

40 CFR Part 799

[OPTS-42051; TSH-FRL 2480-7]

Toxic Substances; Glycidol and Its Derivatives; Response to the Interagency Testing Committee**AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Advance notice of proposed rulemaking.

SUMMARY: In October, 1978, the Interagency Testing Committee (ITC) designated the category "glycidol and its derivatives" for priority consideration for testing under TSCA section 4(a), and recommended testing for carcinogenic, mutagenic, teratogenic, and other adverse health effects. The ITC also recommended that epidemiological studies be conducted. EPA is publishing this Advance Notice of Proposed Rulemaking under section 4(a) of TSCA to (1) inform the public of the rationale EPA proposes to use in its selection of chemicals from this category for testing; (2) define the testing EPA is considering proposing; and (3) seek public comment on EPA's plan to propose a test rule for this category of chemical substances. This action constitutes EPA's response to the ITC for the category "glycidol and its derivatives."

DATE: Written comments should be submitted on or before February 28, 1984.

ADDRESS: Address written comments identified by the document control number (OPTS-42051) in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Room E-108, 401 M St., SW., Washington, D.C. 20460.

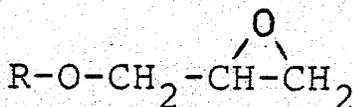
FOR FURTHER INFORMATION CONTACT: Jack P. McCarthy, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Room E-543, 401 M St., SW., Washington, D.C. 20460. Toll Free: (800-424-9065), In Washington, D.C.: (544-1404), Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION:**I. Background**

Section 4(a) of TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et*

seq.) authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances and mixtures by manufacturers and processors in order to develop data relevant to determining the risks that such chemicals may present to health and the environment. In order to make a section 4(a)(1)(A) finding, EPA must determine that the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or any combination of such activities, may present an unreasonable risk of injury to health or the environment, that insufficient data exist to characterize the potential effects of that chemical to human health or the environment and that testing is necessary to develop such data. In order to make a section 4(a)(1)(B) finding, EPA must determine that a substance is produced in substantial quantities and that there is or may be significant or substantial human exposure or substantial environmental release of that substance, that there are insufficient data to characterize the potential effects of that chemical to human health or the environment, and that testing is necessary to develop such data.

Section 4(e) of TSCA established the Interagency Testing Committee (ITC) to recommend to the Administrator of EPA those chemicals that should receive priority consideration for proposed test rules under section 4(a). The ITC transmitted its Third Report to the Administrator of EPA in October, 1978, as published in the Federal Register of October 30, 1978 (43 FR 50630). The ITC designated the category "glycidol and its derivatives" for priority testing consideration and recommended testing to evaluate their potential to cause adverse health effects. The glycidol category was defined by the ITC as all chemicals of the general formula:



where R is any alkyl, aryl, or acyl group. R is unrestricted as to the number and type of substituents it may carry.

Chemicals in this category are used primarily as reactive diluents in epoxy resins, although the major use of glycidol itself is as a stabilizer in the production of vinyl polymers (Ref. 20).

In its report, the ITC recommended that this category be considered for testing for mutagenicity, carcinogenicity, teratogenicity, and other adverse health effects, with particular emphasis on the reproductive system. Epidemiological

studies were also recommended. The category was not recommended for environmental effects testing or environmental fate studies.

II. Response of EPA to the ITC

EPA has reviewed the ITC's report, the data on which its recommendations were based, and information obtained from EPA's own information-gathering activities. The Agency agrees, in general, with the ITC's recommendation that members of the glycidol category be considered for health effects testing. Section 26(c) of TSCA authorizes EPA to regulate categories of chemical substances under any provision of TSCA if the chemicals in a given category are "similar in molecular structure, in physical, chemical, or biological properties * * *"

EPA has previously indicated that although it would generally initiate rulemaking for testing through publication of a proposed rule, it may initiate action on chemical categories and certain complex chemicals through publication of an Advance Notice of Proposed Rulemaking (ANPR). There are several reasons, both general to categories and specific to the glycidol category, why the Agency has chosen to use this approach to initiate rulemaking with respect to the ITC designation of glycidol and its derivatives.

The Agency has found that in developing rules for chemical categories, the issues that require attention are considerably more complex and numerous than those in a rulemaking for a single chemical. These complex issues thus require considerable additional time to resolve.

For example, in order to avoid unnecessary or duplicative testing while assuring that adequate data are developed, the Agency needs to determine whether it is scientifically valid to test one or more representative chemicals rather than to test each individual chemical in a category. One method of achieving this goal is through the use of structure-activity relationships (SAR). The Agency believes that there is a logical basis for pursuing SAR along the lines proposed in this notice (i.e., subcategorization according to structure of the glycidol derivatives).

Identifying appropriate subcategories of glycidol derivatives is only part of the effort necessary for development of a proposed test rule for this category. In addition, EPA must review data related to exposure, release, hazard, testing costs, and economic impact for many chemicals. In the case of the glycidol category, EPA has identified 65 substances on the Public TSCA

Inventory of Chemical Substances that fit within the category definition. Those substances on the Public TSCA Inventory are listed in Table 1. A few additional compounds in this category are on the Confidential TSCA Inventory.

TABLE 1.—GLYCIDOL DERIVATIVES LISTED ON PUBLIC TSCA INVENTORY

| Chemical | CAS No. |
|---|------------|
| Glycidol | 556-52-5 |
| GLYCIDYL ETHERS | |
| Resorcinol diglycidyl ether | 101-90-8 |
| Allyl glycidyl ether | 106-92-3 |
| Phenyl glycidyl ether | 122-60-1 |
| 1,3-Bis [3-(2,3-epoxypropoxy) propyl] tetramethyldisiloxane | 126-80-7 |
| Methyl glycidyl ether | 930-37-0 |
| Bisphenol A diglycidyl ether | 1675-54-3 |
| o-Cresyl glycidyl ether | 2210-79-9 |
| Ethylene glycol diglycidyl ether | 2224-15-9 |
| Diglycidyl ether | 2238-07-5 |
| Hydroquinone diglycidyl ether | 2425-01-6 |
| 1,4-Butanediol diglycidyl ether | 2425-79-3 |
| n-Butyl glycidyl ether | 2426-08-3 |
| 2-Ethylhexyl glycidyl ether | 2461-15-6 |
| Lauryl glycidyl ether | 2461-18-9 |
| 3-(Trimethoxysilyl)propyl glycidyl ether | 2530-83-8 |
| 3-(Methyldiethoxysilyl)propyl glycidyl ether | 2897-60-1 |
| p-tert-Butylphenyl glycidyl ether | 3101-60-8 |
| 2-Methylol-4,4'-isopropylidenediphenol diglycidyl ether | 3188-83-8 |
| Glycerol 1,3-diglycidyl ether | 3566-29-4 |
| Ethyl glycidyl ether | 4016-11-9 |
| Isopropyl glycidyl ether | 4016-14-2 |
| 4-(Diglycidylamino)phenyl glycidyl ether | 5026-74-4 |
| p-Nitrophenyl glycidyl ether | 5255-75-4 |
| p-Nonylphenyl glycidyl ether | 6178-32-1 |
| 1,1,2,2-Tetra(p-hydroxyphenyl)ethane tetraglycidyl ether | 7328-97-4 |
| 3-(Bis(trimethylsiloxy)methyl)propyl glycidyl ether | 7422-52-8 |
| tert-Butyl glycidyl ether | 7665-72-7 |
| Glycerol triglycidyl ether | 13238-02-7 |
| 2,6-Diglycidylphenyl glycidyl ether | 13561-09-5 |
| 1,4-Bis(glycidoxymethyl)cyclohexane | 14228-73-0 |
| Hexadecyl glycidyl ether | 15965-99-8 |
| n-Octadecyl glycidyl ether | 18245-97-9 |
| Neopentyl glycol diglycidyl ether | 17557-23-2 |
| 3-(Dimethylethoxysilyl)propyl glycidyl ether | 17963-04-1 |
| 2,4-Dibromophenyl glycidyl ether | 20217-01-0 |
| 2,6-Dibromo-4-methylphenyl glycidyl ether | 22421-59-6 |
| Cresyl glycidyl ether (mixed isomers) | 24447-14-3 |
| 3-(2-Glycidoxypropyl)-1-glycidyl-5,5-dimethylhydantoin | 32568-89-1 |
| 1,2-Dibromopropyl glycidyl ether | 35243-89-1 |
| 1,3-Bis(5,5-dimethyl-1-glycidylhydantoin-3-yl)-2-glycidyoxypropane | 38304-52-8 |
| Tetradecyl glycidyl ether | 38054-75-5 |
| Bisphenol F diglycidyl ether | 54208-63-8 |
| Allyl glycidyl ether | 60501-41-9 |
| p-Cumylphenyl glycidyl ether | 61578-04-9 |
| 2,2'-[[[2-(Oxiranylmethoxy)phenyl]methylene]bis(4,1-phenyleneoxyethylene)]bis(oxirane) | 67796-03-2 |
| Alkyl (C10-C16) glycidyl ether | 68081-84-5 |
| 1,3-Dimethylbutyl glycidyl ether | 68134-06-5 |
| 6-Methylheptyl glycidyl ether | 68134-07-6 |
| Tris(4-hydroxyphenyl)propane triglycidyl ether | 68517-02-2 |
| Alkyl (C8-C10) glycidyl ether | 68603-96-1 |
| Alkyl (C12-C14) glycidyl ether | 58603-97-2 |
| 1,2,6-Hexanetriol triglycidyl ether | 68959-23-9 |
| Alkyl (C6-C12) glycidyl ether | 68987-80-4 |
| 1,1,1,3,5,7,7-Octamethyl-3,5-bis(6,7-epoxy-4-oxaheptyl)tetrasiloxane | 69155-42-6 |
| 2,2-Bis(p-(2-glycidyoxy-3-butoxypropoxy)phenyl)propane | 71033-08-4 |
| 3-[(3-Chloropropyl)dimethoxysilyl]propyl glycidyl ether | 71808-64-5 |
| 2,2'-[[1-Methylethylidene]bis[4,1-phenyleneoxy-3,1-propanedioldoxy-4,1-phenylene(1-methylethylidene)-4,1-phenyleneoxyethylene]]bis(oxirane) | 72319-24-5 |
| 2,4-Dibromo-6-methylphenyl glycidyl ether | 75150-13-9 |
| GLYCIDYL ESTERS | |
| Glycidyl acrylate | 106-90-1 |
| Glycidyl methacrylate | 106-91-2 |
| Diglycidyl ester of hexahydrophthalic acid | 5493-45-6 |
| Diglycidyl ester of phthalic acid | 7195-45-1 |

TABLE 1.—GLYCIDOL DERIVATIVES LISTED ON PUBLIC TSCA INVENTORY—Continued

| Chemical | CAS No. |
|---|------------|
| Glycidyl ester of neodecanoic acid | 26761-45-5 |
| 1,2,3-Phopaneetriyl ester of 12-(oxiranylmethoxy)-9-octadecanoic acid | 74398-71-3 |

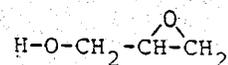
As part of EPA's data-gathering efforts on various substances, including glycidol and its derivatives, the Agency promulgated two rules. The first, published in the Federal Register of June 22, 1982 (47 FR 26992), required, pursuant to section 8(a) of TSCA, that manufacturers of specified chemicals supply the Agency with certain production data and other information relating to potential exposure and release of the substances in question. The second rule, published September 2, 1982 (47 FR 38780), required, pursuant to section 8(d) of TSCA, that manufacturers of the specified chemicals supply the Agency with all unpublished health and safety studies in their possession relating to the chemicals. Publication of the section 8(d) rule has resulted in the submission to EPA of a large number of studies in the period October 4, 1982, to the present. In addition, in June, 1983, an industry trade group, the Epoxy Resins Panel of the Chemical Manufacturers Association (CMA), submitted to EPA its tentative recommendations for the subcategorization of the glycidol derivatives (Ref. 2). CMA's suggested approach, as well as much of the recently submitted health and safety data, are undergoing Agency review.

In addition to the conceptual difficulties EPA has in directly preparing a proposed rule on a category of this size and complexity, EPA believes there are positive advantages in using an ANPR to initiate the process of rulemaking for testing this category of chemicals. Publication of this notice provides an opportunity for public comment on the difficult issues involved in the use of subcategories based on chemical structure before the Agency expends its resources on developing a proposed test rule for glycidol and its derivatives. Due to the complexity of the issues involved, development of a proposed test rule prior to receiving such input may result in needless expenditure of Agency resources and considerable delay in rule promulgation due to the potential volume of public comments on the proposed rule. For these reasons EPA has chosen to initiate rulemaking by issuing an ANPR in response to the ITC designation of the category "glycidol and its derivatives."

III. General Information

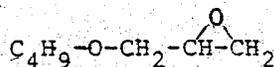
A. Chemical Description

As described in Unit I, the members of this category include glycidol and its derivatives. The term "derivatives" should not be interpreted in the production sense. That is, these derivatives (glycidyl ethers and glycidyl esters) are generally produced using epichlorohydrin and not glycidol itself (see Unit III.B). The structure of glycidol, or 2,3-epoxy-1-propanol (CAS No. 556-52-5), is given below:

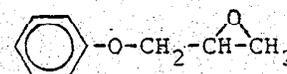


glycidol

Replacing the hydroxyl hydrogen with either an alkyl or aryl group yields a glycidyl ether. Two common glycidyl ethers are n-butyl glycidyl ether (CAS No. 2426-08-6) and phenyl glycidyl ether (CAS No. 122-60-1):

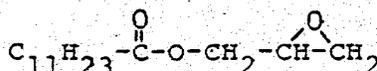


n-butyl glycidyl ether



phenyl glycidyl ether

Replacing the hydroxyl hydrogen with an acyl group results in a glycidyl ester. An example of this type of compound is glycidyl laurate (CAS No. 1984-77-6):



glycidyl laurate

Note that all glycidol derivatives have, by definition, at least one epoxide group. Epoxide compounds in general are known for their strong alkylating ability, and it is this property of glycidol derivatives that makes them particularly useful as reactive diluents in two-part epoxy resins.

B. Manufacturing Processes

The following descriptions of the manufacturing processes for glycidol and its derivatives are taken from two EPA contractor reports (Refs. 20 and 40). The first step in the production of glycidol itself involves the hydrolysis of epichlorohydrin to chloroglycerin; the latter compound is then reacted with sodium methylate to form glycidol. Glycidyl ethers are commercially synthesized in closed systems by the addition of the appropriate alcohol to epichlorohydrin in the presence of a catalyst. Glycidyl esters are commercially produced by reacting sodium salts of carboxylic acids with epichlorohydrin.

C. Production and Use

Over 10 million pounds of glycidyl compounds are produced or imported annually, with glycidyl ethers accounting for most of this amount (Ref. 24).

Glycidol is used primarily as a stabilizer during the production of certain vinyl polymers. To a lesser

extent, it is also used as a raw material for (1) a pharmaceutical intermediate, (2) a constituent in a solid propulsion system, (3) an oil additive, (4) a synthetic hydraulic fluid, and (5) a dyestuff. Glycidol is also used in some epoxy resins.

Glycidyl ethers are used almost exclusively as reactive diluents in epoxy resin systems. These resins in turn are used in a wide variety of situations requiring strong adhesives or coatings. Glycidyl esters are used for the same purposes as the glycidyl ethers, although to a much lesser degree.

D. Potential for Adverse Health Effects

EPA has reviewed much of the literature on the health effects of glycidol and its derivatives (Ref. 19), and it is still reviewing unpublished health and safety studies submitted under TSCA section 8(d) as well as other studies published recently in the scientific literature. Some conclusions, based on EPA's review to date, are given below:

1. Glycidol and some glycidyl ethers and esters appear to be skin irritants and skin sensitizers (Refs. 14, 22, 28, 29, 37, and 42).

2. There is evidence indicating that direct application of some glycidyl ethers to the eyes of laboratory animals causes corneal opacity (Ref. 30). This effect has also been observed in laboratory animals following exposure to the vapors of some glycidyl ethers (Refs. 14 and 25).

3. Some glycidyl ethers have been shown to cause atrophy of lymphoid tissue, as well as changes in blood-forming elements such as polymorphonuclear cells, other types of leukocytes, and myeloid/erythroid ratios in laboratory animals (Ref. 23).

4. One study suggests that triethyleneglycol diglycidyl ether (CAS No. 1954-28-5) may cause nerve damage in dogs (Ref. 1).

5. Glycidol itself appears to cause temporary sterility in rats (Refs. 4, 13, and 18), and some glycidyl ethers may produce testicular atrophy in several laboratory animals (Refs. 15, 27 and 35).

6. Several studies indicate that glycidol and some glycidyl ethers and esters are mutagenic in various test systems (Refs. 5, 6, 10, 17, 21, 27, 31, 32, and 36). This effect may be due to the high degree of chemical reactivity of the epoxide group common to all glycidyl compounds.

7. The limited information available on the oncogenic potential of these chemicals suggests that some of them elicit and oncogenic response in laboratory animals (Refs. 7, 16, and 34), while others may not (Refs. 12, 34, 38, 39, and 41).

E. Potential for Exposure

EPA has reviewed the available information relating to the potential for human exposure to glycidol and its derivatives (Ref. 20). Some of the Agency's preliminary conclusions on the potential for exposure to glycidol and its derivatives are as follows:

1. Because the primary use of glycidol itself, as a stabilizer in the manufacture of vinyl polymers, involves closed reaction vessels, worker exposure to this compound is expected to be low. EPA does note, however, that the use of "closed" systems may result in some exposure, with the potential for higher level, intermittent exposures existing during spills, leaks, or maintenance operations.

2. Glycidyl ethers and esters are more widely used in open systems, and worker exposure, both inhalation and dermal, is more likely to occur at higher levels for these compounds than for glycidol itself.

3. There is a potential for both consumer and commercial exposure to the glycidyl ethers and esters because these compounds, particularly the ethers, appear to be widely used in two-part epoxy resin adhesives.

Preliminary estimates of potential exposure ranges resulting from the consumer and commercial use of epoxy resins containing glycidyl ethers have been generated using the limited, available exposure data and newly developed mathematical models (see Table 2).

TABLE 2.—ESTIMATED HUMAN EXPOSURE TO GLYCIDYL ETHERS

| Use | Exposure (mg/year/individual) | |
|-----------------|--|--|
| | Inhalation | Dermat |
| Consumer..... | 7.1 to 71 | 104 to 1,040 |
| Commercial..... | 1.4×10^8 to 1.4×10^9 | 1.5×10^8 to 1.5×10^9 |

Source: Ref. 40.

The extent of consumer and commercial exposure of glycidyl esters is unclear. Exposure to these compounds is expected to be considerably lower than that for glycidyl ethers (Ref. 40). The Agency is interested in receiving additional information and comment on this issue.

Recent estimates suggest that about three million people in the United States may be exposed to glycidyl ethers through the combined consumer and commercial use of epoxy resins (Ref. 40). In an earlier document (Ref. 26), the National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 118,000 workers in the United States were potentially exposed to glycidyl ethers, and that an additional one million workers may be exposed to epoxy resins. NIOSH recommended 15-minute airborne "ceiling concentration limits" for several glycidyl ethers (see Table 3) based on the results of

TABLE 3.—NIOSH-RECOMMENDED 15-MINUTE EXPOSURE LIMITS FOR GLYCIDYL ETHERS

| Chemical | NIOSH Recommendation (ppm) |
|--------------------------------|----------------------------|
| Isopropyl glycidyl ether..... | 50 |
| Allyl Glycidyl ether..... | 9.6 |
| n-Butyl glycidyl ether..... | 4.4 |
| Phenyl glycidyl ether..... | 1 |
| Di(2,3-epoxypropyl) ether..... | 0.2 |

Source: Ref. 26.

studies with laboratory animals and reported dermal effects in humans. These limits were intended to protect workers from skin irritation and sensitization, as well as other systemic effects. On the basis of its initial review, EPA has determined that exposure data for glycidol and its derivatives are insufficient for the Agency to evaluate the risk potential for human health effects of these compounds. The Agency is thus considering requiring, as part of a test rule for these compounds, the development of such data through monitoring and other exposure studies.

IV. Tentative EPA Decisions and Issues

A. Development of Rulemaking

After reviewing the ITC report and public comments pertaining to it, and after reviewing more recent published

and unpublished studies, EPA believes there is reason to proceed with development of a proposed rule for the testing of glycidol and its derivatives. A bibliography of all published and unpublished studies received by the Agency to date is available for review as part of the Public Record (see Unit VII). The Agency, in publishing this ANPR, wishes to receive early comment on its tentative basis for requiring testing and on the use and composition of the subcategories described herein.

B. Preliminary Findings

At this time, the Agency believes that the category of glycidol and its derivatives may meet the criteria for a finding under section 4(a)(1)(A)(i): That "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." This belief is based on the evidence of the potential for adverse health effects summarized in Units III.D and III.E.

The Agency also believes that this category of compounds may meet the criteria for a finding under section 4(a)(1)(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." Because many glycidol derivatives are present in common consumer products (i.e., epoxy resins), EPA believes there is a potential for substantial exposure of humans (see Unit III.E above).

Further, the Agency currently believes that the available data are inadequate to reasonably determine or predict the adverse health effects of glycidol and its derivatives, and that testing may be necessary to develop such data.

C. Use of Subcategories

The EPA's analysis of a structurally-based chemical category for testing consideration is intended to allow the simultaneous consideration of several chemicals with structural or other similarities. Development of a test rule in such circumstances can be facilitated through the use of structure-activity relationships whereby the biological effects of one compound can be inferred from data on one or more compounds of similar chemical structure.

Two methods for the selection of test candidates that EPA considers realistic are as follows: (1) require testing of only those compounds that are currently

produced in significant quantities and/or those compounds posing the greatest potential for human exposure; or (2) divide this large category of chemicals into smaller groups (subcategories) of chemicals, select representative chemicals from each subcategory to undergo testing (taking into account production and exposure factors to the extent possible), and extrapolate the test results obtained on these chemicals to other chemicals in the group. A similar approach has been proposed for other chemical categories such as the fluoroalkenes (46 FR 53704, October 30, 1980) and phenylenediamines (47 FR 973, January 8, 1982).

EPA considered both options carefully, and the Agency's major reasons for taking the second approach with glycidol and its derivatives are discussed below.

1. *Economic impact.* Although EPA has not completed its assessment of the economic impact of testing chemicals in this category, it appears, from the Agency's preliminary analysis, that the industry cannot financially support the full range of ITC-recommended tests on each glycidol derivative (Ref. 24). While adverse economic effects per se do not preclude the issuance of a test rule, economic impact is an important consideration during test rule development. Consequently, the Agency is seeking to utilize a method that will establish testing requirements for a reasonable number of compounds, and that will enable the test results to be used to reasonably predict the toxic effects of this chemical category.

2. *Nature of the epoxy resins industry.* EPA's preliminary analysis of the epoxy resins industry suggests that substitution of one glycidyl compound for another in a given product is not uncommon. Consequently, a compound that is currently produced in large quantities may be produced in only small quantities in the near future. Likewise, compounds that are not currently produced in large amounts may be produced in much greater quantities in the future because of changes in market demand. Thus, testing only those compounds currently produced in large quantities, without considering how their toxicity relates to that of other category members, may not be the most reliable approach to defining testing requirements with the ultimate goal of protecting human health.

3. *Size and diversity of the category.* The category of glycidol derivatives under consideration for a test rule contains over 60 chemicals listed on the TSCA Inventory. These chemicals vary considerably in structure and molecular size, from the small methyl ether of glycidol (molecular weight=88) to the very large tetra(p-hydroxyphenyl)ethane tetraglycidyl ether (molecular weight=598). It is logical to assume that significant differences among the chemical structures of these compounds are likely to result in significant differences among their physical and chemical properties, pharmacokinetic parameters (e.g., dermal penetration, metabolism), and toxicities. Separation of this large category into several subcategories based on chemical structure will facilitate the Agency's selection of chemicals to be tested and

allow appropriate inferences to be drawn from the test results for subsequent regulatory actions.

4. *Future regulation of glycidol derivatives.* Section 26(c) of TSCA authorizes EPA to regulate chemical categories (see Unit II). Addressing the testing needs for glycidol derivatives using well defined subcategories will facilitate any future Agency action on chemicals that belong, on the basis of structure, in any of these subcategories.

D. Definition of Subcategories

EPA has tentatively decided to organize the derivatives of glycidol under consideration for a test rule into seven subcategories, with glycidol itself addressed separately. The Agency's proposed subcategories are listed in Table 4.

Table 4--Subcategories of Glycidol Derivatives.

| $R-O-CH_2-\overset{O}{\underset{\text{O}}{\text{C}}}-CH_2$ | |
|--|---|
| Subcategory | Description of R |
| I | Small (less than eight carbons) alkyl group with no epoxide moiety. |
| II | Large (eight carbons or more) alkyl group with no epoxide moiety. |
| III | Alkyl group with at least one silicon atom and no epoxide moiety. |
| IV | Aryl group with no epoxide moiety. |
| V | Alkyl group with at least one epoxide moiety. |
| VI | Aryl group with at least one epoxide moiety. |
| VII | Acyl group. |

E. Selection of Chemicals for Testing

As the foregoing discussion explains, the Agency has tentatively decided to select one or more of the chemicals in each subcategory for testing. Although selection of the test chemicals has yet to be completed, it is clear that several factors enter into the selection process. These factors include (1) the extent and quality of completed studies, (2) testing programs that are in progress and those to be initiated in the immediate future, (3) the applicability of SAR for

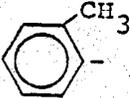
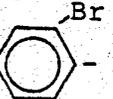
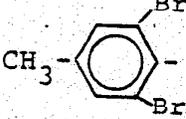
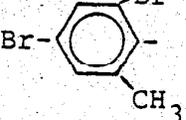
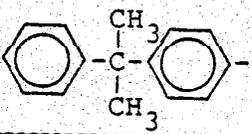
reasonably predicting the particular health effects in question, (4) estimates of current and, if possible, future exposure patterns for the chemicals comprising a subcategory, and (5) the economic impact on the regulated industry.

EPA is in the process of completing its review of the available data on glycidol and its numerous derivations. The following discussion of some of the health effects data for chemicals in Subcategory IV is presented as an example of how the Agency might apply

the above factors in its selection of test chemicals for any subcategory of glycidol derivatives. Commenters are requested to utilize this type of conceptual approach in commenting on the composition and testing needs of the seven subcategories.

Subcategory IV consists of glycidyl ethers where the R group is an aryl group with or without substituents but having no epoxide moiety. Chemicals on the Public TSCA Inventory that fall into this subcategory are listed in Table 5.

Table 5--Subcategory IV Derivatives of Glycidol.

| Chemical Name | CAS No. | Structure of R |
|---|------------|--|
| Phenyl glycidyl ether | 122-60-1 |  |
| o-Cresyl glycidyl ether | 2210-79-9 |  |
| Cresyl glycidyl ether (mixed isomers) | 26447-14-3 |  |
| p-tert-Butylphenyl glycidyl | 3101-60-8 | t-C ₄ H ₉ -  |
| p-Nitrophenyl glycidyl ether | 5255-75-4 | NO ₂ -  |
| 2,4-Dibromophenyl glycidyl ether | 20217-01-0 | Br-  |
| 2,6-Dibromo-4-methylphenyl glycidyl ether | 22421-59-6 | CH ₃ -  |
| 2,4-Dibromo-6-methylphenyl glycidyl ether | 7550-13-9 | Br-  |
| p-Nonylphenyl glycidyl ether | 6178-32-1 | C ₉ H ₁₉ -  |
| p-Cumylphenyl glycidyl ether | 61578-94-9 |  |

1. *Mutagenicity.* The Agency is reviewing the available data on the mutagenic potential of chemicals in Subcategory IV. The interim results of this review indicate that at least five of

these substances may induce gene mutations; these five are phenyl, o-cresyl, mixed cresyl, p-tert-butylphenyl, and p-nitrophenyl glycidyl ethers. Because the mutagenicity data base for the five glycidyl ethers consists

primarily of *in vitro* bacterial assays, the chemicals' gene mutational potential cannot be adequately characterized. Gene mutation data are unavailable for the other compounds in this subcategory.

In considering the need for additional mutagenicity data, the Agency has several alternative methods through which it can develop a suitable testing scheme. For example, the Agency may conclude the phenyl glycidyl ether is an appropriate representative for the entire subcategory. If such is the case, the Agency may require further testing, in insect and/or mammalian species, for only that chemical, subsequently using the results to estimate the gene mutation potential of the remaining chemicals.

On the other hand, the Agency may conclude that, from a SAR viewpoint, another chemical in this subcategory is at least as appropriate a representative as phenyl glycidyl ether. In determining which chemical or chemicals should be tested, the Agency may decide that it is most relevant to test the chemical(s) that is (are) produced in the greatest quantity and/or pose(s) the greatest potential for human exposure.

Another approach the Agency may adopt involves tiered testing of these compounds. For example, the Agency may initially require that all chemicals not previously tested in bacterial systems undergo such testing. Positive test results for any chemical in this system would then lead to the conducting of higher tier mutagenicity testing (e.g., induction of heritable gene mutations in *Drosophila melanogaster* for that chemical. At that stage, the Agency may be able to identify one or more representative chemicals for which further testing, in mammalian species, would be required.

A similar tiered approach, involving such tests as cytogenetic, dominant lethal, and heritable translocation assays, may be adopted to determine the potential of chemicals within a subcategory to induce chromosomal aberrations.

2. Oncogenicity. Phenyl glycidyl ether is the only chemical listed in Table 5 for which an oncogenicity study has been conducted. A preliminary review of this study indicates that phenyl glycidyl ether, administered via inhalation (12 ppm, the air saturation level), induces nasal tumors in rats under the conditions of the bioassay.

Upon review of all relevant data (i.e., metabolism, dermal absorption, etc.) for the assessment of oncogenic potentials of the chemicals in this subcategory, the Agency may conclude that the oncogenicity test data for phenyl glycidyl ether can be used to estimate the oncogenic potential of other chemicals in this subcategory. In such a case, the Agency may have to determine whether additional test data (e.g., pharmacokinetics) for phenyl glycidyl ether and other subcategory members

are needed to estimate the health risks from the available oncogenicity data.

On the other hand, the Agency may conclude that it is more relevant to conduct an oncogenicity study on another chemical(s) in this subcategory. For example, the Agency may choose to require testing on the most potent mutagen (determined from the required mutagenicity tests) or on the chemical posing the greatest likelihood of human exposure.

3. Teratogenicity. The Agency is aware of only one teratology study on a member of this subcategory, that study having been conducted with phenyl glycidyl ether. EPA's preliminary analysis indicates the test was negative. If it is determined that substantial production and human exposure occur for these chemicals, EPA would likely require further teratogenicity testing for this subcategory, unless it could be reasonably predicted from currently available data that a teratogenicity hazard was unlikely.

The Agency believes there is considerable evidence suggesting the epoxide moiety of glycidyl derivatives is the active portion of the molecule with regard to mutagenic and perhaps oncogenic and other effects (Refs. 8, 9, 11, 33, and 41). It is not yet clear whether a similar structure-activity relationship exists with regard to the teratogenic potential of these compounds. Consequently, if another study (e.g., in a second species) is required for this subcategory, the Agency may conclude that the most appropriate test substance is that which currently poses the greatest likelihood of human exposure.

4. Other chronic effects. EPA's preliminary review suggests that phenyl glycidyl ether also causes adverse effects on the liver, lung, kidney, blood, and reproductive system of laboratory animals. As in the case of teratogenicity, however, it is unclear whether the epoxide moiety is the active portion of the molecule with regard to these chronic effects. Thus, the Agency's criteria for selecting test chemicals for any future studies of this type may have less of a SAR basis than the criteria used for mutagenicity or oncogenicity tests.

5. Skin and eye effects. EPA's preliminary review indicates that phenyl glycidyl ether is a skin irritant, and sensitizer, as well as a potential eye irritant, in humans. Because the Agency has data suggesting these effects may be due to the presence of the epoxide moiety, the selection process determining the appropriate test chemical(s) for this subcategory would likely involve an SAR approach.

V. Specific Issues and Questions

Two of the major purposes of this ANPR are to solicit comments on the Agency's tentative plan for requiring testing under section 4 of TSCA, and to solicit additional data from industry and the general public to be used in developing a test rule for glycidol and its derivatives. The specific issues presented here are divided into three groups: (1) the use of subcategories, (2) additional hazard and exposure data, and (3) additional market information.

A. Use of Subcategories

1. The Agency solicits comments on the application of the general approach of subcategorization to the category "glycidol and its derivatives."

2. The Agency solicits comments on the specific composition of subcategories of glycidol derivatives as described in this notice (see Table 4).

3. The Agency solicits comments on its approach, as outlined in this ANPR, to selecting representative chemicals for future testing under section 4 of TSCA. For example, under what circumstances would a single chemical be a suitable representative of an entire subcategory?

4. If the Agency ultimately adopts the subcategory approach described in this ANPR, will the data subsequently obtained be adequate for supporting regulatory action for all category members? If not, is there any other approach the Agency might adopt other than requiring extensive testing of each category member?

5. If the Agency adopts the subcategory approach, it is likely that the selection of chemicals for testing will be partly based, in some instances, on estimates of current exposure potential. Under these circumstances, should the Agency consider follow-up activities such as reporting of significant new uses under section 5 of TSCA?

B. Additional Hazard and Exposure Data

EPA's search of the published literature and the responses to the Agency's reporting rule under section 8(d) of TSCA indicate that a considerable amount of research on glycidol and its derivatives has been conducted recently. The Agency hereby solicits the submission of any exposure (monitoring, environmental release, etc.) or health effects data on these chemicals in the possession of the general public. Manufacturers and processors of glycidol and its derivatives are already under a legal obligation to supply health and safety studies relating to glycidol and its derivatives pursuant to TSCA section 8(d). The Agency solicits

comments on the feasibility of requiring, as part of a test rule, the development of exposure data.

As noted above in Unit I, the ITC recommended this chemical category for epidemiological studies. The Agency solicits comments on the need for such studies, and on the feasibility of identifying a suitable cohort for such studies.

C. Additional Market Information

A considerable amount of production information was submitted to EPA in response to the Agency's requirement for such data reporting under section 8(a) of TSCA. To accurately assess the economic impact of future testing, additional market information is needed. The Agency solicits comments on the following questions:

1. What are the sales value and list price for each chemical in this category?
2. What are the specific end-uses for each chemical, and how have these uses changed during the last five years?
3. What are the key market factors determining the uses of each chemical? For example, does competition take place through price, performance, availability, or other factors?

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VII. Public Record

EPA has established a public record for this ANPR [docket number OPTS-42051]. This record includes the following:

- (1) Federal Register Notice designating the category glycidol and its derivatives to the priority list.
- (2) Letters.
- (3) Contact reports of telephone conversations and meeting summaries.
- (4) Published and unpublished data.

This record, containing the basic information considered by the Agency in developing the ANPR is available for inspection in the Office of Pesticides and Toxic Substances (OPTS) reading room from 8:00 a.m. to 4:00 p.m., Monday through Friday, except legal holidays, in Room E-107, 401 M St., SW, Washington, D.C. 20460. The Agency will supplement the record with additional information as it becomes available.

VIII. Development of Rulemaking

The Agency wishes to receive scientific discussion on all aspects on the use of SAR for this particular category. It will reconsider its position if data and logic indicate that the decision to test using subcategories based on structure-activity relationships is refuted by existing data.

The Agency will analyze all comments on categorization, SAR, exposure, production, and use of available data received from this ANPR. The Agency will also consider any ongoing or planned health effects testing brought to EPA's attention. Protocols should be submitted for all such testing to allow adequate Agency review and evaluation. Except for information claimed as Confidential Business Information (CBI) all of the above will be included in the public record and will form the basis of the Notice of Proposed Rulemaking or of the Decision Not to Test. Any information claimed as CBI will be considered by the Agency in its decisionmaking but will not be released

to the public except in accordance with Agency procedures as prescribed in 40 CFR Part 704.

(Sec. 4, Pub. L. 94-469 90 Stat. 2003; 15 U.S.C. 2601)

Dated: December 21, 1983.

William D. Ruckelshaus,
Administrator.

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