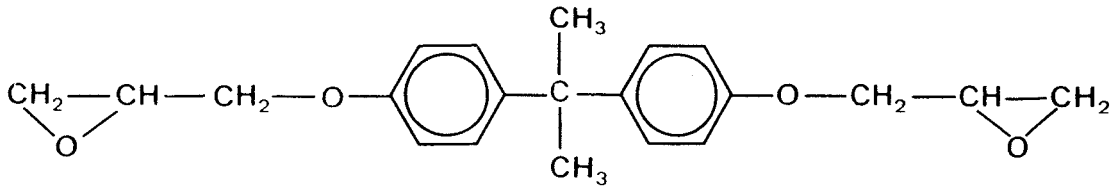
SOME GLYCIDYL ETHERS

This monograph covers bisphenol A diglycidyl ether and phenyl glycidyl ether, for which there were carcinogenicity studies in animals. Data on toxicity, genetic and related effects, as well as basic chemical information, are also included for nine other glycidyl ethers produced in moderate to high volumes.

1. Chemical and Physical Data

1.1 Synonyms

Bisphenol A diglycidyl ether



$C_{21}H_{24}O_4$ Mol. wt: 340.42

Chem. Abstr. Services Reg. No.: 1675-54-3

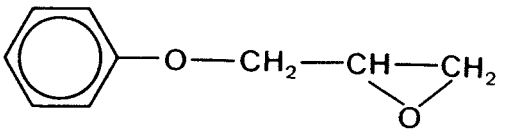
Chem. Abstr. Name: 2,2′-[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)]bis-(oxirane)

IUPAC Systematic Name: 2,2′-[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)]bis(oxirane)

Synonyms: 4,4′-Bis(2,3-epoxypropoxy)diphenyldimethylmethane; 2,2-bis[*para*-(2,3-epoxypropoxy)phenyl]propane; 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane; bis(4-glycidyloxyphenyl)dimethylmethane; 2,2-bis(*para*-glycidyloxyphenyl)propane; 2,2-bis (4-glycidyloxyphenyl)propane; bis(4-hydroxyphenyl)dimethylmethane diglycidyl ether 2,2-bis(*para*-hydroxyphenyl)propane diglycidyl ether; 2,2-bis(4-hydroxyphenyl)propane diglycidyl ether; BPDGE; dian diglycidyl ether; diglycidyl bisphenol A; diglycidyl bisphenol A ether; diglycidyl diphenylolpropane ether; diglycidyl ether of 2,2-bis-(*para*-hydroxyphenyl)propane; diglycidyl ether of 2,2-bis(4-hydroxyphenyl)propane; diglycidyl ether of bisphenol A; diglycidyl ether of 4,4′-isopropylidenediphenol; *para,para*′-dihydroxydiphenyldimethylmethane diglycidyl ether; 4,4′-dihydroxydi-

phenyldimethylmethane diglycidyl ether; diomethane diglycidyl ether; 4,4′-isopropylidenebis[1-(2,3-epoxypropoxy)benzene]; 4,4′-isopropylidenediphenol diglycidyl ether; oligomer 340

Phenyl glycidyl ether



$C_9H_{10}O_2$ Mol. wt: 150.18

Chem. Abstr. Services Reg. No.: 122-60-1

Chem. Abstr. Name: (Phenoxymethyl)oxirane

IUPAC Systematic Name: (Phenoxymethyl)oxirane

Synonyms: 1,2-Epoxy-3-phenoxypropane; 2,3-epoxypropoxybenzene; 2,3-epoxypropyl phenyl ether; glycidol phenyl ether; glycidyl phenyl ether; PGE; phenol glycidyl ether; 1-phenoxy-2,3-epoxypropane; 3-phenoxy-1,2-epoxypropane; phenoxypropene oxide; phenoxypropylene oxide; γ-phenoxypropylene oxide; 3-phenoxy-1,2-propylene oxide; phenyl 2,3-epoxypropyl ether; 3-phenyloxy-1,2-epoxypropane

1.2 Chemical and physical properties of the pure substances

From National Institute for Occupational Safety and Health (1978) unless otherwise noted

Bisphenol A diglycidyl ether

Bisphenol A diglycidyl ether is not produced as a pure monomer but as a mixture of monomer, dimer, trimer and tetramer; therefore, very few, if any, chemical/physical properties are reported for the pure substance.

(*a*) *Spectroscopy data*: Electron impact mass spectral data have been reported (Brown & Creaser, 1980).

(*b*) *Reactivity*: Glycidyl ethers, as epoxide-containing chemicals, react readily with acids, with water and with nucleophiles such as proteins and nucleic acids

(*c*) *Conversion factor*: $mg/m^3 = 13.92 \times ppm$[1]

Phenyl glycidyl ether

(*a*) *Description*: Colourless liquid

(*b*) *Boiling-point*: 245°C

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

(*c*) *Melting-point*: 3.5°C

(*d*) *Volatility*: Vapour pressure, 0.01 mm Hg at 25°C; relative vapour density (air = 1), 4.37 at 25°C

(*e*) *Specific gravity*: 1.1092 at 20°C

(*f*) *Refractive index*: 1.5314

(*g*) *Spectroscopy data*: Infrared, proton and carbon-13 nuclear magnetic resonance, ultraviolet and electron impact mass spectral data have been reported (Patterson, 1954; Shapiro, 1977; Brown & Creaser, 1980; Sadtler Research Laboratories, 1980; Pouchert, 1983, 1985).

(*h*) *Solubility*: Soluble in acetone and toluene; slightly soluble in octane (12.9%); nearly insoluble in water (0.24%)

(*i*) *Reactivity*: Glycidyl ethers, as epoxide-containing chemicals, react readily with acids, with water and with nucleophiles such as proteins and nucleic acids

(*j*) *Viscosity*: 6 cP at 25°C (Urquhart *et al.*, 1988)

(*k*) *Conversion factor*: $mg/m^3 = 6.14 \times ppm$[1]

Other glycidyl ethers

Physical properties of selected other glycidyl ethers are given in Table 1.

1.3 Technical products and impurities

Trade names: Araldite 6005; Araldite® GY 250; Araldite® GY 6010; D.E.R.® 331; Epikote® 815; Epikote® 828; EPI-REZ® 510; EPON® 828; EPOTUF® 37-140; Epoxide A

Bisphenol A diglycidyl ether is available as a medium viscosity, unmodified liquid epoxy resin with the following typical properties: epoxy value, 0.52–0.55 equivalents/100 g; equivalent weight per epoxide, 182–192; viscosity (at 25°C), 12 000–16 000 cP (Ciba-Geigy Corp., 1984).

Trade name: Heloxy® WC-63

Phenyl glycidyl ether is available with the following properties: specific gravity (at 25°C), 1.10–1.12; viscosity (at 25°C), 4–7 cP; equivalent weight per epoxide, 155–170 (Wilmington Chemical Corp., 1987).

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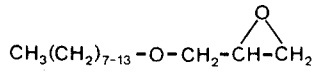
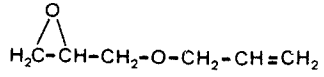
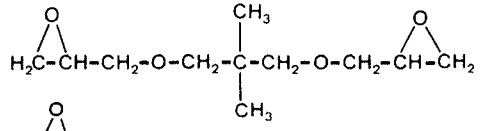
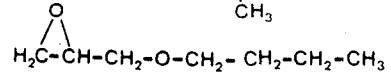
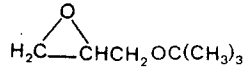
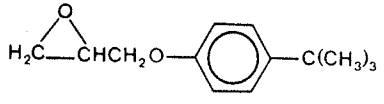
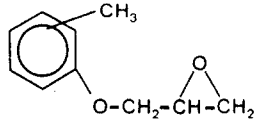
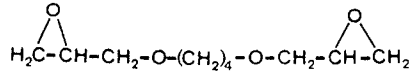
[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25 °C) and pressure (760 mm Hg)

Table 1. Physical properties of selected glycidyl ethers[a]

Compound (CAS No.)	Formula	Molecular weight	Boiling-point (°C)	Melting-point (°C)	Vapour pressure (mm Hg)
C_8–C_{10} Alkyl glycidyl ether[b] (68609-96-1)		229	139.4 (100 mm Hg)	-12	0.08 (21°C)
C_{12}–C_{14} Alkyl glycidyl ether[b] (68609-97-2)		286	215.5 (100 mm Hg)	1.7	0.06 (21°C)
Allyl glycidyl ether (106-92-3)		114.14	153.9	[c]	4.7 (25°C)
1,4-Butanediol diglycidyl ether (2425-79-8)		202.25	-	-	-
n-Butyl glycidyl ether (2426-08-6)		130.21	164	-	3.2 (25°C)
tert-Butyl glycidyl ether (7665-72-7)		130.21	152	-	-
tert-Butylphenyl glycidyl ether (3101-60-8)		206.28	294 (*para*-)	-	-
Cresyl glycidyl ether (26447-14-3)		164.21	-	-	-
Neopentylglycol diglycidyl ether (17557-23-2)		216	-	-	-

[a]From Ulbrich *et al.* (1964); National Institute for Occupational Safety and Health (1978); Hine *et al.* (1981)

[b]Two fractions of straight-chain alcohols derived from reduction of fats, namely the C_8 to C_{10} fraction and the C_{12} to C_{14} fraction, are converted to their respective glycidyl ethers (epoxide 7 and epoxide 8).

[c]Forms a glass at about -100°C

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

The principal commercial market for glycidyl ethers is in epoxy resins, a large proportion of which are based on bisphenol A diglycidyl ether. These resins are produced by a combination of the Taffy process and the fusion process. In the Taffy process, epichlorohydrin (see IARC, 1987) and bisphenol A monomers are reacted in the presence of caustic soda to produce a mixture of bisphenol A diglycidyl ether and its low molecular-weight oligomers – primarily dimers, trimers and tetramers. As the proportion of bisphenol A in the reactant mixture is increased, the average molecular weight of the resultant epoxy resin increases. In the fusion process, low molecular-weight (liquid) bisphenol A diglycidyl ether-based epoxy resins are converted to higher molecular-weight (solid) resins by reaction with more bisphenol A (Urquhart *et al.*, 1988).

Phenyl glycidyl ether is synthesized in a similar manner by adding phenol to epichlorohydrin in the presence of a catalyst. The intermediate chlorohydrin is not isolated and undergoes dehydrochlorination to yield a glycidyl ether (National Institute for Occupational Safety and Health, 1978).

Although specific worldwide figures are not available, relative production of the glycidyl ethers covered in this monograph was reported to be 'ultra high' for bisphenol A diglycidyl ether and 'medium' for phenyl glycidyl ether (Chemical Manufacturers' Association, 1984). Production levels of other glycidyl ethers were classified as 'medium', except for *tert*-butyl glycidyl ether, for which no data were available.

US production of unmodified epoxy resins increased from 81 250 tonnes in 1972 to 196 700 tonnes in 1986. The corresponding figures for modified epoxy resins (those to which reactive viscosity modifiers (usually also epoxy) have been added) were 19 600 and 125 400 tonnes. US production of these glycidyl ethers, reported separately from epoxy resins, was 1700 tonnes in 1984 and 2800 tonnes in 1985 (US International Trade Commission, 1974, 1985, 1986, 1987). Approximately 15% of US epoxy resin production in 1986 was exported (Urquhart *et al.*, 1988).

In 1986, Japan produced approximately 92 000 tonnes, exported approximately 24 000 tonnes and imported approximately 10 000 tonnes of epoxy resins (Shikado, 1987).

(*b*) *Use*

Bisphenol A diglycidyl ether is the most common active component in epoxy resins, although other glycidyl ethers are frequently incorporated into epoxy resin systems as reactive modifiers. For most uses, liquid epoxy resins resulting from the reaction of epichlorohydrin and bisphenol A are too viscous, and modifiers, which are low viscosity liquids, are added to improve flow characteristics. Modifiers also decrease the tendency of curing agents in the

resin formulation to volatilize prematurely, aid in the wetting of fillers in the resin, enhance penetration of the resin into castings, and frequently improve the mechanical properties of the product (Urquhart *et al.*, 1988).

Phenyl glycidyl ether is a monofunctional reactive modifier referred to as a 'chain stopper' or reaction inhibitor. It reduces resin system functionality (by reacting with hydroxyl groups, for example) and decreases system cross-linking density (Urquhart *et al.*, 1988).

The epoxy group of the glycidyl ethers reacts during the curing process, and glycidyl ethers are therefore generally no longer present in completely cured products. Typical curing agents include aliphatic amines (e.g., diethylenetriamine, triethylenetetramine), aromatic amines (e.g., *meta*-phenylenediamine, methylenedianiline, diaminodiphenylsulfone), catalytic curing agents (e.g., boron trifluoride–ethylamine complex) and acid anhydrides (e.g., dodecenylsuccinic anhydride, hexahydrophthalic anhydride; Harper, 1979).

Epoxy resins based on glycidyl ethers are used in a variety of applications, such as protective coatings and reinforced plastics, as well as bonding materials and adhesives, where they exhibit exceptional properties, such as toughness, chemical resistance and superior electrical properties. They are used in both decorative and protective coatings for automobiles, tins and closures, boats and ships, appliances, piping and miscellaneous metal decoration. They are also widely used in the electrical/electronic, structural/composite, adhesive and aggregate applications as adhesives, laminates, encapsulants and grouting compounds (Chemical Manufacturers' Association, 1984; Urquhart *et al.*, 1988). Table 2 presents the use pattern for epoxy resins produced in the USA (Urquhart *et al.*, 1988).

Table 2. US consumption (thousands of tonnes) of epoxy resins by use[a]

Use	1981	1982	1983	1984	1985
Bonding and adhesives	8.2	6.8	6.8	9.1	7.7
Flooring, paving and aggregates	9.1	8.2	8.6	8.1	7.7
Protective coatings	62.1	55.3	59.4	69.4	76.2
Fibre-reinforced laminates and composites	29.9	26.3	33.6	39.5	31.3
Tooling, casting and moulding resins	13.2	10.9	12.7	14.1	10.4
All other uses	9.5	11.3	13.1	13.1	14.1
Exports	18.6	17.7	15.9	18.6	19.1
Total	150.6	136.5	150.1	171.9	166.5

[a]From Urquhart *et al.* (1988)

An increase in the production of epoxy resins in Japan between 1985 and 1986 was due chiefly to the recovery in demand for electrical products such as laminated boards and sealing materials, which are major application fields in Japan and which accounted for 41% of the total epoxy resin demand (Shikado, 1987).

(c) *Regulatory status and guidelines*

The US Food and Drug Administration (1988) permits the use of epoxy resins as components of coatings that may come into contact with food.

Occupational exposure limits for phenyl glycidyl ether in 14 countries are presented in Table 3. Exposure limits have also been set for other glycidyl ethers, including allyl (threshold limit value, 22 mg/m³; short-term exposure limit, 44 mg/m³) and *n*-butyl (threshold limit value, 135 mg/m³) glycidyl ethers (American Conference of Governmental Industrial Hygienists, 1988). No exposure limit has been set for bisphenol A diglycidyl ether.

Table 3. Occupational exposure limits for phenyl glycidyl ethers[a]

Substance and country	Year	Concentration (mg/m^3)[b]	Interpretation[c]
Australia	1984	60	TWA
Belgium	1984	60	TWA
Denmark	1988	5	TWA
Finland	1987	S 60	STEL (15 min)
Germany, Federal Republic of	1988	S 6	TWA
Indonesia	1985	60	TWA
Mexico	1985	60	TWA
Netherlands	1986	6	TWA
Norway	1981	5	TWA
Romania	1984	75	TWA
		100	STEL
Sweden	1987	S 60	TWA
		S 90	STEL
Switzerland	1984	6	TWA
USA[d]			
OSHA	1987	60	TWA
NIOSH	1986	5	Ceiling (15 min)
ACGIH	1988	6	TWA
Yugoslavia	1984	60	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); International Labour Office (1984); Arbeidsinspectie (1986); Cook (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojeluhallitus (1987); US Occupational Safety and Health Administration (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; NIOSH, National Institute for Occupational Safety and Health; ACGIH, American Conference of Governmental Hygienists

2.2 Occurrence

(*a*) *Natural occurrence*

Glycidyl ethers are not known to occur as natural products.

(*b*) *Occupational exposure*

On the basis of a US National Occupational Hazard Survey of 1972–74 and a US National Exposure Survey of 1981–83, the National Institute for Occupational Safety and

Health (1974, 1983) estimated that 45 700 and 13 138 workers, respectively, were potentially exposed to bisphenol A diglycidyl ether in the USA. The corresponding figures for phenyl glycidyl ether were 8554 and 1328.

During use of a powdered spray paint, levels of bisphenol A diglycidyl ether ranged from 0.005 to 0.200 mg/m³ in personal samples and from 0.002 to 0.008 mg/m³ in area samples (Hervin *et al.*, 1979). Personal time-weighted averages (TWAs) for industrial designers at a truck manufacturing plant were 0.0002–0.0004 mg/m³ bisphenol A diglycidyl ether (Boiano, 1981).

(*c*) *Water*

In the late 1970s and early 1980s, a technique was developed for lining cast-iron water pipes with epoxy resin to inhibit corrosion. In the UK, where the technique has been used for in-situ renovation of existing water distribution systems, bisphenol A diglycidyl ether and its dimer and trimer have been detected [not quantified] in drinking-water samples. The epoxy resin components were identified by high-performance liquid chromatography (HPLC) and field desorption mass spectrometry and were estimated to be present 'at the low microgram per litre concentration range or less' (Crathorne *et al.*, 1984).

2.3 Analysis

Methods have been reported for the analysis of various glycidyl ethers in air and water. More volatile glycidyl ethers (e.g., phenyl glycidyl ether) have been collected by drawing air samples through charcoal, silica gel or Tenax adsorption tubes, desorbed with an appropriate solvent and analysed by gas chromatography (Taylor, 1977, 1978; Guenier *et al.*, 1986). Bisphenol A diglycidyl ether has been determined in air by collection on a glass fibre filter (nominal pore size, 1 μm), extraction and analysis by HPLC (Taylor, 1980; Peltonen *et al.*, 1986). Bisphenol A diglycidyl ether has been quantified in water by adsorption on C_{18}-bonded silica and analysis by HPLC (Crathorne *et al.*, 1986).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

Bisphenol A diglycidyl ether

(*a*) *Oral administration*

Mouse: Groups of 30 male Heston A strain mice [age unspecified] were fed a diet containing 2% bisphenol A diglycidyl ether [type and quantity of impurities unspecified] or a

[1]The Working Group was aware of a study in progress on allyl glycidyl ether by inhalation in mice and rats (IARC, 1988).

normal control diet. The study was terminated after 11 months. The incidences of pulmonary tumours in survivors were 12/23 in the epoxy resin-treated group and 15/29 in the untreated control group. No lung tumour was observed in mice that died during the study. The other organs were not examined for tumours (Hine *et al.*, 1958). [The Working Group noted the inadequate description of the test material and that the study was not designed to investigate carcinogenicity in tissues other than the lungs.]

(*b*) *Skin application*

Mouse: Groups of 30 male C3H mice (16–18 g bw) received skin applications of 0.2 ml of a 0.3% solution weekly or a 5% solution of bisphenol A diglycidyl ether [type and quantity of impurities unspecified] in acetone once or three times weekly for 24 months. A control group of 30 male mice received 0.2 ml acetone alone, and a positive control group was treated weekly with a 0.3% solution of 20-methylcholanthrene in acetone. No skin tumour occurred in any of the treated mice. The group treated with 20-methylcholanthrene showed a high incidence of malignant skin tumours (19/20) within six months (Hine *et al.*, 1958). [The Working Group noted the inadequate description of the test material.]

A group of about 40 C3H mice [exact number and sex unspecified], aged 13 weeks, received skin applications of undiluted bisphenol A diglycidyl ether [purity and dose unspecified] on shaved back skin for life (maximum, 23 months). After 16 months of treatment, at which time 32 mice were still alive, a single skin papilloma occurred; no other skin tumour appeared during the experiment. The authors stated that in a second, similar experiment, no skin tumour was observed [details not given] (Weil *et al.*, 1963). [The Working Group noted that the amount of test substance per application was not given and that untreated controls were not included in the experiment.]

Groups of 40 male and 40 female C3H and 20 male and 20 female C57Bl/6 mice, ten to 12 weeks of age, received applications of 0, 5 or 25 mg of commercial-grade bisphenol A diglycidyl ether (containing 10% (w/w) of an epoxidized polyglycol (mol. wt, > 500) and small amounts of phenyl glycidyl ether) in acetone on shaved back skin three times a week for 24 months. At that time, 18–23 C3H mice were still alive, and no skin tumour was observed. In male C57Bl/6 mice, survival was 20, 17 and 15 control, low-dose and high-dose animals, respectively, and survival in females was 15, 15 and 13, respectively. Skin tumours occurred in 0, 1 (papilloma) and 6 (carcinomas) control, low-dose and high-dose males, and in 0, 0 and 2 (1 papilloma and 1 carcinoma) control, low-dose and high-dose females (Holland *et al.*, 1979).

Groups of 50 male and 50 female CF1 mice, six weeks old, received applications of 0, 1 or 10% [equivalent to 2 and 20 mg] Araldite GY 250 (technical grade; main component, bisphenol A diglycidyl ether; containing 4.3 mg/kg epichlorohydrin as a contaminant) in 0.2 ml acetone on shaved back skin twice a week for two years. There was no effect on survival; no skin tumour was observed at the site of application, and there was no significant difference in the occurrence of other tumours. A positive control group that received skin applications of a 2% solution of β-propiolactone showed high incidences of malignant skin tumours (Zakova *et al.*, 1985).

Groups of 50 male and 50 female CF1 mice, six weeks of age, received applications of 0.2 ml of a 1% or 10% solution of pure (analytical grade) bisphenol A diglycidyl ether or of one of two technical grades of bisphenol A diglycidyl ether (EPON 828, containing 29 mg/kg epichlorohydrin, or Epikote 828, containing 3 mg/kg epichlorohydrin) in acetone on shaved back skin twice a week for two years. Positive control groups of 50 males and 50 females received applications of 2% β-propiolactone in acetone; a control group of 100 male and 100 female mice was treated with acetone only. Survival was not affected by treatment with epoxy resins, but was considerably decreased in the β-propiolactone-treated group. In animals treated with EPON 828, one skin carcinoma occurred in high-dose males and one fibrosarcoma of the subcutis in high-dose females. In Epikote 828-treated mice, one squamous-cell papilloma of the skin was observed in low-dose males and three basal-cell carcinomas, in a low-dose and a high-dose male and a high-dose female. In addition, one sebaceous-gland adenoma was observed in a high-dose male. In the animals treated with pure epoxy resin and in the group of acetone controls, no epidermal tumour was observed. Two dermal tumours (haemangiosarcomas) were seen in the high-dose males given the pure epoxy resin. A large number of skin tumours was observed in the β-propiolactone-treated groups – 132 in 30/50 males and 63 in 13/50 females – which were generally malignant epithelial tumours and, to a lesser extent, mesenchymal tumours. The authors reported that no epidermal tumour was seen in 200 females or 100 males used as controls in that laboratory. The incidence of renal and lymphoreticular/haematopoietic tumours was increased in the treated groups. Kidney tumours, mainly carcinomas, were observed only in males: 6/99 (control), 8/50 (10% EPON 828; [$p = 0.05$]), 0/50 (1% EPON), 6/50 (1% Epikote), 2/50 (10% Epikote), 5/50 (1% epoxy resin) and 3/50 (10% epoxy resin). In female mice, an increase in the incidence of lymphoreticular/haematopoietic tumours was observed in animals treated with 1% epoxy resin (23/50) and in those treated with 10% Epikote (24/50), compared to controls (27/100). In the other groups, the incidence of these tumours was comparable to that seen in control female mice (Peristianis *et al.*, 1988).

Rabbit: Each of 16 male albino rabbits [strain and age unspecified] received skin applications [site unspecified] of 0.5 ml acetone thrice weekly, a 0.3% solution in acetone once per week, a 5% solution of bisphenol A diglycidyl ether [type and quantity of impurities unspecified] once or three times per week and a 0.3% solution of 20-methylcholanthrene in acetone. At 24 months, 13/16 rabbits were still alive. Skin tumours were seen only at 20-methylcholanthrene treated sites (Hine *et al.*, 1958). [The Working Group noted the inadequate description of the test material.]

(c) *Subcutaneous injection*

Rat: Groups of 30 male Long-Evans rats (80–100 g bw) were given three weekly subcutaneous injections of bisphenol A diglycidyl ether [type and quantity of impurities unspecified] dissolved in propylene glycol (50% solution; total dose, 2.58 g/kg bw). A negative control group was injected with propylene glycol alone, and a positive control group received three injections of 1,2,5,6-dibenzanthracene. The experiment was terminated after 24 months, at which time survival was 17, 14 and four in the negative control, epoxy resin and positive control groups, respectively. The numbers of malignant tumours at the site of injec-

tion were 0, 4 (fibrosarcomas) and 17 (mainly fibrosarcomas or sarcomas), respectively (Hine *et al.*, 1958). [The Working Gruop noted the inadequate description of the test material.]

(*d*) *Combined exposure*

Groups of 40 male and 40 female C3H mice and 20 male and 20 female C57Bl/6 mice, ten to 12 weeks of age, received 0, 15 or 75 mg per week of a mixture of equal parts of bisphenol A diglycidyl ether and bis(2,3-epoxycyclopentyl)ether (see monograph, p. 233) in acetone on the shaved back skin for 24 months. Survival of C3H mice at 24 months was 22, 20 and 23 for males and 23, 23 and 19 for females in the control, low and high-dose groups. Skin tumours occurred in 14 low-dose males (four papillomas and ten carcinomas) and 32 high-dose males (13 papillomas and 19 carcinomas), in five low-dose females (three papillomas and two carcinomas) and in 19 high-dose females (12 papillomas and seven carcinomas). One skin papilloma was observed in control females, and no skin tumour was seen in control males. In C57Bl/6 mice, survival at 24 months was 20, 15 and four for males and 15, 14 and four for females in the respective dose groups. The difference between control and high-dose groups was statistically significant ($p < 0.05$). Skin tumours (mostly carcinomas) were observed in one low-dose (carcinoma) and 17 high-dose (carcinomas) males and in two low-dose (one papilloma, one carcinoma) and 15 high-dose (two papillomas, 13 carcinomas) females, but not in controls of either sex. When tested alone at the same dose levels, each substance revealed a much lower tumour response (see p. 245 above and the monograph on bis(2,3-epoxycyclopentyl)ether, p. 233), indicating a synergistic effect of the compounds when tested as a mixture (Holland *et al.*, 1979).

(*e*) *Carcinogenicity of metabolites*

Glycidaldehyde is carcinogenic to experimental animals (IARC, 1976, 1987).

Phenyl glycidyl ether

Inhalation

Rat: Groups of 100 male and 100 female Sprague-Dawley rats, six weeks old, were exposed to 0, 1 or 12 ppm (6 or 73.5 mg/m^3) phenyl glycidyl ether vapour (purity, 99.6% with trace amounts of phenol and diglycidyl ether) by inhalation for 6 h per day, on five days per week for 24 months. [No data were given on survival or body weights.] Epidermoid carcinomas occurred in the anterior parts of the nasal cavity in 1/89 male and 0/87 female controls, in 0/83 male and 0/88 female low-dose rats and in 9/85 male [$p = 0.007$] and 4/89 [$p = 0.06$] female high-dose rats. The first nasal tumour was observed in week 89. In the group receiving 12 ppm, squamous metaplasia, rhinitis, epithelial desquamation, regeneration, hyperplasia and dysplasia of the respiratory epithelium were also observed, especially in the anterior parts of the nasal cavity. No such increase in non-neoplastic changes occurred in the group receiving 1 ppm (Lee *et al.*, 1983).

3.2 Other relevant data

(a) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

When ^{14}C-*n-butyl glycidyl* ether was administered orally to rats and rabbits, 91 and 80% of the administered dose was recovered in urine within four days, and most of the radioactivity was excreted during day 1 (Eadsforth *et al.*, 1985a). The main urinary metabolite (23% of total) in rats receiving an oral dose of 20 mg/kg bw was 3-butoxy-2-acetylaminopropionic acid. Other metabolites were 3-butoxy-2-hydroxypropionic acid (9%) and butoxyacetic acid (10%). The same metabolites were found in rabbits, but the main metabolite (35%) was 3-butoxy-2-hydroxypropionic acid (Eadsforth *et al.*, 1985a,b).

When ^{14}C-*bisphenol A diglycidyl ether* (56 mg/kg) was applied to the shaved skin of mice, 67% and 11% of the radioactivity could be recovered from the application site after 24 h and eight days, respectively. Urinary and faecal excretion continued at low levels for at least six days following application. After oral administration of 55 mg/kg bw, 79% and 10% of the radioactivity was eliminated in the faeces and urine, respectively, over eight days; most of the excretion occurred during the first 24 h. Only 0.1% of the administered dose remained in the body after eight days (Climie *et al.*, 1981a).

Bisphenol A diglycidyl ether is rapidly metabolized in mice *via* the epoxide groups to form the corresponding bis-diol. Epoxide hydratase catalyses this reaction, but diols are also formed *via* nonenzymatic hydrolysis. Further oxidation and dealkylation reactions take place. The metabolites excreted in faeces and urine include conjugates (glucuronides and sulfates) of the bis-diol and corresponding carboxylic acids. In the dealkylation steps, glyceraldehyde and glycidaldehyde are putative intermediates (Climie *et al.*, 1981b).

Percutaneous absorption of *phenyl glycidyl ether* was high in rats and rabbits, with absorption rates of 13.5 and 4.2 mg/cm^2 per h, respectively (Czajkowska & Stetkiewicz, 1972).

Phenyl glycidyl ether bound to glutathione in the presence of liver microsomes from different types of birds (Wit & Snel, 1968). *Allyl glycidyl ether, butyl glycidyl ether, phenyl glycidyl ether* and *bisphenol A diglycidyl ether* (Epikote 828) bound nonenzymatically to the *N*-7 position of guanosine *in vitro* (Hemminki *et al.*, 1980).

(ii) *Toxic effects*

1,2-Epoxydodecane (*C_{12} alkyl glycidyl ether*) and epoxide 8 (*C_{12}–C_{14} alkyl glycidyl ether*) gave positive results in the guinea-pig skin maximization test (Thorgeirsson *et al.*, 1975; Thorgeirsson, 1978).

The oral (intragastic) LD_{50} for undiluted *allyl glycidyl ether* has been reported to be 0.4 g/kg bw in mice and 1.6 g/kg bw in rats. Following intragastric administration, focal liver necrosis was observed in some animals and central nervous system depression. The percutaneous LD_{50} has been reported to be 2.6 g/kg bw for rabbits. A 4-h inhalation LC_{50} of 270 ppm (1270 mg/m^3) was reported for mice and an 8-h inhalation LC_{50} of 670 ppm (3150 mg/m^3) for rats (Hine *et al.*, 1956).

In rats receiving two courses of two intramuscular injections of 400 mg/kg bw allyl glycidyl ether, separated by a four-day recovery period, necropsy and histological examination on

day 12 showed thymic atrophy or loss of lymphoid tissue, focal necrosis of the pancreas and testis, and pneumonia (Kodama *et al.*, 1961).

Rats were exposed by inhalation for 7 h per day on five days per week to 260 and 400 ppm (1214 and 1868 mg/m³) allyl glycidyl ether for 50 days and to 600 and 900 ppm (2802 and 4203 mg/m³) for 25 days. The 400-ppm dose induced irritation of the eyes and respiratory tract, reduced body weight gain and increased relative kidney weight. With 600 and 900 ppm, severe irritation of the eyes and respiratory tract, decreased respiratory rate and corneal cloudiness were observed (Hine *et al.*, 1956).

When mice were exposed by inhalation (head only) for 15 min to 1.9–8.6 ppm (8.9–40.4 mg/m³) allyl glycidyl ether, a 50% decrease in respiratory rate was seen at 5.7 ppm (26.8 mg/m³). Exposure of mice by inhalation (whole body) to 7.1 ppm (33.4 mg/m³) allyl glycidyl ether for 6 h per day for four days caused necrosis of respiratory epithelium and complete erosion of olfactory epithelium without pulmonary injury, whereas exposure to 2.5 ppm (11.8 mg/m³) for 14 days caused no nasal or pulmonary injury (Gagnaire *et al.*, 1987).

The oral LD_{50} for *bisphenol A diglycidyl ether* was reported to be 19.6 ml/kg bw in rats and the dermal LD_{50} to be > 20 ml/kg bw in rabbits. Intracutaneous injection of the compound to guinea-pigs sensitized 19/20 animals (Weil *et al.*, 1963). Bisphenol A diglycidyl ether monomer sensitized all animals in a guinea-pig skin maximization test and was classified by the authors as an extreme allergen (Thorgeirsson & Fregert, 1977).

There was a dose-related increase in erythema, exfoliation/fissuring, haemorrhage and oedema of the skin at the application site following daily dermal application to rabbits of 100 or 300 mg/kg bw bisphenol A diglycidyl ether (Breslin *et al.*, 1988).

The oral and dermal LD_{50}s of *1,4-butanediol diglycidyl ether* in rats were 2.98 g/kg bw and 1.13 g/kg bw, respectively; the compound caused skin and eye irritation in rabbits (Cornish & Block, 1959). It gave positive results in the guinea-pig skin maximization test (Thorgeirsson, 1978; Clemmensen, 1984).

The LD_{50}s of n-*butyl glycidyl ether* by oral gavage were 1.5 and 2.3 g/kg bw in mice and rats, respectively (Hine *et al.*, 1956). In another study, the oral and dermal LD_{50}s in rats were 3.4 and 2.3 mg/kg bw, respectively; the compound caused skin and mild eye irritation in rabbits (Cornish & Block, 1959).

tert-*Butylglycidyl ether* gave negative results in the guinea-pig skin maximization test (Rao *et al.*, 1981).

The oral LD_{50} of *cresyl glycidyl ether* in rats was 5.1 mg/kg bw, and that in mice was 1.7 g/kg bw. The LC_{50} in rats was 282 mg/m³, and necrosis of the renal epithelium was reported (Krechkovskii *et al.*, 1985a). The subcutaneous LD_{50} in mice was 980 mg/kg bw (Söllner & Irrgang, 1965). Cresyl glycidyl ether caused sensitization in guinea-pigs previously sensitized to Epoxide 8 (C_{12}–C_{14} alkyl glycidyl ether) or butyl glycidyl ether (Thorgeirsson *et al.*, 1975).

Neopentylglycol diglycidyl ether gave positive results in the guinea-pig skin maximization test (Thorgeirsson, 1978).

The single oral LD_{50} for *phenyl glycidyl ether* has been reported to be 4.3 ml/kg bw in rats and the single skin penetration LD_{50} to be 1.5 ml/kg bw in rabbits (Weil *et al.*, 1963). The LD_{50} by gavage was 1.4 g/kg bw in mice (Hine *et al.*, 1956). Intragastric and cutaneous LD_{50} values

in white rats were 2.6 and 2.1 g/kg bw, respectively (Czajkowska & Stetkiewicz, 1972). The subcutaneous LD_{50} in mice was 760 mg/kg bw (Söllner & Irrgang, 1965). Phenyl glycidyl ether caused moderate skin irritation and corneal injury in rabbits; sensitization of guinea-pigs after intracutaneous injection was low (Weil *et al.*, 1963). Local application of phenyl glycidyl ether produced skin necrosis (Czajkowska & Stetkiewicz, 1972).

Rats and beagle dogs were exposed by inhalation to 1, 5 or 12 ppm (6, 31 or 74 mg/m^3) phenyl glycidyl ether for 6 h per day on five days per week for 90 days. The only significant finding was bilateral hair loss in rats exposed to 5 or 12 ppm. Blood and urine analysis and histopathological examination of all major organs revealed no other treatment-related effect (Terrill & Lee, 1977).

(iii) *Effects on reproduction and prenatal toxicity*

Spermatogenic effects (decreased sperm motility, abnormal sperm morphology, increased numbers of tubules with desquamated epithelium) were seen in male rats, and embryolethality (especially in the pre-implantation periods) in female rats, exposed by inhalation to 0, 2.55 and 19.1 mg/m^3 *cresyl glycidyl ether* (Krechkovskii *et al.*, 1985b).

Groups of 26 pregnant New Zealand white rabbits received daily dermal applications of 0, 30, 100 or 300 mg/kg bw *bisphenol A diglycidyl ether* (purity, 99.1%) on days 6–18 of gestation. The dose was prepared as a solution in propylene glycol 400 and applied under occlusion to a shaved area on the back of the test animal at a rate of 1 ml/kg bw per day. After 6 h, the occlusive bandage was removed; the treated area was not washed. Fetuses were examined by routine teratological techniques on day 28 of gestation. No treatment-related effect was reported, except for dose-related dermatological effects in the mothers (Breslin *et al.*, 1988).

Four groups of eight male adult Sprague–Dawley rats were exposed by inhalation to 0, 1, 5 or 12 ppm (6, 31 or 74 mg/m^3) *phenyl glycidyl ether* [purity unspecified] for 6 h per day on 19 consecutive days. After the last exposure, the rats were shipped to another laboratory, where their reproductive capabilities were assessed. Male fertility was evaluated during six-weekly co-habitation periods with three untreated females, some of which were killed on day 18 of gestation and examined for corpora lutea, implantation sites and resorption sites. Other females were allowed to deliver, and the offspring were followed through production of a second generation. The percentage of females that became pregnant was significantly reduced in the high-dose group in the first breeding week. Histological analysis of the testes indicated atrophy in 1/8 males from each treatment group. [The Working Group noted that it was not stated when the examination was performed.] No other treatment related effect was reported (Terrill *et al.*, 1982).

In a teratology study, four groups of 25 Sprague–Dawley rats were exposed by inhalation to 0, 1, 5 or 12 ppm phenyl glycidyl ether [purity unspecified] for 6 h per day between days 4 and 15 of gestation. The fetuses were examined on day 20 of gestation for external, internal and skeletal abnormalities. No clinical sign of systemic toxicity was observed in the females, and no effect on fetal viability, growth or morphological development was found (Terrill *et al.*, 1982).

(iv) *Genetic and related effects*

Alkyl C_8–C_{14} glycidyl ethers

Octyl and decyl glycidyl ethers were weakly mutagenic to *Salmonella typhimurium* TA1535 and TA100 in the presence of an exogenous metabolic system but were reported not to be mutagenic to TA1537, TA1538 or TA98 [details not given]. Neither octyl nor decyl glycidyl ethers induced unscheduled DNA synthesis in cultured human WI-38 cells. Decyl glycidyl ether was reported to have a marginal effect and octyl glycidyl ether no effect in inducing mutation in mouse lymphoma L5178Y TK$^{+/-}$ cells in the absence of an exogenous metabolic system (Thompson *et al.*, 1981).

Dodecyl glycidyl ether was weakly mutagenic to *S. typhimurium* TA1535 and TA100 in the presence of an exogenous metabolic system but not to strains TA1537, TA1538 or TA98 [details not given]. Tetradecyl glycidyl ether was not mutagenic in any of the five strains tested [details not given for TA1537, TA1538 or TA98]. Neither dodecyl nor tetradecyl glycidyl ether induced unscheduled DNA synthesis in cultured human WI-38 cells or mutation in mouse lymphoma L5178Y TK$^{+/-}$ cells (Thompson *et al.*, 1981). As reported in an abstract, alkyl (C_{12}–C_{14}) glycidyl ether did not induce dominant lethal mutations in B6D2F1 mice after dermal application (Pullin, 1978).

Allyl glycidyl ether was mutagenic to *Escherichia coli* WP2 *uvrA* in the absence of an exogenous metabolic system (Hemminki *et al.*, 1980). It was mutagenic to *S. typhimurium* TA1535 and TA100 in the presence and absence of an exogenous metabolic system but not to TA1537 or TA98 (Wade *et al.*, 1979; Canter *et al.*, 1986). It induced sex-linked recessive lethal mutations in *Drosophila melanogaster* when fed at 5500 ppm (mg/kg) for three days (Yoon *et al.*, 1985).

Bisphenol A diglycidyl ether

As reported in an abstract, Epikote 828 (composed mainly of bisphenol A diglycidyl ether) induced DNA repair in *E. coli* (Nishioka & Ohtani, 1978). It was mutagenic to *E. coli* WP2 *uvrA* in the absence of an exogenous metabolic system (Hemminki *et al.*, 1980). An aqueous emulsion of Epikote 828 was mutagenic to *S. typhimurium* TA100 and TA1535 in the absence of an exogenous metabolic system; in TA1535 its mutagenicity was increased when it was tested in the presence of an exogenous metabolic system (Andersen *et al.*, 1978). Araldite 6005 and EPON 828 (composed mainly of bisphenol A diglycidyl ether) induced mutation in *S. typhimurium* in the presence and absence of an exogenous metabolic system (Ringo *et al.*, 1982) [details not given]. As reported in an abstract, Epikote 828 was mutagenic to *S. typhimurium* TA100 but not TA98 (Nishioka & Ohtani, 1978). In one study, bisphenol A diglycidyl ether was mutagenic to *S. typhimurium* TA100 and TA1535 but not TA98 or TA1537 (Canter *et al.*, 1986); however, in another study, bisphenol A diglycidyl ether was not mutagenic to *S. typhimurium* TA98 or TA100 (Wade *et al.*, 1979).

1,4-Butanediol diglycidyl ether

1,4-Butanediol diglycidyl ether was mutagenic to *S. typhimurium* TA1535, TA98 and TA100 in the presence and absence of an exogenous metabolic system. Results in TA1537 in the absence of an exogenous metabolic system and in the presence of Aroclor 1254-induced

hamster liver were equivocal, but positive findings were obtained using Aroclor 1254–induced rat liver (Canter *et al.*, 1986).

Butyl glycidyl ethers

Butyl glycidyl ether [not further specified] was mutagenic to *E. coli* WP2 *uvrA* in the absence of an exogenous metabolic system (Hemminki *et al.*, 1980). *n*–Butyl glycidyl ether was mutagenic to *S. typhimurium* TA97, TA100 and TA1535 in the presence and absence of an exogenous metabolic system, but not to TA1537, TA1538 or TA98 (Wade *et al.*, 1979; Connor *et al.*, 1980a; Canter *et al.*, 1986). *tert*–Butyl glycidyl ether produced mutations in *S. typhimurium* TA1535 and TA100 in the presence and absence of an exogenous metabolic system (Canter *et al.*, 1986). As reported in an abstract, *n*–butyl and *tert*–butyl glycidyl ether induced dose–related DNA damage in cultured human lymphocytes, as determined by scintillation counting and autoradiography; *tert*–butyl glycidyl ether did not produce micronuclei or chromosomal aberrations in mice treated *in vivo* (Connor *et al.*, 1980b). *n*–Butyl glycidyl ether did not induce morphological transformation of BALBc/3T3 clone A31–1–13 cells. The urine of mice that received oral and dermal administration at various doses and for various times of *n*–butyl glycidyl ether was not mutagenic to *S. typhimurium* TA1535 or TA98. *n*–Butyl glycidyl ether produced micronuclei in bone marrow of female BDF mice when administered intraperitoneally (225–900 mg/kg bw) but not when administered orally (200 mg/kg bw; Connor *et al.*, 1980a). *n*–Butyl glycidyl ether was tested for its ability to induce dominant lethal mutations in BDF hybrid mice at doses of 0.375, 0.750 and 1.5 g/kg bw by topical application. No significant dose–related change in either pregnancy rates or in average number of implants per pregnant female was observed, but a significant increase in fetal death rates occurred at the end of the first week of administration of the highest dose (Whorton *et al.*, 1983).

tert–*Butylphenyl glycidyl ether*

tert–Butylphenyl glycidyl ether was mutagenic to *S. typhimurium* TA100 in the absence, but not in the presence, of an exogenous metabolic system, but was not mutagenic to TA1535, TA1537 or TA98 (Neau *et al.*, 1982; Canter *et al.*, 1986).

Cresyl glycidyl ether

ortho–Cresyl glycidyl ether was mutagenic to *S. typhimurium* TA1535 and TA100 in the absence of an exogenous metabolic system, and *para*–cresyl glycidyl ether was mutagenic to the same strains in the presence and absence of an exogenous metabolic system. These compounds were not mutagenic to TA1537 or TA98 (Canter *et al.*, 1986). As reported in an abstract, dermal application of *ortho*–cresyl glycidyl ether caused a significant reduction in the mean number of implants per pregnancy in a dominant lethal mutation assay in B6D2F1 mice (Pullin, 1978).

Neopentylglycol diglycidyl ether

Neopentylglycol diglycidyl ether was mutagenic to *S. typhimurium* TA1535, TA97 and TA100, but not to TA98, in the presence and absence of an exogenous metabolic system (Canter *et al.*, 1986). As reported in an abstract, it significantly reduced the mean number of

implants per pregnancy in a dominant lethal mutation assay in B6D2F1 mice after dermal application (Pullin, 1978).

Phenyl glycidyl ether

As reported in an abstract, phenyl glycidyl ether gave positive results in assays for DNA repair in *E. coli* (Nishioka & Ohtani, 1978). It was mutagenic to *E. coli* WP2 *uvrA* in the absence of an exogenous metabolic system (Hemminki *et al.*, 1980). Phenyl glycidyl ether was mutagenic to *S. typhimurium* TA1535, TA97 and TA100 but not to TA1537, TA1538 or TA98 in the presence and absence of an exogenous metabolic system (Greene *et al.*, 1979; Ivie *et al.*, 1980; Seiler, 1984; Canter *et al.*, 1986). At an oral dose of 2500 mg/kg, it was active in the host-mediated assay using C57Bl/6 × C3H mice and *S. typhimurium* TA1535, in two out of five animals tested. It did not induce 6-thioguanine-resistant cells in Chinese hamster ovary cells with or without an exogenous metabolic system (Greene *et al.*, 1979). Phenyl glycidyl ether did not induce chromosomal aberrations in Chinese hamster ovary cells (Seiler, 1984). It induced morphological transformation in secondary Syrian hamster embryo cells and enhanced transformation by SA7 virus in primary Syrian hamster embryo cells (Greene *et al.*, 1979). It did not induce micronuclei in the bone marrow of ICR mice after oral administration of 400–1000 mg/kg bw (Seiler, 1984). No evidence of dominant lethal mutation was observed in Sprague-Dawley rats following inhalation of 2–11 ppm (12.3–67.5 mg/m^3) phenyl glycidyl ether, and chromosomal aberrations were not induced in bone-marrow cells of exposed animals (Terrill *et al.*, 1982).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

No data were available to the Working Group.

(ii) *Toxic effects*

Butyl glycidyl ether was found to be a strong contact sensitizer in the skin maximization test in humans (Kligman, 1966).

Phenyl glycidyl ether has also been recognized as a contact allergen using a patch test in a study of persons with dermatitis from occupational contact with epoxy resins (Rudzki & Krajewska, 1979; Rudzki *et al.*, 1983). It was also an allergen in a patch test on eight of 15 workers in a cable production plant who developed dermatosis; phenyl glycidyl ether was present in the plastic insulation material as a stabilizer (Zschunke & Behrbohm, 1965).

Thirty-four workers with occupational dermatitis on the hands, arms and occasionally on the face, all of whom had worked with low molecular-weight epoxy resins in different factories, were given a patch test with *bisphenol A diglycidyl ether* after symptoms had regressed; all gave positive reactions (Fregert & Thorgeirsson, 1977).

Eleven workers handling epoxy resins based mainly on Epikote 815, containing bisphenol A diglycidyl ether (89% w/w) and butyl glycidyl ether (11%), in the production of transformers for television sets developed a scleroderma-like dermatosis and other symptoms, including muscle and joint disease and central nervous system and respiratory disturbances (Tomizawa *et al.*, 1979).

Epoxy dermatitis due to exposure to bisphenol A diglycidyl ether was reported among insulation workers at an electric power station (Niinimäki & Hassi, 1983). Allergic contact dermatitis was also observed on the upper lip of a patient who had used a nasal oxygen cannula made of epoxy resin; analysis indicated the presence of a chemical reported to be related to bisphenol A (Wright & Fregert, 1983).

Out of 20 resin workers, 19 developed contact allergy to epoxy resins; three of them reacted in a patch test to allyl glycidyl ether, two to *n*-butyl glycidyl ether and 14 to phenyl glycidyl ether (Fregert & Rorsman, 1964).

Three workers employed in a brush factory developed a contact allergy from a two-component glue containing epoxy resin (37% w/w bisphenol A diglycidyl ether). The reactive diluents, allyl glycidyl ether, 1,4-butanediol diglycidyl ether, *n*-butyl glycidyl ether, *ortho*-cresyl glycidyl ether, neopentylglycol diglycidyl ether and phenyl glycidyl ether, were recognized as sensitizers in the patch test (Jolanki *et al.*, 1987).

(iii) *Effects on fertility and on pregnancy outcome*

No data were available to the Working Group.

(iv) *Genetic and related effects*

Cytogenetic evaluation was performed in peripheral lymphocytes from 18 workers currently exposed to bisphenol A diglycidyl ether-type epoxy resins. Nine workers had been exposed to a low molecular-weight product (less than 900; main oligomer, MW340-bisphenol A diglycidyl ether) for five to 16 years (median, 6.5 years) and nine to high molecular-weight (about 2000) epoxy resins (for three to ten years; median, seven years). The results were compared with those for an equal number of control individuals matched for sex and age. There was no difference in the frequency of chromosomal aberrations between controls and the groups exposed to epoxy resins (Mitelman *et al.*, 1980).

Chromosomal aberrations were not more frequent in the peripheral lymphocytes of 22 employees in an epoxy resin plant than in those of ten persons from the medical department at the manufacturing site, who were used as control subjects and matched for sex, age and smoking habits. The workers had been exposed to epoxy resins (a mixture of bisphenol A diglycidyl ether and its higher homologues), epichlorohydrin, butyl glycidyl ether and cresyl glycidyl ether for one to four years (11 men) or for than ten years (11 men). Exposure of workers to epichlorohydrin varied from 0.1 to 1.6 mg/m^3; exposure to both butyl glycidyl ether and cresyl glycidyl ether was below 0.07 mg/m^3, and concentrations of a urinary metabolite of epoxy resin (the bis-diol of bisphenol A diglycidyl ether) were below the analytical limit of detection of 0.1 μg/ml (de Jong *et al.*, 1988).

3.3 Epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposures

Glycidyl ethers are basic components of epoxy resins which have been commercially available since the late 1940s. Bisphenol A diglycidyl ether and its oligomers are major components of epoxy resins. Other glycidyl ethers, including phenyl glycidyl ether, are frequently incorporated into epoxy resin systems as reactive modifiers. Epoxy resins based on bisphenol A diglycidyl ether are widely used in protective coatings, including paints, in reinforced plastic laminates and composites, in tooling, casting and moulding resins, in bonding materials and adhesives, and in floorings and aggregates. Occupational exposure to bisphenol A diglycidyl ether and phenyl glycidyl ether may occur during their production, during the production of epoxy products and during various uses of epoxy products, but data on exposure levels are sparse.

4.2 Experimental carcinogenicity data

Bisphenol A diglycidyl ether of various technical grades was tested by skin application in mice in five studies. In one of the studies, an increased incidence of epidermal tumours was found in one of two strains tested. In another study, a small increase in the incidence of epidermal tumours and small increases in the incidences of kidney tumours in male mice and of lymphoreticular/haematopoietic tumours in female mice were observed. No increase in the incidence of skin tumours was observed in two further studies, and the other study was inadequate for evaluation. Following subcutaneous injection of technical-grade bisphenol A diglycidyl ether to rats, a small number of local fibrosarcomas was observed. Following application of technical-grade bisphenol A diglycidyl ether to the skin of rabbits, no skin tumour was observed.

Pure bisphenol A diglycidyl ether was tested in one experiment by skin application in mice; no epidermal but a few dermal tumours were observed in males, and there was a small increase in the incidence of lymphoreticular/haematopoietic tumours in females.

Pure phenyl glycidyl ether was tested for carcinogenicity by inhalation exposure in male and female rats of one strain, producing carcinomas of the nasal cavity in animals of each sex.

4.3 Human data

No data were available to the Working Group.

4.4 Other relevant data

Some glycidyl ethers have been shown to cause allergic contact dermatitis in humans. Glycidyl ethers generally cause skin sensitization in experimental animals. Necrosis of the mucous membranes of the nasal cavities was induced in mice exposed to allyl glycidyl ether.

Prenatal toxicity was not induced in rats exposed by inhalation to phenyl glycidyl ether or in rabbits exposed dermally to bisphenol A diglycidyl ether.

One study of workers exposed to bisphenol A diglycidyl ether showed no increase in the incidence of chromosomal aberrations in peripheral lymphocytes. A study of workers with mixed exposures was inconclusive with regard to the effects of specific glycidyl ethers. Phenyl glycidyl ether, but not *n*-butyl glycidyl ether, induced morphological transformation in mammalian cells *in vitro*. *n*-Butyl glycidyl ether induced micronuclei in mice *in vivo* following intraperitoneal but not oral administration. Phenyl glycidyl ether did not induce micronuclei or chromosomal aberrations *in vivo* or chromosomal aberrations in animal cells *in vitro*. Alkyl C_{12} or C_{14} glycidyl ether did not induce DNA damage in cultured human cells or mutation in cultured animal cells. Allyl glycidyl ether induced mutation in *Drosophila*. The glycidyl ethers were generally mutagenic to bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of phenyl glycidyl ether in experimental animals.

There is *limited evidence* for the carcinogenicity of bisphenol A diglycidyl ether in experimental animals.

No data were available from studies in humans on the carcinogenicity of glycidyl ethers.

Overall evaluation

Phenyl glycidyl ether *is possibly carcinogenic to humans (Group 2B).*

Bisphenol A diglycidyl ether *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

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