n-Butyl Glycidyl Ether (BGE)
[CAS No. 2426-08-6]

Review of Toxicological Literature

March 2004

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Abstract

n-Butyl Glycidyl Ether (BGE) is a high-production-volume chemical with annual production exceeding one million pounds in the United States. It is used primarily as a reactive diluent or chemical intermediate in epoxy resins, which are widely used in electronics, construction, and coating materials. The greatest potential for human exposure occurs in the workplace via inhalation, ingestion, or skin or eye contact. BGE is a mild skin and eye irritant and may be toxic to the immune, neurological, or respiratory system as well as to sense organs. Short-term exposure to BGE can cause irritation to the nose and throat. Long-term exposure can be detrimental to the blood and central nervous system (CNS) and may lead to loss of consciousness. BGE was rapidly absorbed and metabolized in rats and rabbits. The major urinary metabolites were 3-butoxy-2-acetylaminopropionic acid, 3-butoxy-2-hydroxypropionic acid, and butoxyacetic acid. Acute toxic effects in mice and rats included incoordination, delirium, ataxia, depressed motor activity, agitation, excitement, and eventually CNS depression. Pathological findings included irritation of the lungs, pneumonitis, hyperemia of the adrenal glands, adhesions of the stomach to adjacent tissues, and focal inflammation and moderate congestion of central zones in the liver. Toxic effects in subchronic inhalation studies in rats included growth retardation, increased mortality, emaciation, liver necrosis, significant increases in kidney-to-body and lung-to-body weight ratios, increased aspartate transferase levels in serum (males only), and respiratory tract damage. Atrophy of the testes was also seen at high doses. BGE has been reported to cause genetic damage *in vitro* in bacteria, rodent cells, and human peripheral blood lymphocytes. *In vivo*, BGE given via intraperitoneal injection but not gavage produced a dose-related increase in micronuclei in mice. Limited evidence also suggested BGE may cause dominant lethal effects in mice, but the results were inconclusive. Chromosomal aberrations were observed in bone marrow cells of rats treated with BGE.

Executive Summary

Basis for Nomination

n-Butyl glycidyl ether (BGE) was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization, including reproductive toxicity and carcinogenicity studies. The rationale for this nomination is a suspicion of toxicity based on structural features, positive results in genetic toxicity studies, substantial potential for human exposure and a lack of chronic toxicity data. It is a high-production-volume (HPV) chemical used primarily as a reactive diluent in epoxy resins such as bisphenol A diglycidyl ether (BADGE) resins. The widespread use of these epoxy resins in electronics, construction, and coatings leads to potential worker exposure in numerous industries. Glycidyl ethers contain the strained oxirane ring structure. Compounds with this moiety are alkylating agents that may damage DNA. Many compounds containing the epoxy moiety have been shown to be carcinogens (e.g., ethylene oxide and diepoxybutane).

Nontoxicological Data

BGE is a clear, colorless to pale yellow liquid with a slightly unpleasant odor. Contact between BGE and strong oxidizers (e.g., perchlorates, nitrates, and bromine) can result in fires and explosions, while contact with strong caustic agents may cause polymerization with the release of heat. When exposed to light or air, BGE may form explosive peroxides. When heated to decomposition, acrid smoke and fumes such as carbon monoxide are emitted.

Under the 1986, 1990, 1998, and 2002 Inventory Update Rule (IUR), an aggregate production volume ranging between >1 million lb (453,600 kg) to 10 million lb (4,536,000 kg) was reported for BGE. In 1994, the range was from >500,000 lb (226,800 kg) to 1 million lb (453,600 kg). BGE is commercially available from Dow Chemical Company (Freeport, TX, and Deer Park, TX). It is manufactured by Air Products and Chemicals, Inc. (Allentown, PA) as Epodil® 741. Under the 1990, 1994, and 1998 IUR, companies that reported manufacturing or importing BGE included Ciba-Geigy Corporation, Rhone-Poulenc Inc., and Air Products and Chemicals, Inc. There are numerous suppliers of liquid epoxy resins containing BGE as a reactive diluent. BGE is produced through the condensation of *n*-butyl alcohol and epichlorohydrin followed by dehydrochlorination with caustic to form the epoxy ring. It is an HPV chemical with annual production exceeding one million pounds in the United States. BGE is used as a reactive diluent for epoxy resins, serving as a viscosity-reducing agent, an acid acceptor for stabilizing chlorinated solvents, and as a chemical intermediate.

The American Conference of Governmental Industrial Hygienists (ACGIH) time-weighted average (TWA) threshold limit value (TLV) is 25 ppm (135 mg/m^3). The National Institute of Occupational Health (NIOSH) recommends a 15-minute exposure limit of 5.6 ppm (30 mg/m^3). The OSHA eight-hour TWA permissible exposure limit (PEL) is 50 ppm (270 mg/m^3) for BGE as an air contaminant in the general industry, as well as in shipyards and construction. The Environmental Protection Agency (EPA) regulates BGE under the Toxic Substances Control Act (TSCA).

Human Data

Humans are potentially exposed to BGE via inhalation, ingestion, and skin and eye contact. In the workplace, potential exposure to BGE exists until the epoxy resin is completely cured. In the NIOSH National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, an estimated 60,217 workers (14,929 females) were potentially occupationally exposed to BGE.

BGE is a suspected immunotoxicant, neurotoxicant, respiratory toxicant, and skin or sense organ toxicant. It is a mild skin and eye irritant. Short-term exposure to BGE causes irritation to the nose and throat resulting in coughing and wheezing, headache, lightheadedness, dizziness, incoordination, and fainting. Long-term exposure to BGE can result in narcosis, hematopoietic effects, and central nervous system

(CNS) depression. It is reported to be a skin sensitizer, based on the murine local lymph node assay (LLNA), guinea pig maximization tests, and human studies (e.g., contact allergy to epoxy resins or contact and irritant reactions to plastic and glue allergens).

Toxicological Data
No data were available regarding chronic exposure, synergistic/antagonistic effects, and carcinogenicity.

Chemical Disposition, Metabolism, and Toxicokinetics: Oral administration of ^{14}C-BGE (20 mg/kg [0.15 mmol/kg]) to rats and rabbits resulted in rapid absorption and metabolism. Within 24 hours, 87 and 78%, respectively, were eliminated in the urine. After 96 hours, 91.5 and 80%, respectively, of the administered dose were excreted in the urine. The following urinary metabolites were identified (compound; % in rats and % in rabbits): I (not identified; 22 and 4%), II (3-butoxy-2-acetylaminopropionic acid; 26 and 2%), III (3-butoxy-2-hydroxypropionic acid; 10 and 45%), and IV (butoxyacetic acid; 11 and 7%). A major route of biotransformation was via the hydrolytic opening of the epoxide ring, producing a diol that was then oxidized to 3-butoxy-2-hydroxypropionic acid, followed by oxidative decarboxylation to yield butoxyacetic acid.

Acute Toxicity: Numerous TSCATS report acute toxicity data for BGE, either alone or in a mixture (e.g., Epoxide No. 8, Cardura E10, and EPON Resin 815). The studies include primary eye irritation tests and primary skin irritation tests in rats and rabbits, as well as inhalation studies.

Inhalation LC_{50} values for mice and rats were >3500 and >670 ppm [18.64 and 3.57 g/m^3], respectively; intraperitoneal (i.p.) LD_{50} values were 0.70 and 1.14 g/kg [5.38 and 8.76 mmol/kg], respectively. The intragastric (i.g.) LD_{50} value was reported to be 1.53 g/kg [11.8 mmol/kg] in the mouse and 2.26 g/kg [17.4 mmol/kg] in the rat. In rabbits, percutaneous/dermal LD_{50} values between 0.788 and 4.93 g/kg [6.05 and 37.9 mmol/kg] were calculated.

In mice and rats, BGE (5-20% in propylene glycol or undiluted) given via i.g. or i.p. administration produced incoordination, ataxia, depressed motor activity, agitation, excitement, and eventually CNS depression; the animals were usually comatose at the time of death. Dyspnea was also observed. Vapor exposure of mice and rats to BGE (up to 200 ppm [1.07 g/m^3]) for eight hours produced delirium and early depression in the animals, along with dyspnea, lacrimation, salivation, nasal discharge, and aerophagia. Pathological findings from the acute studies included irritation of the lungs, pneumonitis, hyperemia of the adrenal glands, adhesions of the stomach to adjacent tissues, and focal inflammation and moderate congestion of central zones in the liver. In a four-hour inhalation study, BGE (4000 ppm [21.30 g/m^3]) resulted in the death of one of six rats; the maximum time for zero mortality from inhalation of concentrated vapor was two hours. BGE (undiluted) was found to be a mild skin irritant and mild eye irritant in rabbits.

Short-term and Subchronic Exposure: In male rats, exposure to BGE (38, 75, 150, or 300 ppm [0.20, 0.40, 0.799, or 1.60 g/m^3]) for seven hours per day, five days per week for ten weeks resulted in growth retardation and the death of one of ten rats at 150 ppm. At the high dose (300 ppm), increased mortality (50%), emaciation, liver necrosis, rough appearance, and significant increases in kidney to body and lung to body weight ratios were observed. In another rat study, inhalation of BGE (0.1, 0.5, or 1.0 mg/L [18, 94, or 188 ppm]) for six hours per day, five days per week for 28 days produced decreased body weights, increased aspartate transferase levels in serum (males only), and slightly increased hemoglobulin (males only), which was reversible, all at the high dose. At the mid and high doses, degeneration of the olfactory mucosa and metaplasia of the ciliated respiratory epithelium were seen; these were more apparent in males than females.

Dermal application of BGE (100 mg/kg [0.768 mmol/kg]) five times per week for four weeks produced small, white lesions in the liver in one of five rabbits.

Cytotoxicity: BGE (4.1-1000 µg/mL [31-7680 µM]) was toxic in human peripheral blood lymphocytes (HPBL); viability ranged from 85.9% (at 10 µg/mL [77 µM]) to 68.1% (at 1000 µg/mL).

Reproductive and Teratological Effects: Inhalation of BGE (38, 75, 150, or 300 ppm [0.20, 0.40, 0.799, or 1.60 g/m^3]) for seven hours per day, five days per week for ten weeks produced atrophic testes in four of five surviving rats at 300 ppm, very small testes in one of ten rats at 150 ppm, and slight patchy atrophy of the testes in one of ten rats at 75 ppm.

Results from mouse dominant lethal assays are included in the Genotoxicity section below.

Genotoxicity: BGE was mutagenic in a number of *in vitro* genetic toxicity test systems. In *Salmonella typhimurium* strains TA100 and TA1535, BGE (up to 2000 µg/plate [15.36 µmol/plate]) caused base-pair mutations, both with and without metabolic activation (S9). It was mutagenic in the SOS chromotest, the mouse lymphoma assay, and in Chinese hamster V79 cells. BGE induced DNA repair in human blood lymphocytes, WI38 cells, and human peripheral blood lymphocytes (HPBL). It was not mutagenic in body fluid or host-mediated assays in mice. BGE failed to transform mouse embryo cells even at toxic doses.

Mixed results have been obtained in *in vivo* studies. In a mouse dominant lethal assay, BGE (1.5 g/kg [11.5 mmol/kg] body weight [bw]) given daily three times per week for eight weeks produced decreased pregnancy rates, increased fetal deaths, and a decreased proportion of implants per pregnancy in treated versus control animals. In a repeat study using three dose levels of BGE (0.75, 1.5, or 3.0 g/kg [5.8, 12, or 23 mmol/kg] bw), an increase in fetal deaths was reported for the high dose only. Results seen at the 1.5 g/kg dose in the previous study were not reproduced. In a third dominant lethal assay, BGE (0.375, 0.750, or 1.50 g/kg [2.88, 5.76, or 11.5 mmol/kg] bw) resulted in a significant increase in fetal death rate (7.75%) at one week post treatment at the high dose in one experiment. Because this value was comparable to that for controls (7.33%) for the same time period in a second experiment, a positive dominant lethal effect was suggested but uncertain. No dose-related changes in pregnancy rates or in the average number of implants per pregnant female were observed. Additionally, no significant dose-related testicular changes were reported. In the mouse micronucleus assay, BGE did not increase the number of micronuclei when given via gavage but produced dose-related increases in the number of micronuclei when given via i.p. injection. In rats, aberrations in bone marrow cells were observed.

Immunotoxicity: In sensitization tests with guinea pigs, BGE (0.1-25% solution) produced positive results.

Other Data (Hemopoietic Effects): Intramuscular injections of BGE (400 mg/kg [3.07 mmol/kg]) on three consecutive days slightly increased leukocyte counts in rats but had no effects on the number of white blood cells. In male C_3H/Hej mice given a single i.p. injection of BGE (4 mg/mouse [1.1 mmol/kg bw]), a hemoglobin binding index of 1.2 pmol/g globin was reported. This slightly lower value compared to that of propylene oxide (~1.4 pmol/g) suggested rapid detoxification of BGE in the mouse.

Structure-Activity Relationships

Several reviews on glycidyl ethers have been published. Some reports have compared the alkylating and mutagenic reactivity of BGE with related compounds as a potential mechanism for carcinogenesis, while others have reviewed sensitization tests for evaluating structure-activity relationships.

Available toxicity data for *t*-BGE and allyl glycidyl ether (AGE), analogues of *n*-BGE, and for bisphenol A diglycidyl ether (BADGE), the most common active component in epoxy resins, are presented in this section.

tert-Butyl glycidyl Ether (*t*-BGE) [CASRN 7665-72-7]

Short-term or Subchronic Toxicity: In a two-week inhalation study, mice, rats, and rabbits were exposed to *t*-BGE (100-1000 ppm) for six hours per day, five days per week. All species exhibited rhinitis, lethargy, and gait changes. At 300 ppm, liver weights were decreased. At 300 and 1000 ppm, decreases in mean body weights, body fat, thymic size, and lymphoid organs were observed. In a 13-week vapor inhalation study, the three species were exposed to *t*-BGE (25, 75, or 225 ppm) for six hours per day, five days per week. At the high dose, decreased body weight gain, affiliated decreases in organs weights (e.g., thymus), inflammation of the nasal mucosa, and hyperplasia and/or flattening of the nasal respiratory epithelium were reported. The no observable adverse effect level (NOAEL) reported for the two-week inhalation study was 100 ppm and for the 13-week inhalation study was 25 ppm.

Reproductive and Developmental Toxicity: Effects on the reproductive organs in mice, rats, and rabbits exposed to *t*-BGE via inhalation for up to 13 weeks (see short-term studies above) were studied. No adverse effects were observed in any animals in either sex.

Genotoxicity: *t*-BGE was less mutagenic *in vitro* compared to *n*-BGE.

Allyl Glycidyl Ether (AGE) [CASRN 106-92-3]

Short-term or Subchronic Toxicity: In mice exposed to AGE (2.5 or 7.1 ppm) via inhalation for six hours per day for 4, 9, or 14 days, nasal cavity lesions were observed with the higher dose at the four-day exposure period. At 9 and 14 days, restorative responses were reported. A two-week inhalation study in which mice were exposed to concentrations up to 100 ppm AGE and rats to levels up to 500 ppm AGE, 100% mortality was seen in rats at the high dose. All male mice and three of five female mice died at their high dose. Both species showed acute inflammation of the nasal passage and major airways.

In a ten-week inhalation study, rats exposed to AGE (260-900 ppm) for seven hours per day, five days per week had decreased body weight gain. At the lowest dose, slight eye irritation and respiratory distress were observed. At 400 ppm, the kidney/body weight ratio was significantly increased; animals had decreased peritoneal fat, severe emphysema, mottled liver, and enlarged and congested adrenal glands. At ≥600 ppm, abnormal changes in the lungs were seen but to a more severe extent (i.e., bronchopneumonic consolidation, severe emphysema, bronchiectasis, and inflammation).

When rats were exposed to concentrations up to 200 ppm and mice to levels up to 30 ppm for 13 weeks, decreased final mean body weights were reported in male rats at doses ≥10 ppm and in female and male mice at 30 ppm. Histologic lesions included squamous metaplasia of the nasal passage and epithelial erosions in both mice and rats.

Reproductive and Developmental Toxicity: In rats given an i.m. injection of AGE (400 mg/kg) for three nonconsecutive days, testicular degeneration was observed but was not statistically significant. In one of the three surviving rats, focal necrosis of the testis was also seen. When rats were administered AGE vapor (300 ppm) via inhalation for seven hours per day, five days per week for a total of 50 exposures, testicular atrophy occurred in five of ten rats, and small testes was found in one of ten rats. In an eight-week inhalation study of the reproductive effects of AGE in rats (up to 200 ppm) and mice (up to 30 ppm), significant reduction in the mating performance of male rats was observed; however, no effect on sperm morphology, motility, or number was seen. No effects in female rats or male or female mice were reported.

Carcinogenicity: In a National Toxicology Program (NTP) two-year inhalation carcinogenicity study, male and female Osborne-Mendel rats and $B_6C_3F_1$ mice (n=50/sex/dose) were exposed to AGE (5 or 10 ppm) six hours per day, five days per week. The NTP concluded that there was equivocal evidence of carcinogenicity in male rats and female mice, no evidence supporting a carcinogenic effect in female rats, and some evidence for a carcinogenic response in male mice.

Genotoxicity: In *S. typhimurium* strains TA100 and TA1535, AGE was mutagenic with and without S9. In Chinese hamster ovary (CHO) cells, AGE induced SCEs and chromosomal aberrations both in the presence and absence of S9. In *Drosophila melanogaster* male germ cells, AGE (5500 ppm) induced a significant increase in sex-linked recessive lethal mutations. Positive and negative results were obtained in micronucleus tests.

2,2-Bis-[*p*-(2,3-glycidyloxy)phenyl]propane (BADGE) [CASRN 1675-54-3]

Short-term or Subchronic Toxicity: In mice, dermal application of BADGE (1, 10, or 100 mg/kg) for 13 weeks produced mild to moderate chronic active dermatitis. At the high dose, spongiosis and epidermal micro abscess formation were observed. In rats, dermal application of BADGE (10, 100, or 1000 mg/kg) for 13 weeks resulted in a decrease in body weight at the high dose. The no-observable effect level (NOEL) for dermal exposure was 100 mg/kg for both sexes. In a separate study, application of BADGE (same doses and exposure period) not only caused a decrease in body weight but also produced chronic dermatitis at all dose levels in males and at >100 mg/kg in females.

Reproductive and Developmental Toxicity: BADGE (50, 540, or 750 mg/kg) administered to rats via gavage for 14 weeks (P1) or 12 weeks (P2) produced decreased body weight in all males at the mid dose and in both males and females at the high dose, but had no reproductive effects. The NOEL for reproductive effects was 750 mg/kg.

Carcinogenicity: IARC concluded that "there is limited evidence for the carcinogenicity of bisphenol A diglycidyl ether in experimental animals." Its overall evaluation was "Bisphenol A diglycidyl ether is not classifiable as to its carcinogenicity to humans (Group 3)."

Genotoxicity: In *S. typhimurium* strains TA100 and TA1535, BADGE (10-10,000 µg/plate) was mutagenic with and without S9. In a spot test, BADGE (0.05 or 10.00 mg) failed to show mutagenicity in strains TA98 and TA100. Negative results were also obtained in the body fluid test using urine of female BDF and ICR mice (1000 mg/kg BADGE), the mouse host-mediated assay (1000 mg/kg), micronucleus test (1000 mg/kg), and dominant lethal assay (~3000 mg/kg).

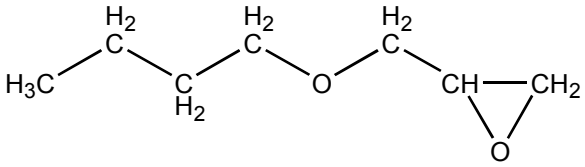
Table of Contents

1.0 Basis for Nomination

n-Butyl glycidyl ether (BGE) was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization, including reproductive toxicity and carcinogenicity studies. The rationale for this nomination is a suspicion of toxicity based on structural features, positive results in genetic toxicity studies, substantial potential for human exposure and a lack of chronic toxicity data. It is a high-production-volume (HPV) chemical used primarily as a reactive diluent in epoxy resins such as bisphenol A diglycidyl ether (BADGE) resins. The widespread use of these epoxy resins in electronics, construction, and coatings leads to potential worker exposure in numerous industries. Glycidyl ethers contain the strained oxirane ring structure. Compounds with this moiety are alkylating agents that may damage DNA. Many compounds containing the epoxy moiety have been shown to be carcinogens (e.g., ethylene oxide and diepoxybutane).

2.0 Introduction

n-Butyl glycidyl ether (BGE)
[2426-08-6]



2.1 Chemical Identification and Analysis

BGE ([$C_7H_{14}O_2$]; mol. wt. = 130.21) is also called:

Ageflex BGE	DY-BP
BRN 0103668	EINECS 219-376-4
1-Butoxy-2,3-epoxypropane	Epi-Rez 501
1-Butyl glycidyl ether	Epodil 741
2,3-Epoxypropyl butyl ether	ERL 0810
2-(Butoxymethyl)oxirane	Ether, butyl 2,3-epoxypropyl
3-Butoxy-1,2-epoxypropane	Ether, butyl glycidyl
BGE-C	Glycidyl butyl ether
BGE-R	HSDB 299
(Butoxymethyl)oxirane	NSC 83413
Butyl 2,3-epoxypropyl ether	Oxirane, (butoxymethyl)- (9CI)
Butyl glycidyl ether	Propane, 1-butoxy-2,3-epoxy- (6CI, 8CI)
(±)-Butyl glycidyl ether	Sipomer BGE
CCRIS 828	TK 10408

Sources: ChemIDplus (undated-a); HSDB (2002); Registry (2003)

In air, BGE can be analyzed using gas chromatographic analysis or solid sorbent sampling. The National Institute for Occupational Safety and Health (NIOSH) Method S81 uses gas chromatography with a flame ionization detector (GC/FID); it has been validated over the range of 133 to 542 mg/m^3 using a 10-L sample (HSDB, 2002; NIOSH, 1988). NIOSH Method 1616, which is Method S81 in a revised format, has a working range of 15 to 60 ppm (80 to 320 mg/m^3) for a 20-L sample (NIOSH, 1994). An Occupational Safety and Health Administration (OSHA) standard method uses absorption on charcoal and then detection by gas-liquid chromatography (GLC) (Gardiner et al., 1993). High performance liquid chromatography (HPLC) allows the determination of BGE at levels down to 1 ppb (1 µg/L) (Ramanujam et al., 1981). Hemoglobin adduct measurements have been suggested for monitoring low-level exposures in humans (Licea Pérez et al., 1997).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Physical State	clear, colorless to pale yellow liquid	HSDB (2002); NIOSH (1988)
Odor	irritating; slightly unpleasant	HSDB (2002); NIOSH (1988)
Boiling Point (^{o}C)	164 @ 760 mm Hg	HSDB (2002); NIOSH (1988)
Melting Point (^{o}C)	59	Registry (2003)
Flash Point (^{o}C)	64	NIOSH (1978)
Vapor Pressure (mm Hg)	3.2 @ 25 °C	HSDB (2002)
Specific Gravity	0.908 @ 25 °C/4 °C	HSDB (2002)
Water Solubility	2% @ 20 °C	HSDB (2002)
Octanol-water partition coefficient (log K_{OW})	0.63	HSDB (2002)

Contact between BGE and strong oxidizers (e.g., perchlorates, nitrates, and bromine) can result in fires and explosions, while contact with strong caustic agents may cause polymerization with the release of heat. When exposed to light or air, BGE may form explosive peroxides. When heated to decomposition, acrid smoke and fumes such as carbon monoxide are emitted. Additionally, BGE can cause deterioration of some forms of plastics, coatings, and rubber (HSDB, 2002; NIOSH, 1988; NJ DHSS, 1998).

2.3 Commercial Availability

BGE is commercially available from Dow Chemical Company (Freeport, TX, and Deer Park, TX) (HSDB, 2002). It is manufactured by Air Products and Chemicals, Inc. (Allentown, PA) as Epodil® 741 (Air Products and Chemicals, Inc., undated; Eastech Chem. Inc., 2002). Under the 1990, 1994, and 1998 Inventory Update Rule (IUR), the following companies reported manufacturing or importing BGE, which was available for sponsorship in the HPV Challenge Program (U.S. EPA, 2003):

- 1990: Ciba-Geigy Corporation, Textile Products; CPS Chemical Company, Inc.; Rhone-Poulenc Inc.
- 1994: Air Product and Chemicals, Inc.; Ciba-Geigy Corporation; Rhone-Poulenc Inc.
- 1998: Air Products and Chemicals, Inc.; Ciba Specialty Chemicals Corporation; Ciba Specialty Chemicals Water Treatment.

Ciba Specialty Chemicals (Tarrytown, NY) provides BGE reactive diluent for epoxy resins used for laminating, flooring, and electrical casting (ChemBuyersGuide, undated). Likewise, numerous suppliers of liquid epoxy resins containing BGE as a reactive diluent exist. For example, Resolution Performance Products (Houston, TX) supplies epoxy resins using modifiers

that include BGE (called H-61 or HELOXY Modifier 61) (RPP, 2001, 2002). Additionally, Araldite GY 506, a bisphenol A diglycidyl ether (BADGE) resin with BGE, is supplied by Electron Microscopy Sciences (Fort Washington, PA) (Electron Microsc. Sci., 1997).

3.0 Production Processes

BGE is produced through the condensation of *n*-butyl alcohol and epichlorohydrin followed by dehydrochlorination with caustic to form the epoxy ring (HSDB, 2002).

4.0 Production and Import Volumes

Under the 1986, 1990, 1998, and 2002 IUR, an aggregate production volume ranging between >1 million lb (453,600 kg) to 10 million lb (4,536,000 kg) was reported for BGE. In 1994, the range was from >500,000 lb (226,800 kg) to 1 million lb (453,600 kg) (U.S. EPA, 2004). Production volumes for BGE were probably greater than 9.08×10^5 g (2000 lb) in 1973 and 1974 (HSDB, 2002). No import volumes were available.

5.0 Uses

BGE is used primarily as a reactive diluent for epoxy resins, serving as a viscosity-reducing agent, an acid acceptor for stabilizing chlorinated solvents, and as a chemical intermediate (Gardiner et al., 1993; HSDB, 2002; Huntsman, undated). BGE as Epodil® 741 is used as an epoxy resin diluent for tooling, electrical applications, flooring, and highly filled coatings (Air Products and Chemicals, Inc., undated). Additionally, it is used as an epoxy resin diluent in coatings, inks, adhesives, rubber, and plastics (Eastech Chem. Inc., 2002).

6.0 Environmental Occurrence and Persistence

The closed bottle test indicated that BGE was partially biodegradable, while the Modified Sturm test showed that BGE had "no evidence of biodegradability." Models (e.g., EPIWIN V3.05) have been used to calculate the rate of photodegradation of BGE, as well as its partitioning among air, water, soil, and sediment. Assuming a reaction time of 12 hours and an average atmospheric concentration of 1.5×10^6 OH/cm^3, the half-life was calculated to be 0.539 days. Using a soil K_{OC} of 1.75 and a log K_{ow} of 0.63, BGE concentrations were reported to be 2.7% in air, 53.5% in water, 43.8% in soil, and <0.1% in sediment (ERSTG, 2002b,c).

7.0 Human Exposure

Humans are potentially exposed to BGE via inhalation, ingestion, and skin and eye contact (HSDB, 2002; NIOSH, 1988, undated). Its use in consumer products (epoxy adhesives, architectural and industrial maintenance coatings, etc.), building materials, and furnishings contribute to indoor air pollution (CARB, 1998; Environmental Defense, 2003). In the workplace, potential exposure to BGE exists until the epoxy resin is completely cured (NIOSH, 1978).

NIOSH has conducted several health hazard evaluation and industrial hygiene walk-through surveys of industrial plants; air concentrations of BGE were generally below the OSHA limit (e.g., Belanger, 1986; Cox, 1979; Evans, 1977; Liss and Chrostek, 1983; Liss and Ruhe, 1983; and Stephenson et al., 1985). In the NIOSH National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, an estimated 60,217 workers (14,929 females) were

potentially occupationally exposed to BGE; results are provided by industry and occupation (NIOSH, 1990).

8.0 Regulatory Status

U.S. government regulations pertaining to BGE are summarized in **Table 1**.

The American Conference of Governmental Industrial Hygienists (ACGIH) time-weighted average (TWA) threshold limit value (TLV) is 25 ppm (135 mg/m^3) (ACGIH, 2003). NIOSH recommends a 15-minute exposure limit of 5.6 ppm (30 mg/m^3) (NIOSH, 1988, undated). The OSHA eight-hour TWA permissible exposure limit (PEL) is 50 ppm (270 mg/m^3) for BGE as an air contaminant in the general industry, as well as in shipyards and construction (see table). The Environmental Protection Agency (EPA) regulates BGE under the Toxic Substances Control Act (TSCA) (e.g., 40 CFR 716.120). In 1992, BGE was added the Master Testing List (MTL) under TSCA; testing action development was in progress (U.S. EPA, 1996).

Table 1. Federal Regulations Relevant to BGE

Reference		Summary of Regulation
OSHA	29 CFR 1910—Occupational Safety and Health Standards; Subpart Z—Toxic and Hazardous Substances; §1910.1000 Air Contaminants (7/1/03)	The permissible exposure limit (PEL) as an 8-hr time weighted average (TWA) is 50 ppm (270 mg/m^3) for BGE.
	29 CFR 1915—Occupational Safety and Health Standards for Shipyards and Shipyard Employment; Subpart Z—Toxic and Hazardous Substances; §1915.1000 Air Contaminants (7/1/03)	The PEL as an 8-hr time TWA is 50 ppm (270 mg/m^3) for BGE.
	29 CFR 1926—Safety and Health Regulations for Construction; Subpart D—Occupational Health and Environmental Controls; §1926.55 Gases, vapors, fumes, dusts, and mists (7/1/03)	The PEL as an 8-hr TWA is 50 ppm (270 mg/m^3) for BGE.
EPA	40 CFR 712—Chemical Information Rules; §712.30 (7/1/90)	Section 8(a) of TSCA requires manufacturers of BGE to report preliminary assessment information concerned with production, use, and exposure to EPA as cited in the preamble of the 51 FR 41329.
	40 CFR 716—Health and Safety Data Reporting; Subpart B—Specific Chemical Listing; §716.120 Substances and listed mixtures to which this subpart applies (7/1/03)	Pursuant to section 8(d) of TSCA, manufacturers, importers, and processors of BGE must submit to EPA copies and lists of unpublished health and safety studies. Its effective date began on 10/04/82 and ended on 10/04/92.

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

BGE is a mild skin and eye irritant. Short-term exposure to BGE causes irritation to the nose and throat resulting in coughing and wheezing. Other symptoms include headache, lightheadedness, dizziness, incoordination, and fainting; high levels can lead to death. Long-term exposure to BGE can result in skin sensitization, narcosis, hematopoietic effects, and central nervous system (CNS) depression (Gardiner et al., 1993; HSDB, 2002; NIOSH, 1988, undated; NJ DHSS, 1998). The concentration immediately dangerous to life and health (IDLH) is 250 ppm (NIOSH, 1996).

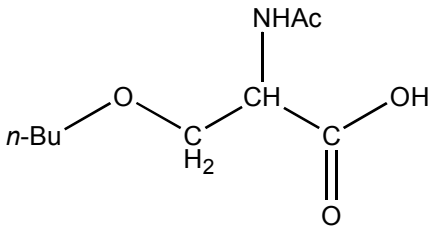
Acute Toxicity: In two workers, exposure to BGE (contained in a grouting compound) via inhalation resulted in coughing, vomiting, ataxia, and headache within two hours. Irritation of the gastrointestinal tract was related to length of exposure. One man was exposed for 90 minutes, the other was exposed for four hours. Within 24 hours, both men were admitted to a hospital. Case I (21 years old) underwent an appendectomy after 17 days of central abdominal pain and was recovering three months later. Case II (42 years old) collapsed with hematemesis and melena four weeks later and continued to suffer from spasmodic headaches, lethargy, anorexia, and vomiting, with evidence of blood three months later (Wallace, 1979).

Immunotoxicity: BGE is reported to be a skin sensitizer, based on the murine local lymph node assay (LLNA), guinea pig maximization tests, and human studies (Basketter et al., 2000; Haneke et al., 2001; IARC, 1989). In a study of 20 patients with contact allergy to epoxy resins, three reacted to BGE (0.25%) (Fregert and Rorsman, 1964). In another study, BGE produced allergic reactions in only two of 140 patients tested (Jolanki et al., 1990; cited by Gardiner et al., 1992). In more recent years, surveys regarding allergic and irritant reactions to plastic and glue allergens have been conducted. Patch testing of BGE (0.25% w/w in petroleum) with a two-day occlusion in 310 patients during a six-year period resulted in only two cases of allergic reaction (0.6%) and one case of irritant reaction (Kanerva et al., 1997, 1999). In another investigation, 839 patients were patched tested with a series of plastic and glue allergens over a period of seven years; no reactions (0 out of 343) to BGE (0.25%) were reported (Tarvainen, 1995). In a bisphenol A-based epoxy resin manufacturing plant in which 26 of 228 workers had work-related skin eruptions during a ten-year period, 19 were patch tested. One subject showed a positive reaction to BGE, as well as epichlorohydrin. At 48 hours, erythema and mild edema were seen; at 72 hours, erythema, edema, and papules were seen (Prens et al., 1986).

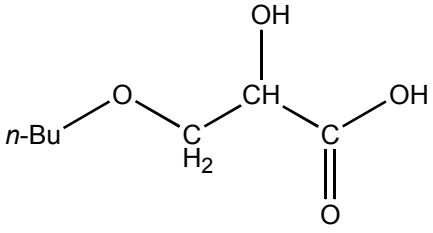
Reproductive Toxicity: A reproductive health survey was initiated due to an unexpected increase in the number of miscarriages at a plastics fabrication facility. Among the chemicals investigated, BGE (in products Epibond 8543-A, Epocast 167-A, and epoxy resins) was associated with one miscarriage. No single agent, however, was identified as a cause (Boeing Co., 1986).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

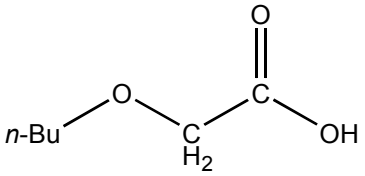
Oral administration of ^{14}C-BGE (20 mg/kg [0.15 mmol/kg]) to male Wistar rats and New Zealand white rabbits resulted in rapid absorption and metabolism. Within 24 hours, 87 and 78%, respectively, were eliminated in the urine. After 96 hours, 91.5 and 80%, respectively, of the administered dose were excreted in the urine. The following urinary metabolites were identified (compound; % in rats and % in rabbits): I (not identified; 22 and 4%), II (3-butoxy-2-acetylaminopropionic acid; 26 and 2%), III (3-butoxy-2-hydroxypropionic acid; 10 and 45%), and IV (butoxyacetic acid; 11 and 7%). A major route of biotransformation was via the hydrolytic opening of the epoxide ring, producing a diol that was then oxidized to 3-butoxy-2-hydroxypropionic acid, followed by oxidative decarboxylation to yield butoxyacetic acid (Shell Oil Co., 1983 [published as Eadsforth et al., 1985]).



II



III



IV

* *n*-Bu represents $CH_3(CH_2)_3$-

9.1.3 Acute Exposure

Acute toxicity values for BGE are presented in **Table 2**. Numerous TSCATS report acute toxicity data for BGE, either alone or in a mixture (e.g., Epoxide No. 8, Cardura E10, and EPON Resin 815). The studies include primary eye irritation tests and primary skin irritation tests in rats and rabbits, as well as inhalation studies (e.g., Ciba-Geigy, 1972, 1977; Confidential, 1983; Procter and Gamble Co., 1979; Reichhold Chem. Co., 1978; Rhone-Poulenc Inc., 1973). Shell (1956, 1957b) conducted and reported data from acute toxicity studies in rats, mice, rabbits, and dogs via various routes (intragastric [i.g.], intraperitoneal [i.p.], inhalation, intramuscular [i.m.], and dermal application). Common signs of toxicity included CNS depression, hyperventilation, dyspnea, and autolysis of the gastric mucosa.

Table 2. Acute Toxicity Values for BGE

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
inh.	mouse (M, strain n.p.)	$LC_{50(4\ hr)}$ >3500 ppm (18.64 g/m^3)	Hine et al. (1956)
	rat (sex and strain n.p.) (M; Long-Evans)	$LC_{50(8\ hr)}$ >670 ppm (3.57 g/m^3) $LC_{50(8\ hr)}$ = 1030 ppm (5.485 g/m^3)	ACGIH (1986; cited by HSDB, 2002) Hine et al. (1956); Shell Oil Co. (1956, 1957b)
i.p.	mouse (M, Webster)	LD_{50} = 0.70 g/kg (5.38 mmol/kg)	Hine et al. (1956); Shell Oil Co. (1956, 1957b)
	rat (M, Long-Evans)	LD_{50} = 1.14 g/kg (8.76 mmol/kg)	
i.g.	mouse (M, Princeton)	LD_{50} = 1.53 g/kg (11.8 mmol/kg)	Hine et al. (1956); Shell Oil Co. (1957b)
	rat (M, strain n.p.)	LD_{50} = 2.26 g/kg (17.4 mmol/kg)	
oral	mouse (M, Webster)	LD_{50} = 1.53 g/kg (11.8 mmol/kg)	Hine et al. (1956); Shell Oil Co. (1956)
	rat (sex and strain n.p.)	LD_{50} = 2.05 g/kg (15.7 mmol/kg)	Weil et al. (1963)
		LD_{50} = 2.26 g/kg (17.4 mmol/kg)	Hine et al. (1956)
perc./ dermal	rabbit (sex and strain n.p.)	LD_{50} = 0.788 g/kg (6.05 mmol/kg)	Lockwood and Taylor (1982; cited by Gardiner et al. (1993)
		LD_{50} = 2.52 mL/kg (17.6 mmol/kg)	Weil et al. (1963)
	(M; New Zealand white)	LD_{50} = 4.93 g/kg (37.9 mmol/kg)	Hine et al. (1956); Shell Oil Co. (1956, 1957b)

Abbreviations: inh. = inhalation; i.g. = intragastric; i.p. = intraperitoneal; LC_{50} = concentration lethal to 50% of test animals; LD_{50} = lethal dose for 50% of test animals; M = male(s); n.p. = not provided; perc. = percutaneous

In mice and rats, BGE (5% in propylene glycol) given via i.g. administration produced incoordination, ataxia, depressed motor activity, agitation, excitement, and eventually CNS depression; the animals were usually comatose at the time of death. Additionally, dyspnea was observed. Intraperitoneal injection of BGE (20% in propylene glycol to mice and undiluted to rats) caused basically the same signs of toxicity as i.g. administration. The LD_{50} values indicate a slight increase in toxicity. Vapor exposure of mice and rats to BGE (up to 200 ppm [1.07 g/m^3]) for eight hours produced delirium and early depression in the animals, along with dyspnea, lacrimation, salivation, nasal discharge, and aerophagia. Pathological findings from the acute studies included irritation of the lungs, pneumonitis, hyperemia of the adrenal glands, adhesions of the stomach to adjacent tissues, and focal inflammation and moderate congestion of central zones in the liver (Hine et al., 1956). In a four-hour inhalation study, BGE (4000 ppm [21.30 g/m^3]) resulted in the death of one of six rats; the maximum time for zero mortality from inhalation of concentrated vapor was two hours (Weil et al., 1963).

BGE (undiluted) was found to be a mild skin irritant and mild eye irritant in rabbits (Hine et al., 1956; Grant, 1974 [cited by HSDB, 2002]; Gardiner et al., 1993).

9.1.4 Short-term and Subchronic Exposure

In male rats, exposure to BGE (38, 75, 150, or 300 ppm [0.20, 0.40, 0.799, or 1.60 g/m^3]) for seven hours per day, five days per week for ten weeks resulted in growth retardation and the death of one of ten rats at 150 ppm. At the high dose (300 ppm), increased mortality (50%),

emaciation, liver necrosis, rough appearance, and significant increases in kidney to body and lung to body weight ratios were observed (Shell Oil Co., 1957a [cited as Andersen et al. (1957) in reviews]).

In another rat study, inhalation of BGE (0.1, 0.5, or 1.0 mg/L [18, 94, or 188 ppm]) for six hours per day, five days per week for 28 days produced decreased body weights, increased aspartate transferase levels in serum (males only), and slightly increased hemoglobulin (males only), which was reversible, all at the high dose. Furthermore, a significant decrease in fasting glucose in a high-dose reversibility group was observed. At the mid and high doses, degeneration of the olfactory mucosa and metaplasia of the ciliated respiratory epithelium were seen; these were more apparent in males than females (Ciba-Geigy, 1985a,b,c).

Dermal application of BGE (100 mg/kg [0.768 mmol/kg]) five times per week for four weeks produced small, white lesions in the liver in one of five rabbits (Confidential, 1964).

9.1.5 Chronic Exposure
No data were available.

9.1.6 Synergistic/Antagonistic Effects
No data were available.

9.1.7 Cytotoxicity
BGE (4.1-1000 µg/mL) was toxic in human peripheral blood lymphocytes (HPBL); viability ranged from 85.9% (at 10 µg/mL [77 µM]) to 68.1% (at 1000 µg/mL) (Frost and Legator, 1982).

9.2 Reproductive and Teratological Effects
Inhalation of BGE (38, 75, 150, or 300 ppm [0.20, 0.40, 0.799, or 1.60 g/m^3]) for seven hours per day, five days per week for ten weeks produced atrophic testes in four of five surviving rats at 300 ppm, very small testes in one of ten rats at 150 ppm, and slight patchy atrophy of the testes in one of ten rats at 75 ppm (Shell Oil Co., 1957a [cited as Andersen et al. (1957) in reviews]). [EPA commented that "in the absence of data to the contrary, it should be assumed that the testicular atrophy…is the result of direct action of BGE" (U.S. EPA, 1979).]

Results from dominant lethal assays using BGE are included in **Section 9.6**.

9.3 Carcinogenicity
No data were available.

9.4 Initiation/Promotion Studies
No data were available.

9.5 Anticarcinogenicity
No data were available.

9.6 Genotoxicity

The details of the following studies are presented in **Table 3**.

[Note: U.S. EPA (1978), in its status report for several of the mutagenicity tests conducted below—Ames test, body fluid analysis, micronucleus test, induction of DNA repair, host-mediated assay, and dominant lethal assay,—noted problems with each test (Microfiche No. OTS0200451, Document No. 8EHQ-0778-0213).]

In Vitro Assays

BGE was found to be positive in a number of *in vitro* genetic toxicity assays. In *Salmonella typhimurium* strains TA100 and TA1535, BGE (up to 2000 µg/plate [15.36 µmol/plate]) produced base-pair type mutations, both with and without metabolic activation (S9). It was positive for mutagenicity in the SOS chromotest, as well as in mouse lymphoma cells and Chinese hamster V79 cells. Furthermore, BGE induced DNA repair in human blood lymphocytes, WI38 cells, and human peripheral blood lymphocytes (HPBL) (Canter et al., 1986; Confidential, 1977; Connor et al., 1980; Frost and Legator, 1982; Procter and Gamble Co., 1979; Pullin, 1977; Thompson et al., 1981; von der Hude et al., 1990, 1991; Wade et al., 1979).

BGE failed to show mutagenic activity in body fluid analyses and a host-mediated assay in mice in *S. typhimurium* strains TA98 and TA1535 and failed to transform mouse embryo cells (when administered up to toxic levels) (Connor et al., 1980; Pullin, 1977).

In Vivo Assays

Mixed results have been obtained in *in vivo* studies. In a mouse dominant lethal assay, BGE (1.5 g/kg [11.5 mmol/kg] body weight [bw]) given daily three times per week for eight weeks produced decreased pregnancy rates, increased fetal deaths, and a decreased proportion of implants per pregnant female in treated versus control animals (Pullin, 1977). In a repeat study using three dose levels, BGE (0.75, 1.5, or 3.0 g/kg [5.8, 12, or 23 mmol/kg] bw) failed to reproduce the above results at 1.5 g/kg. An increase in fetal deaths was seen at 3.0 g/kg. In another dominant lethal assay, BGE (0.375, 0.750, or 1.50 g/kg [2.88, 5.76, or 11.5 mmol/kg] bw) resulted in a significant increase in fetal death rate (7.75%) at one week post treatment at the high dose in one experiment. Because this value was comparable to that for controls (7.33%) for the same period of time in a second experiment, a positive dominant lethal effect was suggested but uncertain. No dose-related changes in pregnancy rates or in the average number of implants per pregnant female were observed. Additionally, no significant dose-related testicular changes were reported (Whorton et al., 1983).

In the mouse micronucleus assay, BGE did not increase the number of micronuclei when given via gavage but produced dose-related increases in the number of micronuclei when given via i.p. injection (CMA, 1984; Connor et al., 1980; Pullin, 1977). In rats, aberrations in bone marrow cells were observed (Procter and Gamble Co., 1979).

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

Table 3. Genotoxicity Studies of BGE

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
***In Vitro* Assays**						
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p.	5, 10, 25, or 100 µL/plate (34.9, 69.7, 174, or 697 mol/plate) of a 0.15% (v/v) solution	positive*: TA100 at ≥25µL/plate and TA1535 at ≥10 µL/plate (-S9); TA1535 at ≥5µL/plate (+S9)	Confidential (1977)
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE (R0065), purity n.p.	8.2, 24.7, 74, 222.2, 666.7, or 2000 µg/mL (0.063, 0.190, 0.57, 1.706, 5.120, or 15.36 mM)	positive* (TA100 and TA1535)	Procter and Gamble Co. (1979)
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, >99% pure	8.2, 24.7, 74.0, 222.2, 666.7, or 2000 µg/plate (0.06, 0.190, 0.568, 1.706, or 15.36 µmol/plate)	positive* (TA100, TA1535); response enhanced with S9	Thompson et al. (1981)
S. typhimurium strains TA97, TA98, TA100, and TA1535	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p.	33, 100, 333, 1000, or 3333 µg/plate (0.25, 0.768, 2.56, 7.680, or 25.60 µmol/plate)	positive* (TA97, TA100, TA1535)	Canter et al. (1986)
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p.	260 µg/plate (2.00 µmol/plate)	positive* (TA100, TA1535); dose-dependent response seen with TA1535 (260-520 µg/plate [2-4 µmol/plate])	Connor et al. (1980)
S. typhimurium strains TA98 and TA1535	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p.	0.5, 1.0, or 2.0 µmol/plate (65, 130, or 260 µg/plate)	positive* (TA1535); dose-dependent response seen; S9 deactivated chemical	Pullin (1977)
S. typhimurium strains TA1535 and TA1538	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p.	0.2, 2, 20, 100, 250, 500, or 2000 µg/plate (0.002, 0.01, 0.15, 0.768, 1.92, 3.84, or 15.36 µmol/plate)	positive	Shell Oil Co. (1978)

Table 3. Genotoxicity Studies of BGE (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
S. typhimurium strains TA98 and TA100	reverse mutation (*his*$^{+/-}$ revertant colonies)	+/-	BGE, purity n.p	0.05 or 10.00 mg (0.38 or 76.80 µmol) [spot tests]	positive* (TA100)	Wade et al. (1979)
S. typhimurium strains TA98 and TA1535	reverse mutation (*his*$^{+/-}$ revertant colonies)	**	BGE, purity n.p.	200 mg/kg (1.54 mmol/kg)	Urine Assay—10F ICR mice were given BGE orally daily for 4 days. negative	Connor et al. (1980)
S. typhimurium strains TA98 and TA1535	reverse mutation (*his*$^{+/-}$ revertant colonies)	**	BGE, purity n.p.	750, 1500, or 3000 mg/kg (5.76, 11.52, or 23.04 mmol/kg)	Urine Assay—10M BDF mice dermally treated with 1500 mg/kg 3x/wk for 8 wk or 15M with 750, 1500, or 3000 mg/kg 3x/wk for 16 wk negative	Connor et al. (1980)
S. typhimurium strain TA1535	reverse mutation (*his*$^{+/-}$ revertant colonies)	**	BGE, purity n.p.	200 mg/kg (1.54 mmol/kg)	Urine Assay—10F $B_6D_2F_1$ and 10F ICR mice were given BGE orally daily for 4 days. negative	Pullin (1977)
S. typhimurium (strains not specified)	reverse mutation (*his*$^{+/-}$ revertant colonies)	n.p.	BGE, purity n.p.	200 mg/kg (1.54 mmol/kg)	Host-mediated Assay—10F ICR mice given BGE orally daily for 5 days; bacteria inoculated into peritoneal cavity of mice. negative	Pullin (1977)
Escherichia coli strain PQ37	SOS chromotest (*recA* response)	+/-	BGE, 98% pure	0.3, 1.0, 3.3, or 10.0 mM (39, 130, 430, or 1300 µg/mL)	positive	von der Hude et al. (1990)
Balb/3T3 cells	transformation	NA	BGE, purity n.p.	10, 33, 100, 330, or 670 µg/mL (0.077, 0.25, 0.77, 2.53, or 5.15 mM)	negative (single 2-h exposure period or exposure split into 2 treatments separated by 24 h)	Connor et al. (1980)

Table 3. Genotoxicity Studies of BGE (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
Mouse lymphoma cells, L5178Y *Tk*+/- locus	gene mutation (TK-deficient mutants)	+/-	BGE, >99% pure	84, 100, 130, 164, 200, 256, 300, 320, 400, 500, 640, or 800 µg/mL (0.65, 0.77, 1.00, 1.26, 1.54, 1.97, 2.30, 2.46, 3.07, 3.84, 4.92, or 6.14 mM)	positive; dose-related mutagenic effect seen between 200-500 µg/mL	Thompson et al. (1981) [See also Procter and Gamble Co. (1979)]
Chinese hamster V79 cells	SCE	NA	BGE, 98% pure	1.25, 2.5, or 5.0 mM (0.163, 0.33, or 0.65 mg/mL)	positive	von der Hude et al. (1991)
WI38 cells	UDS (influx of ^{3}H-TdR in cell)	+/-	BGE, >99% pure	0.24, 0.36, 0.53, 0.8, or 1.2 µL/mL (1.67, 2.51, 3.70, 6, or 8.4 mM) [+S9]; 0.5, 1.0, 2.0, 4.0, or 8.0 µL/mL (4, 7.0, 14, 28, or 56 mM) [-S9]	weak and demonstrable, but not considered positive, response (+S9)	Thompson et al. (1981) [See also Procter and Gamble Co. (1979)]
Human peripheral blood lymphocytes (HPBL)	UDS	NA	BGE, purity n.p.	4.1, 10, 12.4, 37, 100, 111, 333, 500, or 1000 µg/mL (0.031, 0.077, 0.0952, 0.28, 0.768, 0.852, 2.56, 3.84, or 7.680 mM)	positive	Frost and Legator (1982)
HPBL	UDS	NA	BGE, purity n.p.	1, 10, 100, or 500 ppm (0.008, 0.077, 0.768, or 3.84 µM)	positive; linear dose-response relationship seen	Pullin (1977)

Table 3. Genotoxicity Studies of BGE (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
***In Vivo* Assays**						
Mice, BDF hybrid, 8- to 10-wk-old, 10M and F (number n.p.)	chromosomal aberration/germ cell mutation	NA	BGE, purity n.p.	1.5 g/kg (12 mmol/kg) given topically	Dominant Lethal Assay—BGE was topically applied to M 3x/wk for 8 wk, which were then mated to 3F per wk for 3 wk. All F were sacrificed 13-14 days from the midweek of presumptive mating. In comparison to controls, treated animals had a significant increase in fetal deaths (proportion of deaths per pregnancy) at 1 wk post treatment and a significant reduction in the number of implants per pregnancy at 2 wk post treatment. The number of pregnant females in the test group was significantly lower than that in the control group.	Pullin (1977)
Mice, $B_6D_2F_1$, 8- to 10-wk old, 10-20M and F (number n.p.)	chromosomal aberration/germ cell mutation	NA	BGE, purity n.p.	0.75, 1.5, or 3.0 g/kg (5.8, 12, or 23 mmol/kg) given topically	Dominant Lethal Assay—repeat of above experiment using three doses An increase in fetal deaths occurred only at the HD. Significant reductions in pregnancy rates were observed at the MD and HD.	Whorton et al. (1983)

Table 3. Genotoxicity Studies of BGE (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
Mice, BDF hybrid, 8- to 10-wk-old, 155M and 2325F	chromosomal aberration/germ cell mutation	NA	BGE, >95% pure	0.375, 0.750, or 1.50 g/kg (2.88, 5.76, or 11.5 mmol/kg) given topically	Dominant Lethal Assay (2 experiments conducted)—BGE was topically applied to M 3x/wk for 8 wk, which were then mated to 3F per wk for 3 wk. All F were sacrificed 13-14 days from the midweek of presumptive mating. No significant dose-related changes in pregnancy rates or average number of implants per pregnant F were observed. The fetal death rate (7.83%) was increased by the end of wk 1 at the HD in the first experiment; this was comparable to that for controls (7.33%) for the same time period in the second experiment. No significant dose-related testicular changes or changes in sperm count viability were observed.	Whorton et al. (1983)
Mice, BDF, age n.p., 9F (1 died)	micronuclei	NA	BGE, purity n.p.	200 mg/kg (1.54 mmol/kg) given via gavage for 5 days	No increase in micronuclei was observed.	Connor et al. (1980); Pullin. (1977)
Mice, BDF, age n.p., 5F when dose given 1x and 10F when given 2x (1 died in the HD groups)	micronuclei	NA	BGE, purity n.p.	225, 450, 675, or 900 mg/kg (1.73, 3.46, 5.18, or 6.91 mmol/kg) given as an i.p. injection 1x or 2x (24 h apart)	Dose-related increases in micronuclei were observed.	Connor et al. (1980)
Mice, strain, age, number, and sex n.p.	micronuclei	NA	BGE, purity n.p.	200, 225, or 675 mg/kg (1.54, 1.73, or 5.18 mmol/kg) bw daily given as an i.p. injection for 5, 2, or 1 days, respectively	Increased frequency of micronucleated polychromatic erythrocytes was observed at the mid- and high-dose levels.	CMA (1984)

Table 3. Genotoxicity Studies of BGE (Continued)

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results/Comments	Reference
Rat, Sprague-Dawley CR-1:COBS®CD®BR, age n.p., 5M and 5F per dose group	chromosomal aberrations	NA	BGE (R0065), >99% pure	31.3, 104.2, or 312.5 mg/kg (0.240, 0.8002, or 2.400 mmol/kg) bw daily given as an i.p. injection for 5 days	Aberrations in bone marrow cells were observed.	Procter and Gamble Co. (1979)

*Negative results were obtained in the other strains tested. **with or without β-glucuronidase (200 units/plate)
Abbreviations: bw = body weight; F = female(s); h = hour(s); ^{3}H-TdR = tritiated thymidine; i.p. = intraperitoneal(ly); HD = high dose; M = male(s); MD = mid dose; NA = not applicable; n.p. = not provided; TK = thymidine kinase; SCE = sister chromatid exchange; UDS = unscheduled DNA synthesis; wk = week(s); + = presence; - = absence

9.9 Immunotoxicity

The details of the following studies are presented in **Table 4**. In sensitization tests with guinea pigs, BGE (0.1-25% solution) produced positive results (Ciba-Geigy, 1977; Reichhold Chem. Co., 1978; Weil et al., 1963).

9.10 Other Data (Hemopoietic Effects)

Intramuscular injections of BGE (400 mg/kg [3.07 mmol/kg]) on three consecutive days slightly increased leukocyte counts in rats but had no effects on the number of white blood cells; no further investigations were made by the authors (Kodama et al., 1961).

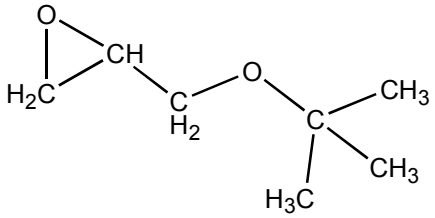
In male C_3H/Hej mice given a single i.p. injection of BGE (4 mg/mouse [1.1 mmol/kg bw]), an hemoglobin binding index of 1.2 pmol/g globin was reported. This slightly lower value compared to that of propylene oxide (~1.4 pmol/g) suggested rapid detoxification of BGE in the mouse (Licea Pérez et al., 1997).

10.0 Structure-Activity Relationships

Several reviews on glycidyl ethers have been published (e.g., Eastman Kodak Co., 1977; ERSTG, 2002a; Gardiner et al., 1992, 1993; IARC, 1989; NIOSH, 1978; and Santodonato et al., 1985). Some reports have compared the alkylating and mutagenic reactivity of BGE with related compounds as a potential mechanism for carcinogenesis (Fishbein, 1981; Hemminki and Vainio, 1980; Hemminki et al., 1980). Others have reviewed sensitization tests for evaluating structure-activity relationships (Dow Chem. Co., 1986).

Available toxicity data for *t*-BGE and allyl glycidyl ether (AGE), analogues of *n*-BGE, and for bisphenol A diglycidyl ether (BADGE), the most common active component in epoxy resins, are presented in this section.

<u>*tert*-Butyl glycidyl Ether (*t*-BGE) [CASRN 7665-72-7]</u>



Acute Toxicity: In mice, an oral LD_{50} of 1.53 g/kg was reported. For rats, the value was >2 g/kg (Hine et al., 1956; Weil et al., 1963). When male rats were given a single dose of *t*-BGE (0.126-2 g/kg bw) via gastric intubation, slight accumulation of darkened material around the external nares and slight edema on the mucosal surface of the stomach were observed at 1 g/kg. One rat died at the high dose (ERSTG, 2002c). When female rats were exposed to *t*-BGE (up to 3333 ppm) for up to seven hours, no signs of toxicity were observed. When a concentration of 16,180 ppm was administered, 80% mortality occurred (Dow Chem. Co., 1982; Gardiner et al., 1992).

Table 4. Immunotoxicity Studies of BGE

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Guinea pigs, strain n.p., age n.p., 17, and sex n.p.	BGE, purity n.p.	intracutaneous injection of 0.1 mL of diluted BGE 3x/wk on alternate days (total of 8 injections); 3-wk incubation period followed by challenge dose; observed at 24 and 48 h	16 of 17 animals showed sensitization.	Weil et al. (1963)
Guinea pigs, Pirbright white, age n.p., 10M and 10F	BGE (called TK10408), purity n.p.	intracutaneous injection of 0.1 mL of a 0.1% dose in saline every 2nd day (total of 10 injections) on the back and/or right flank; challenge dose (0.1 mL of 0.1% dilution) followed 14 days later into skin of left flank; observed 24 h after induction and 24 h after challenge	11 of 19 animals (1 died) showed sensitization.	Ciba-Geigy (1977)
Guinea pigs (albino), strain n.p., age n.p., 12F	BGE, purity n.p.	intradermal injection of 0.1 mL of a 10% dose in propylene glycol 3x, followed by topical application 1 wk later for 48 h and then a challenge dose (patch tested with 0.1% dilution) 2 wk later*	6 of 12 animals showed sensitization. Cross sensitivity to Epoxide No. 8 was found in all animals and to cresyl glycidyl ether in 4 animals.	Reichhold Chem. Co. (1978)
Guinea pigs, Hartley albino, age n.p., 20, sex n.p.	BGE, purity n.p.	patch (induction) application of 25% solution in 80% ethanol 1x/wk for 3 wk on the back, followed by a 2-wk rest period and then a challenge application (1% solution in acetone); observed at 24 and 48 h	1 animal showed moderate erythema, while 18 animals had slight confluent or moderate patchy erythema.	Reichhold Chem. Co. (1978)

*Microfiche OTS0523514 could not be clearly focused and read. The method described may contain errors.
Abbreviations: F = female(s); h= hour(s); M = male(s); n.p. = not provided; wk = week(s)

In rabbits, dermal application of *t*-BGE (dose n.p.) produced blanching with severe erythema, edema, and necrosis. In the eye, slight conjunctival inflammation, slight corneal injury, and iritis, all reversible, were seen (Gardiner et al., 1992).

Short-term or Subchronic Toxicity: In a two-week inhalation study, mice, rats, and rabbits were exposed to *t*-BGE (100-1000 ppm) for six hours per day, five days per week. All species exhibited rhinitis, lethargy, and gait changes. At 300 ppm, liver weights were decreased. At 300 and 1000 ppm, mean body weights were decreased in all animals. Gross pathological examination revealed decreases in body fat, thymic size, and lymphoid organs. At the high dose, 4 of 6 female mice and all rabbits died (ERSTG, 2002b,c).

In a 13-week vapor inhalation study, mice, rats, and rabbits were exposed to *t*-BGE (25, 75, or 225 ppm) for six hours per day, five days per week. All animals appeared normal and healthy throughout the study. At the high dose, decreased body weight gain, affiliated decreases in organs weights (e.g., thymus), inflammation of the nasal mucosa, and hyperplasia and/or flattening of the nasal respiratory epithelium were observed. At the mid dose, minor effects were seen in mice and rats. Additionally, rabbits had atelectasis of the lung at doses ≥75 ppm (ERSTG, 2002b; Gardiner et al., 1992, 1993).

In all three species, the no observable adverse effect level (NOAEL) reported for the two-week inhalation study was 100 ppm and for the 13-week inhalation study was 25 ppm (ERSTG, 2002b).

Cytotoxicity: In HPBL, *t*-BGE (10-3000 µg/mL) was found to be less toxic than *n*-BGE; viability ranged from 94.1 % (at 12.2 µg/mL) to 72.2% (at 3000 µg/mL) (Frost and Legator, 1982).

Reproductive and Developmental Toxicity: Effects on the reproductive organs in mice, rats, and rabbits exposed to *t*-BGE via inhalation for up to 13 weeks were studied (see short-term studies discussed above). No adverse effects were observed in any animals in either sex (ERSTG, 2002b).

Genotoxicity: *t*-BGE was less mutagenic *in vitro* compared to *n*-BGE. In *S. typhimurium* strains TA98 and TA1535, the urine from the treated mice showed mutagenicity with the addition of β-glucuronidase (Connor et al., 1980 abstr.). In *S. typhimurium* strains TA100 and TA1535, *t*-BGE (up to 6666 µg/plate) was mutagenic with and without S9 (Canter et al., 1986; Dow Chem. Co., undated; Gardiner et al., 1992). Other studies reported *t*-BGE (doses n.p.) was mutagenic to TA100 only without S9 and not mutagenic to TA98, TA1535, and TA1537 in the presence or absence of S9 (IARC, 1989). Additionally, mutagenic constituents were found in the urine of mice treated with *t*-BGE (100-400 mg/kg) with the addition of β-glucuronidase (Dow Chem. Co., undated).

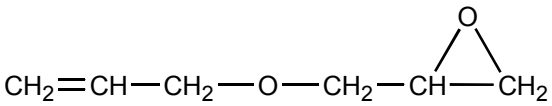
t-BGE (0.3, 1.0, or 3.3 M) was mutagenic in the SOS chromotest with *E. coli* strain PQ37 (von der Hude et al., 1990). In Chinese hamster V79 cells, BGE (0.31-5.0 mM) induced sister chromatid exchanges (SCEs) (von der Hude et al., 1991). In HPBL, *t*-BGE (10-3000 µg/mL) induced UDS at doses up to 333 µg/mL (Dow Chem. Co., undated; Frost and Legator, 1982). *In*

vivo, *t*-BGE (100, 200, or 400 mg/kg) administered orally to mice for five days produced base-pair mutations in *S. typhimurium* strain TA1535.

In *in vivo* studies with mice, negative results were obtained with *t*-BGE (micronucleus test with 100, 200, or 400 mg/kg/day for 5 days and a dominant lethal assay with 385, 750, or 1500 mg/kg three times per week for eight weeks) (Gardiner et al., 1992).

Immunotoxicity: In the guinea pig maximization test, *t*-BGE (study details n.p.) was negative (IARC, 1989). When *t*-BGE was applied topically to guinea pigs as a 5% solution in DOWANOL DPM:Tween 80 (9:1), negative results were also obtained. However, repeated skin contact with *t*-BGE (1% in 80% ethanol for induction and 1% in acetone for challenge) caused weak dermal hypersensitization (Gardiner et al., 1992).

Allyl Glycidyl Ether (AGE) [CASRN 106-92-3]



Human Data: Skin contact with AGE has caused dermatitis, sensitization, irritation, and allergic reactions. Signs and symptoms of occupational dermatitis resulting from exposure to AGE included tenderness, reddening, itching, swelling, blister formation, and whitish macules. In a very early study of workers exposed to AGE at a plant (during the period 1947 to 1956), one case of eye irritation was reported, and four of 23 workers with occupational dermatitis developed sensitivity reactions to AGE. When AGE (diluted to 0.25% in acetone) was used in patch tests in 20 patients, two had allergic reactions to the chemical (Gardiner et al., 1992, 1993).

Acute Toxicity: In mice, an oral LD_{50} value of 390 mg/kg was reported; in rats, the value was 1164 mg/kg for males and 830 mg/kg for females (values up to 1600 mg/kg have been reported). Additionally, a four-hour LC_{50} value of 270 ppm was calculated in mice, while a seven-hour LC_{50} of 308 ppm and an eight-hour LC_{50} of 670 ppm were reported in rats. In rabbits, the dermal LD_{50} was 2550 mg/kg (Gardiner et al., 1992, 1993).

Symptoms of oral administration of AGE included reduced motor activity, incoordination, ataxia, CNS depression, hyperkeratosis, and ulceration. Cutaneous application produced irritation, varying from severe erythema to eschar formation. When male rats were exposed to AGE (100-2600 ppm) for seven hours, 100% mortality was observed within 72 hours in groups receiving ≥375 ppm, while two of six rats died at a dose of 300 ppm. At ≥300 ppm, the rats had dyspnea, aerophagia, irritation of the nasal turbinates and pulmonary tract, nasal discharge, and discoloration and gross pathologic effects in liver and kidneys. In another inhalation experiment, mice and rats were exposed to graded concentrations of AGE that approached saturation (doses n.p.). Pneumonitis and discoloration of liver and kidneys were generally observed; hepatic focal inflammatory cells and moderate congestion of the central zones were occasionally observed. Pulmonary toxicity was also reported in mice administered AGE (105-185 ppm) via tracheal cannulation for two hours (Gardiner et al., 1992, 1993).

In the Draize test, AGE was found to be a severe eye irritant and a moderate skin irritant (Gardiner et al., 1992, 1993).

Short-term or Subchronic Toxicity: In mice exposed to AGE (2.5 or 7.1 ppm) via inhalation for six hours per day for 4, 9, or 14 days, nasal cavity lesions (necrosis of the respiratory epithelium and erosion of the olfactory epithelium) were observed with the higher dose at the four-day exposure period. At 9 and 14 days, restorative responses were reported (Gardiner et al., 1992). A two-week inhalation study in which mice were exposed to concentrations up to 100 ppm AGE and rats to levels up to 500 ppm AGE, 100% mortality was seen in rats at the high dose. All male mice and three of five female mice died at their high dose. Both species showed acute inflammation of the nasal passage and major airways (NTP, 1990).

In a ten-week inhalation study, rats exposed to AGE (260-900 ppm) for seven hours per day, five days per week had decreased body weight gain. At the lowest dose, slight eye irritation and respiratory distress were observed. At 400 ppm, the kidney/body weight ratio was significantly increased; animals had decreased peritoneal fat, severe emphysema, mottled liver, and enlarged and congested adrenal glands. At ≥600 ppm, abnormal changes in the lungs were seen but to a more severe extent (i.e., bronchopneumonic consolidation, severe emphysema, bronchiectasis, and inflammation). In addition, two rats had necrotic spleens at the highest dose tested (Gardiner et al., 1992, 1993).

When rats were exposed to concentrations up to 200 ppm and mice to levels up to 30 ppm for 13 weeks, decreased final mean body weights were reported in male rats at doses ≥10 ppm and in female and male mice at 30 ppm. Irritation of the upper respiratory tract and eyes were also observed in the animals. Histologic lesions included squamous metaplasia of the nasal passage and epithelial erosions in both mice and rats (NTP, 1990).

Reproductive and Developmental Toxicity: In rats given an i.m. injection of AGE (400 mg/kg) for three nonconsecutive days, testicular degeneration was observed but was not statistically significant. In one of the three surviving rats, focal necrosis of the testis was also seen (Gardiner et al., 1992). When rats were administered AGE vapor (300 ppm) via inhalation for seven hours per day, five days per week for a total of 50 exposures, testicular atrophy occurred in five of ten rats, and small testes was found in one of ten rats (Gardiner et al., 1993).

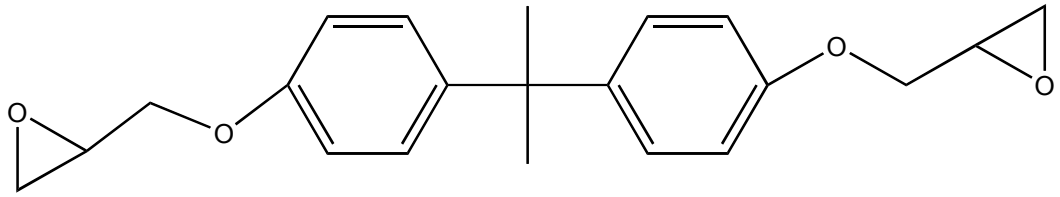
In an eight-week inhalation study of the reproductive effects of AGE in rats (up to 200 ppm) and mice (up to 30 ppm), significant reduction in the mating performance of male rats was observed; however, no effect on sperm morphology, motility, or number was seen. No effects in female rats or male or female mice were reported (NTP, 1990).

Carcinogenicity: In a two-year inhalation carcinogenicity study, male and female Osborne-Mendel rats and $B_6C_3F_1$ mice (n=50/sex/dose) were exposed to AGE (5 or 10 ppm) six hours per day, five days per week. At the higher dose, male rats had one papillary adenoma and one squamous cell carcinoma both of respiratory epithelial origin and one poorly differentiated adenocarcinoma of olfactory epithelial origin in the nasal turbinates. At the lower dose, one female rat had a papillary adenoma of the respiratory epithelium. At 10 ppm, three adenomas of the respiratory epithelium, dysplasia in four males, and focal basal cell hyperplasia of the

respiratory epithelium in the nasal passages of seven males were observed. Female mice had one adenoma of the respiratory epithelium, and seven of the animals had focal basal cell hyperplasia of the respiratory epithelium. It was concluded that there was equivocal evidence of carcinogenicity in male rats and female mice, no evidence supporting a carcinogenic effect in female rats, and some evidence for a carcinogenic response in male mice (NTP, 1990, 2004).

Genotoxicity: In *S. typhimurium* strains TA100 and TA1535, AGE was mutagenic with and without S9; negative results were seen in strains TA98 and TA1537 (Gardiner et al., 1992; NTP, 1990). In Chinese hamster ovary (CHO) cells, AGE induced SCEs and chromosomal aberrations both in the presence and absence of S9. In *Drosophila melanogaster* male germ cells, AGE (5500 ppm) induced a significant increase in sex-linked recessive lethal mutations. Positive and negative results were obtained in micronucleus tests (NTP, 1990, 2004).

2,2-Bis-[*p*-(2,3-glycidyloxy)phenyl]propane (BADGE) [CASRN 1675-54-3]



[Note: No attempt to summarize the BADGE studies contained in the International Agency for Research on Cancer (IARC) Monograph for glycidyl ethers (1989, Vol. 47, pp. 237-261) was made. Instead, the reader is directed to that source. Several studies mentioned below, however, are included in the monograph. Their inclusion here was the result of the papers simultaneously reporting BGE and BADGE data.]

Human Data: Surveys regarding occupational skin diseases from exposure to epoxy resins, including BADGE epoxy resins, have been conducted (e.g., see Jolanki, 1991). In a recent study, patch testing of BADGE (1.0% w/w in petroleum) with a two-day occlusion in 1416 patients resulted in 46 cases of allergic reaction (3.2%) (Kanerva et al., 1999). Furthermore, an investigation of occupational contact dermatitis in workers utilizing immersion oil for microscopy found BADGE (28-30%) in the oil using HPLC analysis (Le Coz et al., 1999).

Acute Toxicity: In rats, the oral LD_{50} value was reported as 19.6 mL/kg. In rabbits, the dermal LD_{50} was calculated to be >20 mL/kg (Weil et al., 1963).

Short-term or Subchronic Toxicity: In mice, dermal application of BADGE (1, 10, or 100 mg/kg) for 13 weeks produced mild to moderate chronic active dermatitis. At the high dose, spongiosis and epidermal micro abscess formation were observed. In rats, dermal application of BADGE (10, 100, or 1000 mg/kg) for 13 weeks resulted in a decrease in body weight at the high dose. The no-observable effect level (NOEL) for dermal exposure was 100 mg/kg for both sexes. In a separate study, application of BADGE (same doses) five times per week for ~13 weeks not only caused a decrease in body weight but also produced chronic dermatitis at all dose levels in males and at >100 mg/kg in females (as well as in a satellite group of females given 1000 mg/kg) (U.S. EPA, 1997).

Reproductive and Developmental Toxicity: BADGE (50, 540, or 750 mg/kg) administered to rats via gavage for 14 weeks (P1) or 12 weeks (P2) produced decreased body weight in all males at the mid dose and in both males and females at the high dose, but had no reproductive effects. The NOEL for reproductive effects was 750 mg/kg (U.S. EPA, 1997).

Carcinogenicity: IARC concluded that "there is limited evidence for the carcinogenicity of bisphenol A diglycidyl ether in experimental animals." Its overall evaluation was "Bisphenol A diglycidyl ether is not classifiable as to its carcinogenicity to humans (Group 3)" (IARC, 1989).

In a lifetime tumorigenicity study in which 90-day-old C3H mice received three dermal applications per week of BADGE (undiluted dose) for 23 months, only one out of 32 animals developed a papilloma after 16 months. A retest, in which skin paintings were done for 27 months, however, produced no tumors (Weil et al., 1963). In another lifetime skin-painting study, BADGE (dose n.p.) was also reported to be noncarcinogenic to the skin of C3H mice; it was, however, weakly carcinogenic to the skin of C57BL/6 mice (Holland et al., 1979; cited by Canter et al., 1986). In a two-year bioassay, female Fisher 344 rats dermally exposed to BADGE (1, 100, or 1000 mg/kg) showed no evidence of dermal carcinogenicity but did have low incidences of tumors in the oral cavity (U.S. EPA, 1997).

Genotoxicity: In *S. typhimurium* strains TA100 and TA1535, BADGE (10-10,000 µg/plate) was mutagenic with and without S9; negative results were obtained in TA98 and TA1537 (Canter et al., 1986; Pullin, 1977). In a spot test, BADGE (0.05 or 10.00 mg) failed to show mutagenicity in strains TA98 and TA100 (Wade et al., 1979). Negative results were also obtained in the body fluid test using urine of female BDF and ICR mice (1000 mg/kg BADGE), the mouse host-mediated assay (1000 mg/kg), micronucleus test (1000 mg/kg), and dominant lethal assay (~3000 mg/kg) (Pullin, 1977).

Immunotoxicity: Intracutaneous injection of diluted BADGE (0.1 mL) three times per week on alternate days (total of 8 injections) followed by a three-week incubation period and a challenge dose produced sensitization in 19 of 20 guinea pigs (Weil et al., 1963).

Other Structurally Related Compounds

A structural similarity search was performed using the ChemIDplus chemical database (undated-b; URL http://chem.sis.nlm.nih.gov/chemidplus/cmplxqry.html; last accessed on December 2, 2003). A total of 26 chemicals, including AGE, were identified that have chemical structures which are >80% similar to that of BGE. These chemicals are listed in **Table 5** along with their percentage of similarity to BGE.

Table 5. Structural Analogues of BGE

Chemical Name	CASRN	Formula	Structural Similarity (%)
((Pentyloxy)methyl) oxirane	7297-11-2	C8-H16-O2	95.36
Oxirane, ((hexyloxy)methyl)- (9CI)	5926-90-9	C9-H18-O2	94.17
Oxirane, ((2-butoxyethoxy)methyl)-	13483-47-1	C9-H18-O3	92.37
Dodecyl glycidyl ether	2461-18-9	C15-H30-O2	92.07
Oxirane, ((tetradecyloxy)methyl)-	38954-75-5	C17-H34-O2	92.07
Oxirane, ((hexadecyloxy)methyl)-	15965-99-8	C19-H38-O2	92.07
Oxirane, ((octadecyloxy)methyl)-	16245-97-9	C21-H42-O2	92.07
((Octyloxy)methyl)oxirane	3385-66-8	C11-H22-O2	92.07
((Decyloxy)methyl)oxirane	3497-06-1	C13-H26-O2	92.07
((Nonyloxy)methyl)oxirane	10580-65-1	C12-H24-O2	92.07
Propane, 1,2-epoxy-3-propoxy-	3126-95-2	C6-H12-O2	91.77
Oxirane, (((9Z)-9-octadecenyloxy)methyl)-	60501-41-9	C21-H40-O2	87.79
Ethyl glycidyl ether	4016-11-9	C5-H10-O2	87.60
Oxirane, (((2-ethylhexyl)oxy)methyl)-	2461-15-6	C11-H22-O2	84.64
((Isopentyloxy)methyl)oxirane	15965-97-6	C8-H16-O2	84.63
((Isononyloxy)methyl)oxirane	28965-88-0	C12-H24-O2	84.11
1,4-Bis(2,3-epoxypropoxy)butane	2425-79-8	C10-H18-O4	83.42
Denacol EX-131	930-37-0	C4-H8-O2	82.79
Octene-1,2-oxide	2984-50-1	C8-H16-O	82.14
Oxirane, 2,2'-(1,6-hexanediylbis(oxymethylene))bis-	16096-31-4	C12-H22-O4	81.73
Heptane, 1,2-epoxy- (8CI)	5063-65-0	C7-H14-O	81.64
Hexane, 1,2-epoxy-	1436-34-6	C6-H12-O	81.56
Allyl glycidyl ether	106-92-3	C6-H10-O2	80.63
Bis(1,2-epoxypropylether)ethanediol	2224-15-9	C8-H14-O4	80.42
(Isobutoxymethyl)oxirane	3814-55-9	C7-H14-O2	80.31
((Cyclohexyloxy)methyl)oxirane	3681-02-5	C9-H16-O2	80.30

11.0 Online Databases and Secondary References

11.1 Online Databases

National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
IRIS
TOXLINE

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
BIOTECHNO	NIOSHTIC
CABA	NTIS
CANCERLIT	Registry
EMBASE	RTECS
ESBIOBASE	TOXCENTER

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

National Archives and Records Administration
Code of Federal Regulations (CFR)

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
µg/L = microgram(s) per liter
µg/m^3 = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
ACGIH = American Conference of Governmental Industrial Hygienists
AGE = allyl glycidyl ether
BADGE = 2,2-Bis-[*p*-(2,3-glycidyloxy)phenyl]propane; bisphenol A diglycidyl ether
BGE = butyl glycidyl ether
bw = body weight
CNS = central nervous system
EPA = Environmental Protection Agency
F = female(s)
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
HD = high dose
HPBL = human peripheral blood lymphocytes
HPV = high production volume
HSDB = Hazardous Substances Data Bank
i.g. = intragastric
i.p. = intraperitoneal(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC = liquid chromatography
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
LD = low dose
M = male(s)
MD = mid dose
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
NIOSH = National Institute for Occupational Safety and Health
n.p. = not provided

NTP = National Toxicology Program
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
ppb = parts per billion
ppm = parts per million
TSCA = Toxic Substances Control Act
TWA = time-weighted average
wk = week(s)
yr = year(s)

Appendix B: Description of Search Strategy and Results

n-Butyl Glycidyl Ether; BGE; (Butoxymethyl)oxirane (CAS RN 2426-08-6; ILS CODE X0010)

Nomination

(±)-*n*-Butyl glycidyl ether (BGE) is a high-production-volume (HPV) chemical used primarily as a reactive diluent in epoxy resins such as bisphenol A diglycidyl ether (BADGE) resins. The widespread use of these epoxy resins in electronics, construction, and coatings leads to potential worker exposure in numerous industries. (The cured resins, however, pose little hazard.) Glycidyl ethers contain the strained three-ring oxirane structure. Compounds with this moiety are alkylating agents that may damage DNA. Many compounds containing the epoxy moiety have been shown to be carcinogens (e.g., ethylene oxide and diepoxybutane).

Search Strategy

The searches began at the U.S. EPA web site to retrieve the Test Plans and Robust Summaries for BGE produced by the Epoxy Resin Systems Task Group (ERSTG) of the Society of the Plastics Industry in response to EPA's HPV Challenge. General Internet searches with the Google search engine began on October 6 and continued through October 19. In the advanced search mode, searches may include exact phrases (generally synonyms or the CAS RN) and Boolean logic. One particularly fruitful approach was to require that all retrievals be in pdf file format. For example, **"2426 08 6" filetype:pdf** retrieves 468 URLs as of this writing. URLs for pdf files that were printed are in an attachment. Specific government sites visited included EPA, NIOSH, OSHA, NLM TOXNET, OEHHA, and the Code of Federal Regulations at http://frwebgate.access.gpo.gov. The IPCS Inchem site was searched for any publications by the World Health Organization (WHO), IARC, and other organizations listed on the home page (http://www.inchem.org). TOXNET databases searched with the CAS RN included ChemIDplus, HSDB, IRIS (no retrievals), TOXLINE, and EMIC. Internet links listed in the ChemIDplus record were followed if they had not already been discovered. A PubMed search was disappointing because the NLM search engine did not recognize exact phrases within quotation marks. Most of these searches were done by October 10.

Retrievals in PubMed (12, excluding three "false drops" that occurred by combining the search terms with AND) and EMIC (15) were also in the TOXLINE results. TOXLINE added the trade names Ageflex BGE and Sipomer BGE to the CAS RN. The 158 TOXLINE retrievals included about 60 unique publications and 85 TSCATS records. The flat ASCII text files retrieved from NLM do not distinguish the search terms in any way. Bolding was added to keywords during post-processing. The TOXLINE TSCATS records were missing information that was later found when searching the TSCATS file on RTKNet and at the Syracuse Research Corporation (SRC) web site. For example, one cannot tell from the TOXLINE records whether BGE was tested singly or merely in a mixture.

Simultaneous searches of the files MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, CABA, BIOTECHNO, EMBASE, ESBIOBASE, IPA, BIOSIS, TOXCENTER, and NTIS were done in

the STN International fee-based system on October 10. The history of the search session is reproduced below.

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L1        237 S 2426-08-6
L2          0 S 85858-60-2
L3        186 S BUTYL(W)GLYCIDYL(W)ETHER
L4        197 S GLYCIDYL(2A)BUTYL(W)ETHER
L5          2 S BUTOXYMETHYL(W)OXIRANE
L6          6 S BUTOXY(3A)EPOXYPROPANE
L7       1269 S BGE
L8        203 S L3 OR L4 OR L5 OR L6
L9        310 S L1 OR L8
L10        71 S L3 NOT L1
L11        39 S L10 NOT N(W)BUTYL
L12        11 S L11 AND (TERT(W)BUTYL OR T(W)BUTYL)
L13        11 SORT L12 1-11 TI
=> SET DUPORDER FILE
=> DUP REM L9
L14       246 DUP REM L9 (64 DUPLICATES REMOVED)
            ANSWERS '1-8' FROM FILE MEDLINE
            ANSWERS '9-10' FROM FILE CANCERLIT
            ANSWERS '11-31' FROM FILE NIOSHTIC          [Four used in search package]
            ANSWER '32' FROM FILE CABA
            ANSWERS '33-35' FROM FILE BIOTECHNO
            ANSWERS '36-38' FROM FILE EMBASE            [Two used in search package]
            ANSWERS '39-43' FROM FILE BIOSIS            [Two used in search package]
            ANSWERS '44-231' FROM FILE TOXCENTER        [Eighteen used in search package]
            ANSWERS '232-246' FROM FILE NTIS            [Two used in search package]
=> SAVE L9 X0010BIORAW/A
ANSWER SET L9 HAS BEEN SAVED AS 'X0010BIORAW/A'
=> SORT L14 TI 1-246
L15       246 SORT L14 1-246 TI
```

In a later session, the 33 hits for butylglycidyl(w)ether OR glycidylbutyl(w)ether retrieved a useful EMBASE record that was not in the original retrievals. A printout of TOXLINE citations in order by title was compared with titles of results from the STN International searches. Because the composite file TOXCENTER now contains most of the component files of TOXLINE, the STN International search retrieved the same literature as TOXLINE plus an additional 28 unique records included in the search package. The only duplications not removed automatically after the DUP REM command were those internal to TOXCENTER. These are easily recognized by viewing the titles in alphabetical order. Unique relevant records that were not in TOXLINE were printed. The records retrieved from STN International automatically include boldfaced search terms. The cost of the two STN sessions was $88.82. If a TOXLINE search had not been done, the cost would have been about $150 more. Approximately, eight extra hours of searcher labor were required to use the “free databases” TOXLINE, PubMed, and EMIC. (Labor cost to the project was at least three times the cost of paying for the extra STN records. In addition, the searcher was set back a day in preparing the search package.) Extra steps included (1) manual removal of internal duplicates and duplicates among the databases from the full downloaded set of retrievals, (2) manual comparison of TOXLINE citations with the titles resulting from the STN International search, and (3) manual boldfacing of keywords in the records retrieved from the free databases.

Search Results

The search package comprises unique database records (except for six "false drops" or topics of no interest) and first pages of relevant full documents retrieved from the Internet searches. They are grouped by arbitrary ILS alphanumeric and numeric codes that were used in the previous contract. Except for the reviews, which are discussed first, the topics are generally organized in the following discussion in the order in which they would appear in the report.

Authoritative Reviews (Subject Code 05)

Several reviews prepared by government agencies considered authoritative sources are available. However, many are brief and often repeat the same limited information. Among the brief reviews are the following:

- Documentation of the Threshold Limit Values and Biological Exposure Indices (ACGIH, 2001), 2 pp. on BGE
- NIOSH Pocket Guide to Chemical Hazards (NIOSH, undated web page), 1 page
- Occupational Safety and Health Guidelines for Chemical Hazards (NIOSH, 1988), 6 pp. on BGE
- Glycidyl Ether, NIOSH Current Intelligence Bulletin (NIOSH, 1979), 11 pp. from web site
- Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs), 1.5 pp.
- Hazardous Substance Fact Sheet (NJ DHHS, 1998), 6 pp.
- International Chemical Safety Card (WHO/IPCS/ILO, 1998), 2 pp.

Longer reviews identified are the following:

- "Some Glycidyl Ethers" in IARC Monographs, Vol. 47 (IARC, 1989), 25 pp.
- Occupational Exposure to Glycidyl Ethers (Criteria for a Recommended Standard) (NIOSH, 1978), 197 pp. [Three segments were retrieved from the NIOSH web site.]
- Occupational Toxicants, Vol. 4. by the [German] Commission for the Investigation of Health Hazards of Chemical Compounds (CIHHCC, 1992), 385 pp. on numerous compounds

A health effects review on BGE may be in 57 FR 26002-26601 (OSHA, 1992) [proposed amendments to existing standards for the maritime and construction industries]

Other Reviews (11)

Recently the Epoxy Resin Systems Task Group (ERSTG) of the Society of the Plastics Industry, Inc., submitted revised Test Plans and Robust Summaries for BGE in response to the U.S. EPA HPV Challenge. The summaries review the literature and describe some new studies (ERSTG, 2002a,b). ERSTG has also submitted similar documents for Alkyl (C_{12}-C_{14}) Glycidyl Ether, which may be useful for discussions of structure-activity relationships (SAR) as will the extensive discussion of *tert*-butyl glycidyl ether (*t*-BGE) studies in the BGE documents. Summaries include physical-chemical properties as well as health effects.

Sandodonato et al. (1985) of Syracuse Research Corporation (SRC) covered many of the topics of the present report in their review on glycidyl ethers (34 pp., 36 references). Another SRC review on epoxy resins also included information on BGE. Gardiner et al. (1992) of Shell Oil Company published a toxicology review of glycidyloxy compounds used in epoxy resin systems. The BGE review covers about five pages.

Other reviews include profiles in HSDB (2002), RTECS (2002), and the NTP repository database (Radian, 1991).

Chemical Identification (13a)

BGE is a low-molecular-weight glycidyl ether, Hill formula $C_7H_{14}O_2$. BGE synonyms and trade names may be found in the ChemIDplus and Registry records. The compound of commerce is racemic. Synonyms include 2-(butoxymethyl)oxirane, 1-butoxy-2,3-epoxypropane, and butyl 2,3-epoxypropyl ether.

Chemical-Physical Properties (13b)

Experimental and calculated chemical-physical properties may be found in the Registry record. Other sources collected include HSDB (2002), NIOSH (1978) (segment G of the criteria document), ERSTG (2002b), Shell (1983), and Shell (1999). Resolution Performance Products' reactive diluent product Heloxy Modifier 61 (principally BGE) has the lowest flashpoint of the modifiers offered by RPP (RPP, 2002b).

Analytical Methods (13c)

Sources of sampling and analysis methods for BGE include HSDB (2002). Levin et al. (1988) of NIOSH evaluated several solid adsorbents for glycidyl ethers in air. BGE in samples was best determined by gas chromatography with a flame ionization detector (GC/FID). Analytical method SCP-S81 by NIOSH (1975 [see also SRI, 1975]) has been revised and designated NIOSH Method 1616 (NIOSH, 1994). OSHA generalized Method 07 for organic vapors is also a GC/FID method with sampling by charcoal adsorption and organic solvent extraction (OSHA, undated). NIOSH Method 1616 is referenced for BGE. OSHA (2000) offered a secondary sampling and analysis method for BGE that uses an infrared spectrophotometer. The analytical method for passive sampling badges for personnel is also GC/FID (SKC Inc., 2003).

Commercial Availability

Producers (01a)

HSDB (2002) lists Dow Chemical USA and Shell Chemical Company as manufacturers. U.S. EPA OPPT HPV (2003) lists manufacturers in 1990, 1994, and 1998, including Ciba-Geigy, Ciba Specialty Chemicals, Rhone-Poulenc, and Air Products and Chemicals. Resolution Performance Products LLC (RPP) now operates the former Shell Chemical resins business independently. The BGE diluents and viscosity modifiers Epodil 741 and Heloxy Modifier 61 (H-61) are the brand names of Air Products and Chemicals and RPP, respectively.

Suppliers (01b)

Eastech Chemical, Inc. (2000) supplies BGE manufactured by Air Products and Chemicals. No U.S. suppliers/producers were listed in Chemcyclopedia 2003. Ciba Specialty Chemicals sells Ageflex BGE reactive diluent (ChemBuyersGuide, undated [web site]).

Numerous suppliers of liquid epoxy resins containing BGE as reactive diluent may be identified by searching for material safety data sheets or product data sheets in conjunction with the CAS RN using an Internet search engine. For example, see Electron Microscopy Sciences (1997), which supplies Araldite GY 506, a BADGE resin with BGE. An RPP epoxy resin containing BGE is EPON 815.

Production Processes (01d)

After condensation of n-butyl alcohol with epichlorohydrin, the product is dehydrochlorinated with caustic to form the epoxy ring (HSDB, 2002).

Production and Import Volumes (01c)

Huntsman (undated) in an analysis of the market for reactive diluents and flexibilizers for liquid epoxy resins indicated that the U.S. market for BGE is 1.4 million pounds or about 10% of the total market. U.S. EPA IUR (1998) listed the production volume of BGE as between less than 1 and 10 million pounds. U.S. EPA OPPT (1997) gave the production range as 3,469,790 to 5,243,788 lb (3.5 to 5.2 million pounds).

Other Processes (01e)

No other processing information was collected.

Uses (01f)

BGE has been the major reactive diluent added to liquid epoxy resins to reduce their viscosity for easier mixing and handling. Liquid epoxy resin producers are moving to less toxic reactive diluents such as propylene carbonate (Huntsman, undated). Ciba Specialty Chemicals' Ageflex BGE Reactive Diluent is marketed for "epoxies, laminating, flooring, electrical casting..." (ChemBuyersGuide, undated). Markets for Air Products and Chemicals' BGE product are diluents for epoxy resins used in coatings, inks, adhesives, and plastics (Eastech Chemicals, 2000). Tooling, electrical applications, and highly filled coatings are uses listed by Air Products and Chemicals (undated). BGE use in transmission electron microscopy was described by Arnold and Boer (1986).

Environmental Releases, Occurrence, and Fate (04)

No review was included in HSDB (2002), which is usually a good source for review of such studies if they exist. Some relevant studies were described or planned by ERSTG (2002b). Shell (1999) described evaporative losses before and after complete reaction in the epoxy resin systems..

Exposure Potential (02)

BGE is listed in the EPA Consumer Products database (Calif. EPA ARB, 1998). NIOSH has conducted several health hazard evaluation and industrial hygiene "walk-through" surveys of industrial plants. Air concentrations of BGE were generally below the OSHA limit (e.g., Belanger, 1986). Results from the National Occupational Exposure Survey (NOES) in 1981-1983 (NIOSH, 1990) for potential exposure to BGE (total 60,217 workers) are broken down by industry and by occupation. Biological monitoring of exposure includes analysis of expired air

and pulmonary function tests (OSHA, undated). Cytogenetic monitoring was not found to be useful (de Jong, 1988).

Regulations (24)

FDA (2003) regulates certain glycidyl ethers (but not BGE) for coatings for food-contact surfaces and packaging (21 CFR 175.300). OSHA (2003) has the same workplace air exposure limits for shipyards (29 CFR 1915.1000) and the construction industry (29 CFR 1926.55) as for general industry (29 CFR 1910.1000) (50 ppm or 270 mg/m^3). U.S. EPA regulates BGE under TSCA (e.g., 40 CFR 716.120). Pertinent sections of the following regulations have not yet been retrieved: 40 CFR 704, 40 CFR 712 (BGE not mentioned as of May 15, 2002), and 40 CFR 799. Requirements for the revision of the BGE Robust Summaries and Test Plans submitted by ERSTG in 2001 may be found in the letter designated in the search package as U.S. EPA OPPT (2002 lett.).

General Toxicology

In its proposed test rule action for glycidol and its derivatives, EPA reported results regarding health effects; reproductive/fertility effects; acute, subchronic and chronic toxicity; genotoxicity; and carcinogenicity in laboratory animals and bacteria (U.S. EPA, undated [TSCATS]).

A toxicological review of glycidyloxy compounds used in epoxy resin systems also provides a summary of available acute toxicity, subchronic toxicity, metabolism, and genetic toxicity studies, which includes studies reported below (Gardiner et al., 1992).

In September 2002, the Epoxy Resin Systems Task Group (ERSTG) published a review under the EPA High Production Volume (HPV) Chemical Challenge Program regarding the basic physical chemistry, environmental fate, ecotoxicity, and health effects information on BGE. When no data for BGE were available, information for *t*-butyl glycidyl ether, a surrogate chemical, was used. ERSTG gives a Klimisch rating (1, 2, and 4 were noted) for each reference. In addition, studies were rated on reliability using the following system: 1 w/o restriction; 2 w/ restriction; 3 not reliable; and 4 not assignable. The code was then usually followed with a reason.

Aquatic toxicity data are from Shell Oil Company [TSCATS]; 1 of the 4 TSCATS showed up in the TOXLINE search results. Acute toxicity: ERSTG reported an acute toxicity study using *t*-butyl glycidyl ether; the compound was found to be not highly toxic, and therefore, further testing was not recommended. Subchronic toxicity: Two inhalation studies for *t*-butyl glycidyl ether are presented. Immunotoxicity: Source showed up in search results. Using a 10% solution in DOWANOL DPM glycol ether/Tween 18 surfactant (9:1), application of 0.1 mL to the occluded back for 48 hours 3 separate times (induction phase) followed by application two weeks later to the unoccluded skin (challenge phase) did not induce delayed contact hypersensitivity (Dow Chem. Co., 1986 [TSCATS]). Genotoxicity: Both sources showed up in search results. In *Salmonella typhimurium* strains TA100 and TA1535, BGE (8.2-2000 µg/plate) was found to be positive in the presence and absence of metabolic activation (S9). In the mouse lymphoma assay, BGE (84-800 µg/mL) was also mutagenic with and without S9, while the compound (0.24-8.0 µL/mL) was not mutagenic in the unscheduled DNA synthesis test

(Thompson et al., 1981). In a dominant lethal assay in mice, BGE produced equivocal results at 1.5 g/kg (Whorton et al., 1983).

Human Data (18)

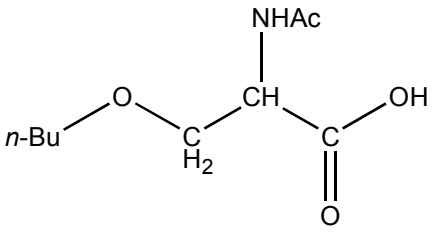
Acute toxicity: In two workers, exposure to BGE (contained in a grouting compound) via inhalation resulted in coughing, vomiting, ataxia, and headache within two hours. Irritation of the GI tract was related to length of exposure. One man was exposed for 90 minutes, the other for 4 hours. Within 24 hours, both men were admitted to a hospital. Minor effects on the central nervous system were also observed, while irritation of the respiratory tract was mild and of short duration (Wallace, 1979).

Immunotoxicity: Studies of the sensitization of epoxy resins have found the allergy due to resins of the glycidyl ether type (Berhbohm et al., 1975; Fregert and Rorsman, 1964; Jolanski, 1991; Kanerva et al., 1999; Prens et al., 1986). In a study of 20 patients, 14 reacted to phenyl glycidyl ether, 3 to BGE, and 2 to allyl glycidyl ether (Fregert and Rorsman, 1964). In a more recent study, occupational contact dermatitis from an immersion oil for microscopy found the presence of BADGE at a ±30% rate by HPLC (Le Coz et al., 1999).

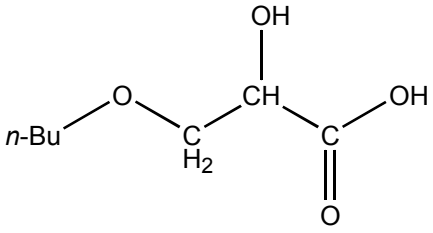
Reproductive toxicity: An Auburn reproductive health survey was conducted; among the chemicals tested was BGE (Boeing Company, 1988 [TSCATS]).

ADME (12)

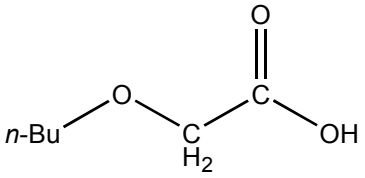
The metabolism of ^{14}C-BGE (20 mg/kg) was tested in Wistar rats and New Zealand white rabbits. Elimination was rapid, with most excreted in the first 24-hour period. After 96 hours, 91.5 and 80%, respectively, of the administered dose were excreted in the urine. The following urinary metabolites were identified (name; % in rats and % in rabbits): I (not further identified; 22 and 4%); II (3-butoxy-2-acetylaminopropionic acid; 26 and 2%); III (3-butoxy-2-hydroxypropionic acid; 10 and 45%); and IV (butoxyacetic acid; 11 and 7%) (Shell Oil Co., 1983 [TSCATS] [note: published as Eadsforth et al., 1985]).



II



III



IV

* *n*-Bu represents $CH_3(CH_2)_3$-

Acute Toxicity (03)

Numerous TSCATS (n>35) report acute toxicity for BGE, either alone or in a mixture; of these studies, 17 are classified as "Confidential." The studies include primary eye irritation tests and primary skin irritation tests in rats and rabbits. In rats, a dermal LD_{50}>2150 mg/kg bw has been reported, while in rabbits, an LD_{50} value of 778 mg/kg has been calculated (Ciba-Geigy, 1972; Dow Chem. Co., 1982). Additionally, inhalation studies have been conducted in both species. An LC_{50}>20 mg/L was reported for rats (Confidential, 1968; Proctor and Gamble Co., 1979). An acute oral toxicity study in rats showed that BGE (1.86-5.10 mg/kg bw) decreased respiratory rate and produced loss of righting reflex, loss of corneal reflex, papillary response, blanching, salivation, abdominal gripping, and motor activity. An oral LD_{50} value of 2.81 mg/kg was calculated (Confidential, 1969).

Shell Oil Co. (1956, 1957) conducted and reported data from acute toxicity studies in rats, mice, rabbits, and dogs via various routes (intragastric [i.g.], intraperitoneal [i.p.], inhalation, intramuscular [i.m.], and dermal application). From these, LD_{50} and LC_{50} values were calculated. Acute toxicity in rats has also been evaluated via intravenous (i.v.) injection. BGE (0.125 mL/kg bw) produced a pale kidney in one rat and a blotchy kidney and full GI tract in another rat (Proctor and Gamble Co., 1979).

Short-Term and Subchronic Toxicity (06a)

A 28-day inhalation study of BGE in rats has been reported; an abstract was not available (Ciba-Geigy, 1985 [TSCATS]).

Dermal application of BGE (1.5 g/kg per day, 3x per week for 8 weeks) to the clipped skin of male mice produced an increased incidence of necrosis at the site of application (Shell Oil Co., 1979c [TSCATS]). In 1 out of 5 rabbits dermally exposed to BGE (100 mg/kg per day, 5x/week for 4 weeks), small white lesions were observed in the liver (Confidential, 1964 [TSCATS]). In a subchronic percutaneous study in rabbits, the toxic effects seen in acute inhalation, oral, or i.p. injection studies were not observed (Procter and Gamble Co., 1979 [TSCATS]).

Chronic Toxicity (06b)

Several TSCATS may report chronic exposure data; no abstract was available for confirmation (Eastman Kodak Co., 1972; Shell Oil Co., 1956, 1957; U.S. EPA, undated).

Reproductive and Developmental Toxicity (10)

In a dominant lethal assay in mice, BGE (0.375, 0.750, or 1.5 g/kg bw per day, 3x per week for 8 weeks) produced no significant dose-related changes in pregnancy rates or average number of implants per pregnant female. At the high dose, fetal death rates were increased by the end of week one (Cardello, 2002 letter; Thompson et al., 1981; Whorton et al., 1983). In a modified dominant lethal test of male mice exposed to BGE (same doses and exposure period) and then mated to females at three weeks, the following significant differences were observed between treated and control animals: decreased pregnancy rates, increased implants per pregnant female, and a decreased proportion of death implants (Cardello, 2002 letter; Shell Oil Co., 1979a,c [TSCATS]).

Carcinogenicity (07a)

As noted above, EPA may have carcinogenicity test results for BGE reported in its proposed test rule action for glycidol and its derivatives (U.S. EPA, undated).

Genotoxicity (09)

In Vitro Assays

Several studies have been conducted in *S. typhimurium* strains. In general, BGE was mutagenic in strains TA100 and TA1535 in the presence and/or absence of metabolic activation but not in TA98, TA1537, and TA1538 (Confidential, 1977 [TSCATS]; Dow Chem. Co., 1977, 1982 [TSCATS]; Shell Oil Co., 1977 [TSCATS]; Procter and Gamble Co., 1979 [TSCATS]; Wade et al., 1979). Urinary metabolites from mice orally treated with BGE (200 mg/kg bw per day for 5 days) were not mutagenic in the test system (Dow Chem. Co., 1977 [TSCATS]). Additionally, BADGE was found to be equivocal in the Ames test and positive in a cytogenetic test (Shell Oil Co., 1979b [TSCATS]).

In mouse lymphoma cells, BGE (100, 200, 300, 400, or 500 μg/mL) increased the mutation frequency of the thymidine kinase locus without activation (Procter and Gamble Co., 1979 [TSCATS]).

In human mononucleated cells, BGE (1, 10, 100, 500, or 1000 ppm) increased the rate of unscheduled DNA synthesis (UDS) at doses up to 100 ppm (Dow Chem. Co., 1977 [TSCATS]; Shell Oil Co., 1977 [TSCATS]). This was also observed in normal human peripheral blood lymphocytes at doses up to 333 μg/mL (Frost and Legator, 1982). In human diploid WI-38 fibroblasts, BGE (up to 6.25 μL/mL) produced a "weak" increase in UDS in the presence of metabolic activation (Procter and Gamble Co., 1979 [TSCATS]).

In Vivo Assays

In a modified dominant lethal assay conducted in mice, BGE (0.375, 0.750, or 1.5 g/kg bw) was mutagenic to male germ cells (Dow Chem. Co., 1977, 1982 [TSCATS]; Shell Oil Co., 1979a [TSCATS]). [Noted: Other TSCA test submissions (e.g., Shell Oil Co. 1978a, 1979a) using the same strain and high dose concluded that BGE was not mutagenic. The full reports will need to be reviewed.]

In mouse, i.p. injection of BGE (200, 225, or 675 mg/kg bw per day for 5, 2, or 1 days, respectively) caused an increase in the frequency of micronucleated polychromatic erythrocytes at the mid- and high-dose levels (Chem. Manuf. Assoc., 1984 [TSCATS]). Oral administration, however, failed to produce the change (Connor et al., 1980; Dow Chem. Co., 1982 [TSCATS]; Shell Oil Co., 1977 [TSCATS]; U.S. EPA, 1978 [TSCATS]). In rats, i.p. injection of BGE was clastogenic at dose levels as low as 31.3 mg/kg (Procter and Gamble Co., 1979 [TSCATS]).

Immunotoxicity (08)

Primary dermal sensitization studies using BGE in guinea pigs have been reported in several TSCATS (e.g., Ciba-Geigy, 1973, 1977; Confidential, 1969; and Dow Chem. Co., 1982). No TOXLINE or SRC abstracts, however, were available.

BGE was among the allergens tested in the DEREK skin sensitization rulebase and the murine local lymph node assay (LLNA) (Barratt and Langowski, 1999; Basketter et al., 1994, 2000; Haneke et al., 2001).

Other Biological Activities (14)

When mice i.p. injected with BGE (4 mg/mouse) and blood samples collected 24 hours after treatment, hemoglobin binding indices of 1.1-1.2 pmol/g globin were observed, similar to that of propylene oxide (~1.4 pmol/g globin) (Perez et al., 1997).

Structure-Activity Relationships (25)

Some reports have compared the alkylating reactivities of BGE and related compounds, which may indicate a mechanism for carcinogenesis (Hemminki and Vainio, 1980a,b; Hemminki et al., 1982). Other reports have compared the mutagenicities of BGE and related compounds as potential mechanisms of carcinogenesis (Dow Chemical, 1982; Fishbein, 1981). Still others have used sensitization tests for structure-activity correlations (e.g., Dow Chemical, 1984, 1986). Others have described other toxicity endpoints (e.g., inhalation toxicity of *t*-BGE and a five-week feeding study with Cardura E10 by Shell, 1981). The Test Plans and Robust Summaries for BGE (ERSTG, 2002a,b) used toxicity studies for *t*-BGE when comparable studies were unavailable for BGE. ERSTG (2002) has also summarized toxicity for longer-chain alkyl glycidyl ethers.