BISPHENOL A DIGLYCIDYL ETHER

Data were last evaluated in IARC (1989).

1. Exposure Data

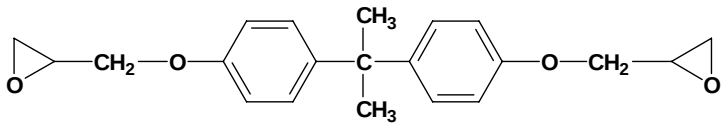
1.1 Chemical and physical data

1.1.1 *Nomenclature*

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

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

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{21}H_{24}O_4$ Relative molecular mass: 340.42

1.2 Production, use and human exposure

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 may occur during its production, during the production of epoxy products and during various uses of epoxy products, but data on exposure levels are sparse (IARC, 1989).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Bisphenol A diglycidyl ether of various technical grades was tested for carcinogenicity by skin application in mice in five studies. In one of the studies, an increased incidence of epidermal tumours was found in C57BL/6 mice, but not in C3H mice. In a study with CF1 mice, 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, one with CF1 mice, the other with C3H mice and the remaining study with C3H mice was inadequate for evaluation. Following subcutaneous injection of technical grade bisphenol A diglycidyl ether to male Long-Evans rats, a small number of local fibrosarcomas was observed. Following application of technical grade bisphenol A diglycidyl ether to the skin of albino rabbits, no skin tumour was observed.

Pure ('analytical grade') bisphenol A diglycidyl ether was tested in one experiment by skin application in CF1 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 (IARC, 1989). No subsequent studies were available to the Working Group.

It was noted that glycidaldehyde, a metabolite of bisphenol A diglycidyl ether, is carcinogenic to experimental animals and classified as *possibly carcinogenic* to humans (*group 2B*) (see this volume).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

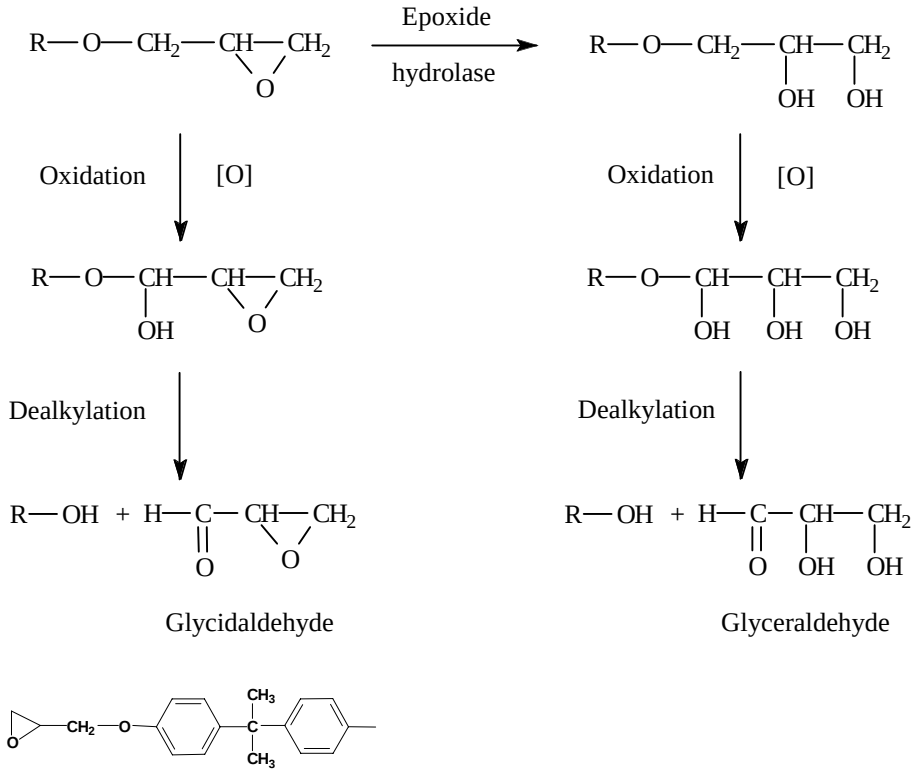
No data were available to the Working Group.

4.1.2 *Experimental systems*

A dose of approximately 55 mg/kg bw [^{14}C]bisphenol A diglycidyl ether to mice was well absorbed after administration by either the oral or dermal route. Most of the orally administered material was excreted within 24 h. After eight days, 79% was recovered from faeces and 10% from urine following oral dosing. Following dermal dosing, 67% and 11% of the radioactivity could be recovered from the application site after 24 h and 8 days, respectively. Bisphenol A diglycidyl ether is rapidly metabolized in mice, the major route involving hydration to the corresponding bis-diol, which occurs both enzymatically, through the epoxide hydrolase, and nonenzymatically. This hydration is followed by mono-

oxygenase-mediated dealkylation to form a phenol and glyceraldehyde. It also appears that bisphenol A diglycidyl ether may be directly oxidized with the release of glycidaldehyde (Figure 1). Urinary and faecal metabolites include glucuronides and sulfates of the bis-diol and corresponding carboxylic acids (IARC, 1989).

Figure 1. Two possible routes of oxidative dealkylation of the glycidyl moiety of bisphenol A diglycidyl ether



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From Climie *et al.* (1981)

4.2 Toxic effects

4.2.1 *Humans*

Bisphenol A diglycidyl ether is a contact allergen among people who have worked with low-molecular-weight epoxy resins (IARC, 1989).

4.2.2 *Experimental systems*

Bisphenol A diglycidyl ether has low oral and dermal lethal toxicity in rats and rabbits, respectively, but it is irritant to rabbit skin. It is a highly reactive allergen, according to a guinea-pig skin maximization test (IARC, 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Bisphenol A diglycidyl ether applied to the skin of pregnant rabbits had no effect upon fetal development (IARC, 1989). Daily oral administration by gavage during gestational days 6–15 of up to 640 mg/kg bw per day to rats and 1250 mg/kg bw per day to mice had no effect upon the incidence of malformations in either species. These maternally toxic doses produced fetal toxicity in mice, but not in rats (Morrissey *et al*., 1987).

4.4 Genetic and related effects

4.4.1 *Humans*

One study of workers exposed to bisphenol A diglycidyl ether showed no increase in chromosomal aberrations in peripheral blood lymphocytes (IARC, 1989).

4.4.2 *Experimental systems*

The compound is mutagenic to bacteria (IARC, 1989).

A single major DNA adduct has been observed in the skin of C3H mice treated cutaneously with [^{14}C]bisphenol A diglycidyl ether. Initially it was proposed that this was a reaction product of glycidaldehyde and deoxyguanosine, based upon co-chromatography on an XAD-resin (Bentley *et al*., 1989). Later studies with higher resolution high-performance liquid chromatography on a C-18 column demonstrated that the adducts of bisphenol A diglycidyl ether and glycidaldehyde with DNA are indeed identical, but that the mouse skin adduct is probably hydroxymethylethenodeoxyadenosine-3′-monophosphate, by comparison with a synthetic reference standard. The alkylation frequency was 0.1–0.8 adducts/10^6 nucleotides following dosing with 2 mg bisphenol A diglycidyl ether per mouse and 166 adducts/10^6 nucleotides after a similar dose of glycidaldehyde (Steiner *et al*., 1992a,b).

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bisphenol A diglycidyl ether were available.

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

Overall evaluation

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

6. References

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