Donohue, T.L. "Reproductive toxicity of the industrial solvent 2-ethoxyethanol in rats and interactive effects of ethanol." *Environmental Health Perspectives*, 57:255-259. (1984).
- (50) Nelson, B.K., Brightwell, W.S., Setzer, J.V., Taylor, B.J., Hornung, R.W. "Ethoxyethanol behavioral teratology in rats." *Neurotoxicology* 2:231-249. (1981).
- (51) Shuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V., and Smith, K. "Results of testing fifteen glycol ethers in a short-term in vivo reproductive toxicity assay." *Environmental Health Perspectives*, 57:141-146. (1984).
- (52) Hall, D.E., Lee, F.S., Austin, P., and Fairweather, F.A. "Short-term feeding study with diethylene glycol monoethyl ether in rats." *Food and Cosmetics Toxicology*, 3:263-268. (1966).
- (53) Nagano, K., Nakayama, E., Oobayashi, H., Nishizawa, T., Okuda, H., and Yamazaki, K. "Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan." *Environmental Health Perspectives*, 57:75-84. (1984).
- (54) Nelson, B.K., Setzer, J.V., Brightwell, W.S., Mathinos, P.R., Kuczak, M.H., Weaver, T.E., and Goad, P.T. "Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats." *Environmental Health Perspectives*, 57:261-271. (1984).
- (55) Hardin, B.D., Goad, P.T. and Burg, J.R. Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Cincinnati, Ohio, and Intox Laboratories, Inc., Redfield, Arkansas. "Teratogenicity of diethylene glycol monomethyl ether in the rat." Submitted by Union Carbide, Danbury, CT 06817-0001 to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington DC (August 2, 1985).
- (56) Bringmann, G. and Kuhn, R. "Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test." *Water Research*, 14(3):231-241. (1980).
- (57) Nelson, B.K. Division of Biomedical and Behavioral Science National Institute of Occupational Safety and Health, U.S. Department of Health and Human Services, Cincinnati, OH. Summarized telephone conversation with R. Platz, Dynamac Corporation, 11140 Rockville Pike, Rockville, MD 20852. (February 15, 1984).
- (58) Von Oettingen, W.F., Jirouch, E.A. "The pharmacology of ethylene glycol and some of its derivatives in relation to their chemical constitution and physical chemical properties." *Journal of Pharmacology and Experimental Therapeutics*, 42(3):355-372. (1931).
- (59) Eastman Kodak, Rochester, New York. Comments on Advance Notice of Proposed Rulemaking on 2-(2-Butoxyethoxy)Ethyl Acetate. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington DC 20460. (February 26, 1985).
- (60) Chemical Manufacturers Association, Washington, DC 20037. Comments on EPA's Advance Notice of Proposed Rulemaking on 2-(2-Butoxyethoxy) Ethyl Acetate. Submitted to the Office of Toxic Substances, U.S. Environmental Protection Agency, Washington DC 20460. (February 19, 1985).
- (61) The Dow Chemical Company, Midland, Michigan, 48674. Reference: OPTS-42062. Submitted to U.S. Environmental Protection Agency, Washington DC 20460. (May 5, 1985).
- (62) USEPA. U.S. Environmental Protection Agency. Economics and Technology Division. "Economic Impact Analysis of Proposed Test Rule for Diethylene glycol monobutyl ether and acetate." (May 1986).
- (63) USEPA. U.S. Environmental Protection Agency. Exposure assessment for DGBE and DGBA. Intraagency memorandum from Craig Matthiessen, Chemical Engineering Branch, to Catherine Roman, Test Rules Development Branch, Office of Toxic Substances, Washington, DC 20460. (April 11, 1986).
- (64) Zahn, R. and Wellens, H. "Examination of biological degradability through the batch method—further experience and new possibilities of usage." *Zeitschrift für Wasser und Abwasser Forschung*, 13:1-7. (1980).
- (65) Bridie, A.L., Wolff, C.J.M., and Winter, M. "BOD and COD of some petrochemicals." *Water Research*, 13:62-7630. (1979).
- (66) Lamb, J.C. and Chapin, R.E. "Experimental models of male reproductive toxicology", *Endocrine Toxicology*, pp. 85-115. Eds. J.A. Thomas, K.S. Korach, J.A. McLachlan. New York, NY: Raven Press. (1985).
- (67) Johnson, L., Petty, C.S., and Neaves, W.B. "A comparative study of daily sperm production and testicular composition in humans and rats", *Biology of Reproduction*, 22:1233-1243. (1980).
- (68) Blazak, W.F., Ernst, T.L., and Stewart, B.E. "Potential indicators of reproductive toxicity: Testicular sperm production and epididymal sperm number, transit time and motility in Fischer 344 rats", *Fundamental and Applied Toxicology*, 5:1097-1103. (1985).
- (69) Sadleir, R.M.F.S. "Cycles and Seasons." In *Reproduction in Mammals*:1.

Germ Cells and Fertilization. Eds. C.R. Austin and R.V. Short. Chapter 4. Cambridge Press, New York. (1978).

(70) Mattison, D.R. and Thorgierson, S.S. "Ovarian aryl hydrocarbon hydroxylase activity and primordial oocyte toxicity of polycyclic aromatic hydrocarbons in mice." *Cancer Research*. 39:3471-3475. (1979).

(71) Pederson, T. and Peters, H. "Proposal for classification of oocytes and follicles in the mouse ovary." *Journal of Reproduction and Fertility*. 17:555-557. (1968).

(72) Creasy, D.M. and Foster, P.M.D. "The morphological development of glycol ether-induced testicular atrophy in rat." *Experimental and Molecular Pathology*. 40:169-176. (1984).

(73) Bringmann, G. and Kuhn, R. "Testing of substances for their toxicity threshold: Model organisms *Microcystis (diplocystis) aeruginosa* and *Scenedesmus quadricauda*." *Mitteilungen-Internationale Vereinigung fuer Theoretische und Angewandte Limnologie*. 21:275-284. (1978).

(74) Dawson, G.W., Jennings, A.L., Drozdowski, D., and Rider, E. "The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes." *Journal of Hazardous Materials*. 1(4):303-318. (1977).

(75) Koneman, H. "Quantitative structure-activity relationships in fish toxicity studies. Part I: Relationship for 50 industrial pollutants." *Toxicology*. 19(3):209-221. (1981).

(76) Bridie, A.L., Wolff, C.J.M., Winter, M. "The acute toxicity of some petrochemicals to goldfish." *Water Research*. 13(7):623-626. (1979).

(77) Juhnke, I. and Luedmann, D. "Results of the investigation of 200 chemical compounds for acute fish toxicity with the golden orfe test." *Zeitschrift fur Wasser und Abwasser Forschung*. 11(5):161-164. (1978).

(78) Linden, E., Bengtsson, B.E., Svanberg, O., and Sandstrom, G. "The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the bleak (*Alburnus alburnus*) and the harpacticoid (*Nitocra spinipes*)." *Chemosphere* 11(12):843-851. (1979).

(79) Bringmann, G. and Kuhn, R. "The toxicity of waterborne contaminants towards *Daphnia magna*." *Zeitschrift fur Wasser und Abwasser Forschung*. 10(5):161-166. (1977).

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 in the OPTS Reading Rm. NE-G004, 401 M St., SW., Washington, DC, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

X. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, the EPA must judge whether a regulation is "Major" and therefore subject to the requirement of a Regulatory Impact Analysis. The EPA has determined that this test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order, i.e., it

will not have an annual effect on the economy of at least \$100 million, will not cause a major increase in prices, and will not have a significant adverse effect on competition or the ability of U.S. enterprises to compete with foreign enterprises.

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

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), the EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses because: (1) They will not perform testing themselves, or will not participate in the organization of the testing effort; (2) they will experience only very minor costs in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The information collection requirements contained in this rule have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and have been assigned OMB number 2070-0033. Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs; OMB; 726 Jackson Place; Washington, DC 20503 marked "Attention: Desk Officer for the EPA." The final rule package will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Parts 795 and 799

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

Dated: July 23, 1986.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 795—[AMENDED]

Therefore, it is proposed that 40 CFR Chapter I be amended as follows:

1. In proposed Part 795 (51 FR 15803):
a. The authority citation for Part 795 continues to read as follows:

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

b. By adding § 795.225 to read as follows:

§ 795.225 Pharmacokinetics test standard.

(a) *Purpose*. The purpose of these studies is to compare: (1) The absorption of diethylene glycol butyl ether (DGBE) after administration by the oral and dermal routes,

(2) The biotransformation of DGBE administered orally and dermally, and

(3) The dermal absorption of DGBE and diethylene glycol butyl ether acetate (DGBA).

(b) *Test procedures*—(1) *Animal selection*—(i) *Species*. The species utilized for investigating DGBE and DGBA shall be the rat, a species for which historical data on the toxicity and carcinogenicity of many compounds are available and which is used extensively in percutaneous absorption studies, and the guinea pig, a species whose skin more closely resembles human skin.

(ii) *Animals*. Adult female Fischer 344 rats and Hartley guinea pigs shall be used. The rats shall be 7 to 9 weeks old and weigh 125 to 175 grams, and the guinea pigs, 5 to 7 weeks old and weigh 400 to 500 grams. Prior to testing, the animals shall be selected at random for each group. Animals showing signs of ill health shall not be used.

(iii) *Animal care*. (A) The animals should be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms should be maintained at a temperature of 25 ± 2 °C and humidity of 50 ± 10 percent with a 12 hour light/dark cycle per day. The rats and guinea pigs should be kept in a quarantine facility for at least 7 days prior to use.

(B) During the acclimatization period, the rats and guinea pigs should be housed in cages on hardwood chip bedding. All animals shall be provided with conventional laboratory diets and water *ad libitum*.

(2) *Administration of DGBE and DGBA*—(i) *Test compounds*. These studies require the use of both nonradioactive DGBE and DGBA, and of ¹⁴C-labeled DGBE and DGBA. The use of ¹⁴C-DGBE and ¹⁴C-DGBA is required to investigate items under paragraph (a) (1), (2), and (3) of this section because they will facilitate the work and improve the reliability of quantitative determinations.

(ii) *Dosage and treatment*. (A) Two doses shall be used in the study, a "low" dose and a "high" dose. When administered orally, 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) The same "high" and "low" doses shall be administered orally and dermally.

(C) Oral dosing shall be performed by gavage or by administering encapsulated compounds.

(D) For dermal treatment, the doses shall be applied in a volume adequate to deliver the prescribed doses. The backs of the rats and guinea pigs should be lightly shaved with an electric clipper shortly before treatment. The dose shall be applied with a micropipette on a specific area (2 cm² for rats, 5 cm² for guinea pigs) on the freshly shaven skin. The dosed areas shall be occluded with an aluminum foil patch which is secured in place with adhesive tape.

(iii) *Washing efficiency study.* Before initiation of the dermal absorption studies described in paragraph (b)(2)(iv)(A) and (B) of this section, an initial washing efficiency experiment shall be performed to assess the extent of removal of the applied DGBE and DGBA by washing with soap and water. Groups of four rats and 4 guinea pigs should be lightly anesthetized with sodium pentobarbital. These animals shall then be treated with dermal doses of test compound at the low dose level. Soon after application (5 to 10 min) the treated animals shall be washed with soap and water then housed in individual metabolism cages for excreta collection. Urine and feces shall be collected at 8, 24, and 48 hours following dosing. Collection of excreta shall continue every 24 hours if significant amounts of DGBE, DGBA or metabolites continue to be eliminated.

(iv) *Determination of absorption, biotransformation, and excretion.* (A) Rat studies. (1) Eight animals shall be dosed once orally with the low dose of ¹⁴C-DGBE.

(2) Eight animals shall be dosed once orally with the high dose of ¹⁴C-DGBE.

(3) Eight animals shall be dosed once dermally with the low dose of ¹⁴C-DGBE.

(4) Eight animals shall be dosed once dermally with the high dose of ¹⁴C-DGBE.

(5) Eight animals shall be dosed once dermally with the low dose of ¹⁴C-DGBA.

(6) Eight animals shall be dosed once dermally with the high dose of ¹⁴C-DGBA.

(7) In the oral studies, the animals shall be placed in individual metabolic cages for collection of excreta at 8, 24, 48, 72 and 96 hours following administration.

(8) In the dermal studies, doses of ¹⁴C-DGBE and ¹⁴C-DGBA shall be kept on the skin for the duration of the study (96 hours). After application, the animals

shall be placed in metabolism cages for excreta collection. Urine and feces shall be collected at 8, 24, 48, 72 and 96 hours.

(B) *Guinea pig studies.* The same procedures shall be followed as specified in paragraph (b)(2)(iv)(A) (7) through (8) of this section.

(3) *Observation of animals—(i) Urinary and fecal excretion.* The quantities of total ¹⁴C excreted in urine and feces by rats dosed as specified in paragraph (b)(2)(iv)(A) of this section and guinea pigs dosed as specified in paragraph (b)(2)(iv)(B) of this section shall be determined 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). Four animals from each group shall be used for this purpose.

(ii) *Biotransformation after oral and dermal dosing.* Appropriate qualitative and quantitative methods shall be used to assay urine specimens collected from rats dosed with DGBE as specified in paragraph (b)(2)(iv)(A) of this section and from guinea pigs as specified in (b)(2)(iv)(B) of this section. Any metabolite which comprises greater than 10 percent of the dose shall be identified.

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

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

(3) *Test report.* In addition to the reporting requirements as specified in the TSCA Good Laboratory Practice Standards, 40 CFR Part 792, Subpart J, the following specific information shall be reported:

(i) Species, strain, and supplier of laboratory animals.

(ii) Information on the degree (i.e., specific activity for a radiolabel) and site(s) of labeling of the test substances.

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

(iv) Relative percent absorption by the dermal route for rats and guinea pigs administered low and high doses of ¹⁴C-DGBE and ¹⁴C-DGBA.

(v) Quantity of isotope, together with percent recovery of the administered dose, in feces and urine.

(vi) Biotransformation pathways and quantities of DGBE and metabolites in urine collected after administering single high and low oral and dermal doses to rats and guinea pigs.

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. By adding § 799.1560 to read as follows:

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

(a) *Identification of test substances.* (1) Diethylene glycol butyl ether (DGBE), CAS Number 112-34-5 and diethylene glycol butyl ether acetate (DGBA), CAS Number 124-17-4 shall be tested in accordance with this section.

(2) Compounds of at least 95 percent purity shall be used as the test substances.

(b) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture or process DGBE and/or DGBA other than as an impurity, from the effective date of this section (44 days after the publication date of the final rule in the **Federal Register**) to the end of the reimbursement period, shall submit letters of intent to conduct testing, submit study plans, and conduct tests or submit exemption applications in accordance with Part 792 of this chapter. Those conducting tests of DGBE must submit data as specified in this section other than the test for DGBA in § 799.1560(c)(6), Subpart A of this Part, and Part 790 of this chapter for single-phase rulemaking. Only persons who manufacture or process DGBA are subject to the requirements for DGBA in § 799.1560(c)(6).

(c) *Health effects testing—(1) Subchronic toxicity—(i) Required testing.* (A) A 90-day subchronic toxicity test of DGBE shall be conducted in rats by dermal application in accordance with § 798.2250 of this chapter.

(B) Modifications: The following modifications shall be incorporated in § 798.2250 of this chapter for testing DGBE.

(1) *Dose level and dose selection.* The requirement under § 798.2250(e)(4)(iii) of this chapter is modified so that the lowest doses to be administered will be 1 mg/kg/day and 15 mg/kg/day.

(2) *Observations.* The requirement under § 798.2250(e)(9)(iv) of this chapter is modified so that cage-side observations shall include daily examination for hematuria.

(3) *Hematology.* The requirement under § 798.2250(e)(10)(i)(A) of this chapter is modified so that hematology determinations shall be carried out 1, 2, 4, 6, 10, and 14 days following initiation of dosing in addition to the other times specified. At all hematologic determinations additional

measurements shall include a platelet count and mean corpuscular volume.

(4) *Clinical biochemistry.* The requirement under § 798.2250(e)(10)(i)(B) of this chapter is modified so that clinical biochemistry determinations shall be carried out 24 to 48 hours following initiation of dosing in addition to the other times specified.

(5) *Urinalysis.* The requirement under § 798.2250(e)(10)(ii)(B) of this chapter is modified so that urinalyses shall be done at least three times during the test period: just prior to initiation of dosing (baseline data), after approximately 30 days on test and just prior to terminal sacrifice at the end of the test period. The animals shall be kept in metabolism cages, and the urine shall be examined microscopically for the presence of erythrocytes and renal tubular cells, in addition to measurement of urine volume, specific gravity, glucose, protein/albumin and blood.

(6) *Fertility test.* A satellite group to evaluate fertility shall be established. Control males and males administered the high dose shall be mated to non-exposed partners. Control females and females administered the high dose shall be mated to non-exposed partners. If the animals in the high dose group exhibit marked toxicity (e.g. greater than 20 percent weight loss), then the fertility tests shall be conducted in the next highest dose group. Endpoints to be evaluated for the male fertility test shall include percent mated, percent pregnant, pre- and post-implantation loss (with females sacrificed on day 15 of pregnancy). Endpoints to be evaluated for the female fertility test shall include length of gestation, litter size and viability, sex of offspring, birth weight, and survival to day 4.

(7) *Liver-function tests.* The requirement under § 798.2250(e)(10)(ii) of this chapter is modified to add required testing for liver clearance using five rats per sex per dose with sulfobromophthalein (BSP) and a like number using indocyanine green (ICG). The same animals shall be tested at three times during the test period: just prior to initiation of dosing (baseline data), after approximately 30 days on test and just prior to terminal sacrifice at the end of the test period.

(8) *Organ weights.* The requirement under § 798.2250(e)(11)(ii) of this chapter is modified so that the prostate gland, the epididymes, seminal vesicles and pituitary gland weights shall be determined wet, as soon as possible after dissection.

(9) *Gross pathology.* The requirement under § 798.2250(e)(11)(iii) of this chapter is modified so that the following additional organs shall be preserved in a

suitable medium for future histopathologic examination: The vas deferens, the oviducts and the vagina.

(10) *Histopathology.* The requirement under § 798.2250(e)(12)(i) of this chapter is modified so that the accessory genital organs (epididymides, prostate, seminal vesicles) and the vagina shall be examined histopathologically. In addition, the integrity of the various cell stages of spermatogenesis shall be determined, with particular attention directed toward achieving optimal quality in the fixation and embedding; preparations of testicular and associated reproductive organ samples for histology should follow the recommendations of Lamb and Chapin (1985) under paragraph (d)(1) of this section, or an equivalent procedure. Testicular spermatid counts shall be performed; the method described by Johnson *et al.* (1980) and Blazak *et al.* (1985) under paragraph (d) (2) and (3) of this section or an equivalent procedure should be used. Epididymal sperm count and sperm morphology shall also be done. Data on female cyclicity shall be obtained by performing vaginal cytology over the last two weeks of dosing; the method of Sadleir (1978) under paragraph (d)(4) of this section or an equivalent method should be used. The histopathology of the ovary to evaluate oocyte toxicity shall be performed; the method of Mattison (1979) and Pederson (1968) under paragraph (d) (5) and (6) of this section or an equivalent method should be used.

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

(B) Progress reports shall be submitted to the Agency every 6 months, beginning 6 months from the effective date of the final rule.

(2) *Neurotoxicity/behavioral effects—*(i) *Required testing.* Neurotoxicity/behavioral tests of DGBE shall be conducted according to a functional observational battery (§ 798.6050 of this chapter), motor activity (§ 798.6200 of this chapter), and neuropathology (§ 798.6400 of this chapter). The tests shall be performed in the rat by dermal administration for a period of 90 days.

(ii) *Modification.* If these three tests are combined, at least ten animals per sex per dose level shall be used.

(iii) *Reporting requirements.* (A) The neurotoxicity/behavioral tests shall be completed and final results submitted to the Agency within 15 months of the effective date of the final rule.

(B) Progress reports shall be submitted to the Agency every 6 months, beginning

6 months from the effective date of the final rule.

(3) *Mutagenicity—*(i) *Required testing.* (A) A somatic cells in culture assay of DGBE using Chinese hamster ovary (CHO) cells shall be conducted in accordance with § 798.5300 of this chapter.

(B) An *in vivo* cytogenetics test of DGBE shall be conducted in rats or mice or hamsters by oral gavage in accordance with § 798.5385 of this chapter.

(C) A dominant lethal assay of DGBE shall be conducted in rats or mice by oral gavage in accordance with § 798.5450 of this chapter if the *in vivo* cytogenetics test is not negative.

(D) A heritable translocation test of DGBE shall be conducted in mice by oral gavage in accordance with § 798.5460 if the dominant lethal assay is positive.

(ii) *Reporting requirements.* (A) Mutagenicity tests shall be completed and final results submitted to the Agency as follows: somatic cells in culture using CHO cells, within 6 months; *in vivo* cytogenetics, within 8 months; dominant lethal assay (if triggered), within 18 months of the effective date of the final rule; and heritable translocation, if required, within 45 months of the effective date of the final rule.

(B) A progress report for the *in vivo* cytogenetics test will be submitted to the Agency within 6 months of the effective date of the final rule. A progress report for the dominant lethal assay shall be submitted to the Agency within 6 months of the date when the test is triggered. Progress reports for the heritable translocation test shall be submitted every 6 months, beginning 6 months after the test is triggered.

(4) *Oncogenicity—*(i) *Required testing.* An oncogenicity test of DGBE shall be required unless negative results are obtained in both of the following tests: the somatic cells in culture assay using Chinese hamster ovary cells and the *in vivo* cytogenetics test. The test shall be performed by dermal application in accordance with § 798.3300 of this chapter. The test species shall be rats and mice.

(ii) *Reporting requirements.* (A) The oncogenicity test, if triggered, shall be completed and the final results submitted to the Agency within 56 months of the effective date of the final rule.

(B) Progress reports shall be submitted every 6 months, beginning 6 months after the test is triggered.

(5) *Developmental neurotoxicity—*(i) *Required testing.* A developmental

neurotoxicity test of DGBE shall be performed in rats in accordance with § 795.250 of this chapter by dermal application as specified under § 798.3300 (b)(6)(ii) of this chapter as published in the *Federal Register* of May 15, 1986 (51 FR 17883).

(ii) *Reporting requirements.* (A) The developmental neurotoxicity test shall be completed and the results submitted to the Agency within 1 year of the effective date of the final test rule.

(B) A Progress report shall be submitted to the Agency 6 months from the effective date of the final rule.

(6) *Pharmacokinetics*—(i) *Required testing.* Pharmacokinetics tests of DGBE and DGBA will be conducted in rats and guinea pigs by the dermal (DGBE and DGBA) and oral (DGBE only) routes of administration in accordance with § 795.225 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetics tests shall be completed and final results submitted to the Agency within 1 year of the effective date of the final rule.

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

(d) *References.* For additional background information the following references should be consulted:

(1) Lamb, J.C. and Chapin, R.E. "Experimental models of male reproductive toxicology", *Endocrine Toxicology*, pp. 85-115. Eds. J.A. Thomas, K.S. Korach, J.A. McLachlan. New York, NY: Raven Press. (1985).

(2) Johnson, L., Petty, C.S., and Neaves, W.B. "A comparative study of daily sperm production and testicular composition in humans and rats", *Biology of Reproduction*, 22:1233-1243. (1980).

(3) Blazak, W.F., Ernst, T.L., and Stewart, B.E. "Potential indicators of reproductive

toxicity: Testicular sperm production and epididymal sperm number, transit time and motility in Fischer 344 rats", *Fundamental and Applied Toxicology*, 5:1097-1103. (1985).

(4) Sadleir, R.M.F.S. "Cycles and Seasons." In *Reproduction in Mammals: I. Germ Cells and Fertilization*. Eds. C.R. Austin and R.V. Short. Chapter 4. Cambridge Press, New York. (1978).

(5) Mattison, D.R. and Thorgiersson, S.S. "Ovarian aryl hydrocarbon hydroxylase activity and primordial oocyte toxicity of polycyclic aromatic hydrocarbons in mice." *Cancer Research*, 39:3471-3475. (1979).

(6) Pederson, T. and Peters, H. "Proposal for classification of oocytes and follicles in the mouse ovary." *Journal of Reproduction and Fertility*, 17:555-557. (1968).

(Information collection requirements approved by the Office of Management and Budget under control number 2070-0033)

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