Health Council of the Netherlands

Bisphenol A diglycidyl ether

Evaluation of the carcinogenicity and genotoxicity

2013/25

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Bisphenol A diglycidyl ether*
Uw kenmerk : DGV/BMO-U-932542
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Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan bisfenol A diglycidylether.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

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Evaluation of the carcinogenicity and genotoxicity

to:

the Minister of Social Affairs and Employment

No. 2013/25, The Hague, October 18, 2013

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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INAHTA

This report can be downloaded from www.healthcouncil.nl.

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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de Subcommissie Classificatie van carcinogene stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie bisfenol A diglycidylether onder de loep.

Bisfenol A diglycidylether en zijn oligomeren zijn de hoofdbestanddelen van epoxyharsen. De epoxyharsen op basis van bisfenol A diglycidylether worden wijd gebruikt als beschermingslagen, met inbegrip van verven, in versterkt plastic laminaat en mengsels, in het bewerken, gieten en vormen van harsen, in kleefstoffen, en in bevloering.

Op basis van de beschikbare gegevens is de commissie van mening dat de gegevens over bisfenol A diglycidylether als zuivere stof niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3).* Overigens maakt de commissie zich zorgen over de mogelijke carcinogeniteit van niet volledig gezuiverd (technische kwaliteit) bisfenol A diglycidylether.

* Volgens het classificatiesysteem van de Gezondheidsraad (zie bijlage G).

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on the Classification Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In this report, the Committee evaluated bisphenol A diglycidyl ether.

Bisphenol A diglycidyl ether and its oligomers are major components of epoxy resins. 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 flooring and aggregates.

The Committee is of the opinion that the available data on pure bisphenol A diglycidyl ether are insufficient to evaluate the carcinogenic properties (Category 3).* In addition the Committee is of the opinion that exposure to technical grades of bisphenol A diglycidyl ether may pose concern for potential carcinogenic effects.

* According to the classification system of the Health Council (see Annex G).

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex G).

This report contains the evaluation of the carcinogenicity of bisphenol A diglycidyl ether.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the Minister can be found in Annex C.

In May 2013 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of bisphenol A diglycidyl ether, such an IARC-monograph is available of which the summary and conclusion is inserted in Annex E.

A search was performed for more recently published data from the online databases Medline, Toxline, Chemical Abstracts, RTECS and ECHA. The last updated online search was in August 2013.

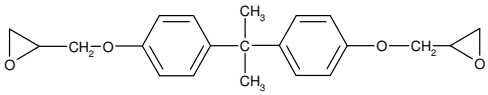
Chapter 2

General information

2.1 Identity and physico-chemical properties

The data have been retrieved from the IARC evaluation of Bisphenol A diglycidyl ether,[1,2] the European Substance Information System (ESIS, which can be accessed via http://esis.jrc.ec.europa.eu/) and the Hazardous Substances Data Bank (HSDB, which can be accessed via http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

Chemical name	:	2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis-(orixane)
CAS registry number	:	1675-54-3
EINECS number	:	216-823-5
Synonyms	:	4,4'-Bis(2,3-epoxypropoxy)diphenyldimethylmethane; 2,2-bis(para-(2,3-epoxypropoxy)phenyl)propane; 2,2-bis(4-(2,3-epoxypropyloxy)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; bisphenol A diglycidyl 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'-dihydroxydiphenyldimethylmethane diglycidyl ether; diomethane diglycidyl ether; 4,4'-isopropylidenebis[1-(2,3-epoxypropoxy)benzene]; 4,4'-isopropylidenediphenol diglycidyl ether; oligomer 340.
Appearance	:	A medium viscosity, unmodified liquid epoxy resin

Use	:	Bisphenol A diglycidyl ether and its oligomers are major components of epoxy resins. 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 flooring and aggregates.
Chemical formula	:	C21H24O4
Structural formula	:	
Molecular weight	:	340.42
Boiling point	:	no data
Melting point	:	8-12ºC
Vapour pressure	:	1.1.10-7 mmHg
Vapour density (air = 1)	:	no data
Solubility	:	0.7 mg/L at 25ºC (in water)
Conversion factor	:	mg/m^3 = 0.072 ppm at 25ºC and 101.3 kPa ppm = 13.92 mg/m^3 at 25ºC and 101.3 kPa
EU Classification (100% solution)	:	Eye Irrit. 2: H319 (Causes serious eye irritation) Skin Irrit. 2: H315 (Causes skin irritation) Skin Sens.1: H317 (May cause an allergic skin reaction)

2.2 IARC classification

There is *limited evidence* in experimental animals for the carcinogenicity of bisphenol A diglycidyl ether and bisphenol A diglycidyl ether is mutagenic to bacteria. Based on this information IARC has classified bisphenol A diglycidyl ether as *not classifiable as to its carcinogenicity to humans* (Group 3) (see Annex E).

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

No information on human studies related to the carcinogenicity of bisphenol A diglycidyl ether has been retrieved from the IARC monographs.[1,2] No additional human studies in the period after the IARC monograph were retrieved from the literature.

3.2 Carcinogenicity studies in animals

The information on bisphenol A diglycidyl ether in animal studies is selected from the IARC monographs,[1,2] the EFSA review (2004)[3] and the ECHA website.[4] No studies on inhalation exposure were available. The Committee is aware that only a limited number of animal studies exists using pure (analytical grade) bisphenol A diglycidyl ether while all other studies use technical grade material, containing various impurities. Moreover, in a number of studies the test material was inadequately described.

Oral exposure

In the study by Hine et al. (1958)[5] (cited in IARC[1]), groups of 30 male Heston A strain mice were fed a diet containing 2% bisphenol A diglycidyl ether (no further details regarding the test material are available) or a normal 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. [The IARC Working Group noted the inadequate description of the test material and that the study was not designed to investigate carcinogenicity in tissues other than lungs.]

Stebbins and Dryzga (2003)[6] (cited in EFSA[3] and ECHA[4]) administered pure bisphenol A diglycidyl ether (purity >99%) to groups of 65 male and 65 female Fischer 344 rats by oral gavage. Bisphenol A diglycidyl ether was suspended in Tween_ 80 and methylcellulose and given at dose levels of 0 (controls), 2, 15, or 100 mg/kg/day for up to two years. Ten rats per sex and per dose level were necropsied after one year of treatment (chronic toxicity group), and 50 rats per sex per dose level were dosed for up to two years (oncogenicity group). Daily examinations and periodic body weight and feed consumption were monitored throughout the study. Clinical pathology examinations (haematology, clinical chemistry, electrolytes, and urinalysis) were conducted at regular intervals throughout the study. Ophthalmic examinations were conducted on all rats before the start of the study and on all surviving rats prior to the scheduled necropsies. Histopathological examination of an extensive set of organs was performed on all control and high-dose level rats and all rats removed from the study early. Histopathological examination of survivors from the low and intermediate dose levels was limited to the liver, kidneys, lungs, spleen, and relevant gross lesions. The study was performed in compliance with Good laboratory Practice, following the OECD guideline 453 on chronic toxicity/carcinogenicity studies.

After 24 months there were no statistically significant differences in mortality among study groups.

Males given 15 or 100 mg/kg/day had treatment-related statistically significant decreases in body weights and body weight gains. After one year of dosing, body weight gains for males given 15 or 100 mg/kg/day were 4.0% and 12.9% lower than controls. At study termination body weights of the males given 15 or 100 mg/kg/day were 3.5% and 7.4% lower than controls, respectively. There were no treatment-related effects on body weights of males given 2 mg/kg/day nor of females from any dose group.

Males given 100 mg/kg/day and females given 15 or 100 mg/kg/day had treatment-related, statistically significant increases in serum cholesterol after 3 and 12 months of bisphenol A diglycidyl ether administration. In addition, there was a treatment-related, non-statistically identified increase in serum cholesterol

of males given 100 mg/kg/day at 24 months. No treatment related alterations were observed in haematology, urinalysis and electrolytes.

Males and females given 100 mg/kg/day had treatment-related, statistically significant increases in coecal size and weight. There were no histopathologic alterations in the enlarged caecums. The coecal enlargement was interpreted to be non-adverse, and reflective only of a physiologic adaptive change in the caecum. Males given 100 mg/kg/day also had a treatment related, statistically significant decreases in absolute and relative spleen weights. Very slight atrophy of the red pulp of the spleen was noted in these animals, and interpreted to be reflective of lower body weight gain rather than a primary toxic effect.

No increase in neoplasms was observed in either male or female rats at any dose level. The authors conclude that bisphenol A diglycidyl ether did not show oncogenic potential under the conditions of this study.

Dermal exposure

In a study by Peristianis et al. (1988)[7] (cited in IARC[1]) 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 in acetone on shaved back skin twice a week for two years. In addition, a control group of 100 male and 100 female mice was treated with acetone. A positive control group of 50 males and 50 females received an application of ß-propiolactone in acetone.

Survival of both male and female mice was not affected by treatment with the pure epoxy resin when compared to the acetone controls and was considerably less than survival in the positive (ß-propiolactone) controls.

Treatment with the pure epoxy resin did not lead to the development of any epidermal tumours in both male and female animals (Annex F, Table 1). No epidermal tumour was observed in the acetone controls (Annex F, Table 1). Two dermal tumours (haemanchiosarcomas) were seen in the high-dose males (Annex F, Table 1). One male mouse in the acetone control group developed a dermal tumour (fibrosarcoma) of the treated site (Annex F, Table 1). In the positive control groups (treated with ß-propiolactone) a large number of skin tumours was observed in both males (132 tumours in 30 of 50 animals) and and females (63 tumours in 13 of 50 animals). These tumours were generally malignant epithelial tumours and, with a lower incidence, mesenchymal tumours.

The incidence of systemic tumours was generally comparable to those seen in control mice. However, in female mice a slight increase was observed for the incidence of thymic lymphosarcomas (2 of 50 animals after low-dose treatment

(1%) and 5 of 50 animals after high-dose (10%) treatment, compared with 6 of 100 females in the acetone control group). [The Committee is aware that only a very small amount of bisphenol A diglycidyl ether is able to penetrate human, mouse and rat skin unchanged, and is metabolized to its corresponding -diol (Boogaard et al. (2000).[8]]

Stebbins and Baker (1998)[9] (cited in EFSA[3] and ECHA[4]) evaluated pure bisphenol A diglycidyl ether (purity 99.3%) for chronic toxicity and oncogenicity potential following two years of repeated dermal administration. Groups of 70 male B6C3F1 mice/dose level were dosed dermally with bisphenol A diglycidyl ether in acetone solutions at concentrations of 0, 0.005%, 0.5%, or 5.0% (w/v). The dosing volume was 50 ml/application which corresponded to approximate dosages of 0, 0.1, 10 or 100 mg Bisphenol A diglycidyl ether/kg body weight per application. Each dose group followed a 3 applications/week (monday, wednesday, friday) dosing regimen. Twenty mice/dose level were necropsied after one year of exposure, while the remaining 50 mice/dose level were necropsied after two years of exposure or until removal from study due to death or moribund condition. Data were collected on the following: clinical appearance and behavior, dermal irritation at the test site, body weights, food consumption, clinical pathology, organ weights, gross pathology, and histopathology.

Bisphenol A diglycidyl ether applied to the skin of male B6C3F1 mice three times per week for two years at dosages of 0.1,10 or 100 mg/kg/application caused no apparent systemic toxicity. Slight to severe epidermal hyperplasia, slight to moderate chronic or chronic-active dermal inflammation, and epidermal crusts were observed histopathologically at dosages of 10 and 100 mg/kg/ application. In addition, epidermal ulcers accompanied the dermal inflammation in a few animals given 10 or 100 mg/kg/application. There were no treatment-related dermal alterations in mice given 0.1 mg/kg/application.

One mouse given 10 mg/kg/application had a squamous cell carcinoma of the skin at the test material application site. The single occurrence of a squamous cell carcinoma at the test site of this mid-dose animal was not an indicator of oncogenic potential, because there were no tumors at the test material application sites of animals from the high-dose group. The occurrence of one squamous cell carcinoma was also within the historical control incidence range of epidermal squamous cell tumors occurring in B6C3F1 mouse oncogenicity studies performed by this laboratory.

Dermal application of Bisphenol A diglycidyl ether at doses up to 100 mg/kg/application for two years produced neither systemic toxicity nor oncogenicity in any tissue in the male B6C3F1 mouse.

Crissmann and Jeffries (1998)[10] (cited in EFSA[3] and ECHA[4]) applied pure bisphenol A diglycidyl ether (purity 99.3%) to the unoccluded skin of female Fischer 344 rats five times per week for up to two years at dosages of 0, 1, 100, and 1,000 mg/kg/application.

Animals receiving 1,000 mg/kg/application gained weight more slowly than control animals during the first few months of the study; but at the end of two years there were no differences in body weights, body weight gains, or food consumption.

The only in-life observations attributed to treatment were an increase in the number of 1,000 mg/kg/application dose group rats with periocular soiling and urine soiling in the perineal area.

Histopathologically, there was dose-related mild chronic dermatitis at the dermal test site of rats in the 100 and 1,000 mg/kg/application groups. In the liver there was centrilobular hepatocyte hypertrophy at the 1,000 mg/kg/application dose, and an increase in several types of foci of cellular alteration at 100 and 1,000 mg/kg/application. Liver effects were also observed as mild elevations in several clinical chemistry enzymes in rats given 1,000 mg/kg/application.

The incidence of epithelial neoplasms in and around the mouth, although not statistically different from concurrent controls, was slightly higher than observed in historical controls. These neoplasms were attributed to embedded hair foreign bodies in oral tissues and peri-oral skin, and thus were considered an artifact of the study methodology. Thus, there were no neoplasms in any tissue that were statistically increased or directly attributable to the effects of the test material.

Under the conditions of this 2-year dermal ononcogenicity bioassay, bisphenol A diglycidyl ether at doses up to 1,000 mg/kg/application did not cause neoplasia in any tissue in female Fischer 344 rats.

In the abovementioned study by Peristianis et al. (1988)[7] (cited in IARC[1]) two technical grade preparations of bisphenol A diglycidylether (EPON 828, containing 29 mg/kg epichlorohydrin and Epikote 828, containing 3 mg/kg epichlorohydrin) were also included.

Treatment of both male and female mice with EPON or Epikote did not affect the survival of the animals when compared to the acetone-treated control. ln animals treated with EPON 828, one skin carcinoma occurred in high-dose males and one fibrosarcoma of the subcutis in a high-dose female (Annex F, Table 1).

ln Epikote 828-treated mice, one squamous cell papilloma of the skin was observed in a low-dose male and three basal-cell carcinomas, one in a low-dose and one in a high-dose male and one in a high-dose female (Annex F, Table 1). ln addition, one sebaceous-gland adenoma was observed in a high-dose male (Annex F, Table 1).

The incidence of systemic tumours in all treatment groups was generally comparable to those seen in control mice. However, in males treated with 1 and 10 % EPON 828 a slight increase in the incidence of kidney tumours, mainly carcinomas, was observed (0 of 50 and 8 of 50 males respectively, with 6 of 99 males in the acetone control group). Moreover, in female mice, treated with Epikote 828 a slight increase in the incidence of both lymphoreticular/ haematopoietic tumours and reticulum-cell sarcoma was observed. The treatment with 1 and 10% Epikote 828 resulted in the development of lymphoreticular/ haematopoietic tumours in 14 of 50 females and in 24 of 50 females respectively, with 27 out of 100 females in the acetone control group). In addition, in female mice, reticulum-cell sarcoma's developed in 11 of 50 and 15 of 50 animals after treatment with 1 and 10% respectively (with 16 of 100 females in the control group).

In a study by Holland et al.(1979)[11] (cited in IARC[1]) groups of 40 female and 40 male C3H and 20 female and 20 male C57BL/6 mice, ten to 12 weeks of age, received applications of 5, or 25 mg of technical grade bisphenol A diglycidyl ether (containing 10% (w/w) of an epoxidised polyglycol (mol wt >500) and small amounts of phenyl glycidyl ether) in acetone on their shaved back skin three times a week for 24 months. Vehicle controls were treated with acetone. After the 24-month exposure period, all surviving mice were weighed and the average weight of treated animals was compared with that of the controls.

In C3H mice, no significant change in average terminal body weight was observed. Survival in control, mid, and high dose groups, respectively, was 23, 21, and 21 in males and 21, 23, and 18 in females, and no skin tumours were observed.

In C57BL/6 mice, significant weight loss was observed in high-dose males. Survival in control, mid, and high dose groups, respectively, was 20, 17, and 15 in males and 15, 15, and 13 in females. Skin tumours ocurred in low-dose and high-dose males (1 papilloma and 6 carcinomas, respectively, with no tumours in the control) and in high-dose females (1 papilloma and 1 carcinoma, with no tumours in the low dose and control group).

It was also examined in this study whether bisphenol A diglycidyl ether penetrated the skin and could lead to the development of tumours in other organs.

The incidence of histologically confirmed tumours observed at death is given in Annex F (Table 2) for both C3H and C57BL/6 mice. The tumour incidence fluctuated greatly and was either uncorrelated with dose or was comparable to that in the control. [The IARC Working Group noticed the increased incidence of lung tumours in female C3H mice, a finding that was not further discussed in the paper by Holland et al.[11]]

In the same study of Holland et al. (1979)[11] (cited in IARC[1]) 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 15, or 75 mg per week of a mixture of equal parts of technical grade bisphenol A diglycidyl ether and bis(2.3-epoxycyclopentyl)ether in acetone on their shaved back skin for 24 months. Vehicle controls were treated with acetone.

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, respectively. 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 and 17 high-dose males and in two low-dose (one papilloma and one carcinoma) and 15 high-dose (two papillomas and 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, indicating a synergistic effect of the compounds when tested as a mixture.

In another study, Zakova et al. (1985)[12] (cited in IARC[1]), 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 twice a week for two years. There was no effect on survival; no skin tumour was observed on 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.

Hine et al. (1958)[5] (cited in IARC[1]) studied the effect of bisphenol A diglycidyl ether (no further details regarding the test material are available) on skin of male C3H mice. Groups of 30 male C3H mice (with body weights of 16-18 g) received skin applications of 0.2 mL of a 0.3% solution weekly or a 5% solution of bisphenol A diglycidyl ether in acetone once or three times weekly for 24 months. A control group of 30 male animals 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 in malignant skin tumours (19/20) within six months. [The IARC Working Group noted the inadequate description of the test material.]

In a study by Weil et al. (1963)[13] (cited in IARC[1]) a group of about 40 C3H mice (exact number and sex not specified), aged 13 weeks, received skin applications of undiluted bisphenol A diglycidyl ether (purity and dose not specified) 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). [The IARC Working Group noted that the amount of test substance per application was not given and that untreated controls were not included in the experiment.]

In the abovementioned study of Hine et al. (1958)[5] (cited in IARC[1]) each of 16 male albino rabbits (strain and age not specified) received skin applications (site not specified) of 0.5 mL acetone thrice weekly, a 0.3% solution in acetone once per week, a 5% solution of bisphenol A diglycidyl ether (no further details regarding the test material are available) 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. [The IARC Working Group noted the inadequate description of the test material.]

Subcutaneous injection

In the study of Hine et al. (1958)[5] (cited in IARC[1]) groups of 30 male Long-Evans rats (with body weights of 80-100 g) were given three weekly subcutaneous injections of bisphenol A diglycidyl ether (no further details regarding the test material are available) 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 animals in the negative control, epoxy resin and positive control groups, respectively. The numbers of malignant tumours at the site of injection were 0, 4 (fibrosarcomas) and 17 (mainly fibrosarcomas or sarcomas), respectively. [The IARC Working Group noted the inadequate description of the test material.]

Carcinogenicity of metabolites

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 monooxygenase-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[1], 1999[2]). As the epoxy hydrolase activity for polycyclic aromatic hydrocarbons in liver and skin of man is greater than in mouse and rat, metabolic deactivation of bisphenol A diglycidy ether can also be expected in man.[3]

Carcinogenicity of glycidaldehyde and glyceraldehyde

Glycidaldehyde is classified by IARC (see Annex E) as *possibly carcinogenic to humans (Category 2B)* on the basis of sufficient evidence in experimental animals (IARC 1976[14], 1987[15], 1999[2]): glycidaldehyde is carcinogenic in mice by skin application and by subcutaneous injection and in rats. It produced malignant tumours at the site of application in both species. No epidemiological data relevant to the carcinogenicity of glycidaldehyde are available.

For glyceraldehyde no experimental and human data regarding carcinogenicity are found in the literature and no IARC classification is available.

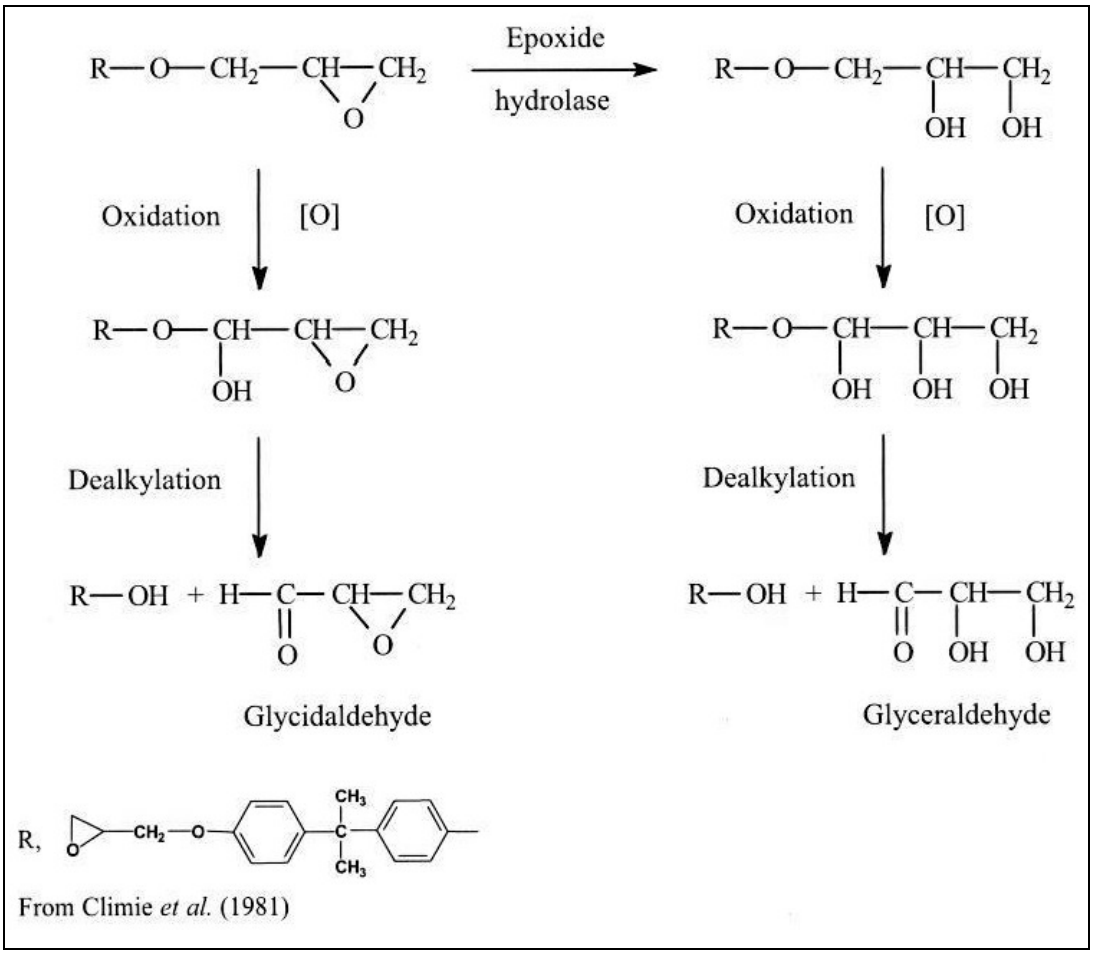


Figure 1 Two possible routes of oxidative dealkylation of the glycidyl moiety of bisphenol A diglycidyl ether (IARC, 1999).[2]

Carcinogenicity of epichlorohydrin

Technical grade preparations of Bisphenol A diglycidyl ether may contain epichlorohydrin (Peristianis et al. (1988))[7]. The carcinogenicity of epichlorohydrin has been evaluated by IARC (1976[14], 1987[15], 1999[2]). They concluded that there is inadequate evidence in humans for the carcinogenicity of epichlorohydrin but sufficient evidence for the carcinogenicity in experimental animals. As overall evaluation IARC considered epichlorohydrin *probably carcinogenic to humans (Group 2A)* by IARC. Previously, the Dutch Expert

Committee on Occupational Standards (DECOS) has concluded that epichlorohydrin is a genotoxic carcinogen (WGD86)[16] and calculated additional lifetime cancer risks (No. 2000/10OSH).[17]

3.3 Summary of the carcinogenicity studies

No human data on the carcinogenicity of bisphenol A diglycidyl ether are available.

The experimental study in CF1 mice by Peristianis et al. (1988)[7], represents the oldest 2 year skin application study that tested pure ('analytical grade') bisphenol A diglycidyl ether. No increase in the incidence of skin tumours was observed under these conditions, only a slight increase in the incidence of thymic lymphosarcomas was observed in female CF1 mice, a strain known for its high background of this tumour type. A more recent two-year dermal study in B6C3F1 mice by Stebbins and Baker (1998)[3,9] produced no clear evidence of any oncogenic activity of pure bisphenol A diglycidyl ether. The single squamous cell carcinoma detected at the test site in one mid-dose animal cannot be interpreted as evidence for an oncogenic potential because no tumours had occurred at the test site in any other dose group and this incidence falls within the historical control rate. In a two-year study in F344 rats by Crissman and Jeffries (1998)[3,10] with pure bisphenol A diglycidyl ether no skin carcinogenic effects were observed but there was evidence of hepatotoxicity. The observed squamous cell carcinomas of the oropharyngeal region were all associated with the presence in the carcinoma cells of rat hair as intracellular foreign body inclusion.

The only reliable oral study in Fisher 344 rats receiving daily administration of pure bisphenol A diglycidy ether by gavage for two-years showed no oncogenic potential in the gastrointestinal tract or in other tissues (Stebbins and Dryzga, 2003).[3,4,6]

In the 2 year skin application study with mice by Peristianis et al.[7], additionally two technical grades of bisphenol A diglycidyl ether were tested. One of the two investigated technical grades induced a slight increase in the incidence of epidermal tumours and slight increases in the incidences of kidney tumours in male mice, whereas the other technical grade induced a slight increase in the incidence of lymphoreticular/ haematopoietic tumours and reticulum cell sarcoma's in female mice. A role for epichlorohydrin, a contaminant of the technical-grade preparations, may not be excluded in these observations.

Apart from this study by Peristianis et al.[7] quite a number of experimental studies also investigated the carcinogenicity of technical grades bisphenol A diglycidyl ether, most also being of limited design. Five of these studies concerned skin application in mice, and limitations in the design of these studies comprised the small number of animals used, the use of only a single dose level, or microscopical examination of only a single or a couple of organs or tissues for tumour formation. In the study by Holland et al.[11], application of a high dose resulted in an increased incidence of epidermal tumours in only one of two strains tested. The incidence of systemic tumours in this study[11] fluctuated greatly and was either uncorrelated with dose or comparable to the control with a possible exception for lung tumors in one of the strains tested. No increase in the incidence of skin tumours was observed in the other, limited, studies. Also, no skin tumours were observed following 2 year application of technical-grade bisphenol A diglycidyl ether to the skin of rabbits[5].

Chapter 4

Genotoxicity

4.1 Gene mutation assays

4.1.1 In vitro

In one early study, bisphenol A diglycidyl ether was not mutagenic to *S. typhimurium* TA98 and TA100 (Wade et al. (1979)[18] cited in IARC[1]), while in a later study, bisphenol A diglycidyl ether was mutagenic to *S. typhimurium* TA100 and TA1535 but not to TA98 and TA1537 (Canter et al. (1986)[19] cited in IARC[1]).

This finding by Canter (see Section 4.1.2) was more recently confirmed by Sueiro et al. (2001)[1,20] who investigated the mutagenicity of bisphenol A diglycidyl ether, its first and second hydrolysis products (the diol epoxide and bis-diol of bisphenol A diglycidyl ether, respectively) and the bis-chlorohydrin of bisphenol A diglycidyl ether using the Ames *Salmonella* assay with strains TA98, TA100, TA1535 and TA1537. The assays were performed in the absence and presence of various concentrations of rat liver S9 fraction. The results obtained confirm the mutagenic activity of bisphenol A diglycidyl ether in strains TA100 and TA1535 and show a positive response to the diol epoxide of bisphenol A diglycidyl ether in these strains, although the latter compound was ~10 times less potent than the former. A lack of mutagenic activity of the bis-diol of bisphenol A diglycidyl ether and the chlorohydrin under study is also shown. Similar results were obtained by the same authors (Sueiro et al. (2006[21])) using

the *E. coli* tryptophan reverse mutation test with strains WP2, WP2*uvr*A and IC3327.

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)[22] cited in IARC[1]). In line with this an abstract reported that EPIKOTE 828 was mutagenic to *S. typhimurium* TA100 but not to TA98 (Nishioka & Ohtani, 1978;[23] cited in IARC[1]).

As reported in an abstract, EPIKOTE 828 (composed mainly of bisphenol A diglycidyl ether) induced DNA repair in *E. coli* (Nishioka & Ohtani, 1978[23]; cited in IARC), and was mutagenic to *E. coli* WP_2 *uvrA* in the absence of an exogenous metabolic system (Hemminki et al. (1980)[24] cited in IARC[1]).

A forward mutation assay in mouse lymphoma cells without exogenous metabolic activation system using a single dose of 0.03 µg/ml was positive for TK 12386 (specification not available)[25] (cited in EFSA[3]).

Bisphenol A diglycidyl ether (>98% pure) was tested in a *hprt* gene mutation test with V79 cells. Bisphenol A diglycidyl ether but not its hydrolysis product, induced gene mutations at the *hprt* locus of these cells (see also Paragraph 4.2.1) (cited in ECHA[4] (gen. tox. vitro 015)).

4.1.2 In vivo

No in vivo mutagenicity studies of bisphenol A diglycidyl ether were recovered from either the IARC monograph or a later date.

4.2 Cytogenetic assays

4.2.1 In vitro

The effect of bisphenol A diglycidyl ether on the formation of chromosomal aberrations in human peripheral lymphocytes was examined. Chromosomal preparations of leukocytes cultured from human peripheral blood were treated with 5-100 ug/mL bisphenol A diglycidyl ether in DMSO. Bisphenol A diglycidyl ether did not cause a significant increase in the number of cells with chromosome aberrations over control levels at dose levels as high as 50 µg/ml. At 100 ug/ml cytotoxicity was noted as only a few mitotic cells were scored (cited in ECHA[4] (gen. tox. vitro 021)).

Bisphenol A diglycidyl ether (>98% pure) was tested in a micronucleus assay with and without S9 activation (aroclor-treated male rats) (cited in ECHA[4] (gen. tox. vitro 015)). Chinese hamster lung fibroblasts (V79 cells) were treated with the test material in DMSO for 3-6 hours. The cytotoxicity was measured in the *hprt* test with V79 cells described in 4.1.1. Bisphenol A diglycidyl ether is very stable in the absence of metabolizing enzymes (S9-mix) but is rapidly hydrolyzed to a diglycol by S9-mix. Bisphenol A diglycidyl ether but not the diglycol, induced an increase in cells with micronuclei and an increase in the *hprt* mutant frequency. The induced micronuclei were characterized with CREST antikinetochore antibodies and consisted of acentric chromosomal fragments and did not contain whole chromosomes/chromatids. It was concluded that bisphenol A diglycidyl ether exhibits clastogenic and mutagenic potential, which is lost after hydrolysis of the epoxide rings and converted to aneuploidogenic potential after cleavage to bisphenol A.

Rat liver (RL1 or RL4) cells in slide cultures were exposed for 24 h to culture medium containing EPIKOTE 828 or bisphenol A diglycidyl ether (cited in ECHA[4] (gen. tox. vitro 014)). Upon treatment with EPIKOTE 828 in tested cultures of RL4 there was a concentration-related increase in cells with chromosome aberrations in cultures treated with 10 or 20 µg/mL. Consequently, EPIKOTE 828 was considered genotoxic in this chromosome aberration test in vitro.

Upon treatment with bisphenol A diglycidyl ether in tested cultures of RL1 cells, a substantial increase in cells with chromosomal aberrations (exchange figures) was seen at the highest dose (15 µg/mL) only. Bisphenol A diglycidyl ether is considered genotoxic in this chromosome aberration test in vitro.

Suarez et al. (2000)[26] examined the epoxy resin bisphenol A diglycidyl ether, its hydrolysis products and a chlorohydrin of bisphenol A diglycidyl ether (BADGE.2HCl) for their genotoxicity in the micronucleus test with human peripheral blood lymphocytes in vitro, in the presence and absence of an exogenous metabolizing system. The concentrations tested ranged from 12.5 to 62.5 µg/ml of bisphenol A diglycidyl ether, 12.5 to 2.5 µg/ml of first hydrolysis product (BADGE.H(2)O), 25.0 to 100.0 µg/ml of second hydrolysis product (BADGE.2H(2)O) and 6.25 to 50.0 µg/ml of BADGE.2HCl. These compounds are able to induce both cytotoxic and genotoxic effects in cultured human lymphocytes, as revealed by the increases observed in the cytokinesis block proliferation index and an increase in cells with micronuclei, respectively.

4.2.2 *In vivo*

The results of a test for nuclear abnormalities including micronuclei and polyploidy in Chinese hamster bone marrow was carried out with bisphenol A diglycidyl ether (TK 12386: purified Araldite GY250, 80%-85% monomer, 15%-20% oligomers, epichlorhydrin<1ppm, BPA<5ppm). The substance, dissolved in polyethylene glycol, was given by gavage on 2 consecutive days to groups of 3 male and 3 female hamsters at 825, 1,650 and 3,300 mg/kg bw/day. Animals were sacrificed 24 hours after the last treatment. No nuclear abnormalities were detected[27] (cited in EFSA[3] and ECHA[4]).

A test for chromosome aberrations in Chinese hamster bone marrow cells with 2 consecutive oral daily administrations of 825, 1,650 and 3,300 mg/kg bw/day of bisphenol A diglycidyl ether (TK 12386: purified Araldite GY250, 80%-85% monomer, 15%-20% oligomers, epichlorhydrin<1 ppm, BPA<5ppm) dissolved in polyethylene glycol was performed. Two males and 2 females per dose group were sacrificed 6 hours after the second administration. The result was negative. However, the small size of the experimental groups is noted[28] (cited in EFSA[3]).

In a test for structural chromosome aberrations in mouse spermatogonia, bisphenol A diglycidyl ether (TK 10490: Araldite GY250, 80%-85% monomer, 15%-20% oligomers, epichlorhydrin<10 ppm, BPA<5 ppm) dissolved in polyethylene glycol was administered at daily doses of 375, 750, 1,500 and 3,000 mg/kg bw/day to groups of 8 male mice/dose on five consecutive days by gavage. The result was considered negative, since only 1 exchange was detected at the low dose, 2 chromosome breaks at the middle dose, 1 chromosome fragment at the high dose and none in 800 scored control cells[29] (cited in EFSA[3] and ECHA[4]).

In another chromosomal aberrations test in mouse spermatocytes, bisphenol A diglycidyl ether (TK 12386: purified Araldite GY250, 80%-85% monomer, 15%-20% oligomers, epichlorhydrin<1 ppm, BPA<5 ppm) was administered daily for 5 days at doses of 1,000 mg/kg and 3,000 mg/kg bw/day dissolved in polyethylene glycol to groups of 8 male mice/dose. Animals were sacrificed 3 days after the last treatment. From each animal 100 metaphases of primary and secondary spermatocytes were examined. Results were considered inconclusive because of the inadequate study protocol. The time interval between the last DNA synthesis and first meiotic division in mouse male germ cells is 11 days:

therefore, because most chemical clastogens are S-phase dependant, sampling for cytogenetic analysis of spermatocytes should have been done 11 or more days after treatment instead of 8[30] (cited in EFSA[3] and ECHA[4]).

A dominant lethal test was carried out in mice using a single oral administration of bisphenol A diglycidyl ether (TK 12386: purified Araldite GY250, 80%-85% monomer, 15%-20% oligomers, epichlorhydrin<1 ppm, BPA<5 ppm) at doses of 3,333 and 10,000 mg/kg bw. A biological relevant increase in dominant lethals was not observed. as the study lacked a positive control group, the historical data using TEM at 0.25 mg/kg-0.5 mg/kg bw ip were used[31] (cited in EFSA[3]).

4.3 Miscellaneous

4.3.1 In vivo

The induction of liver DNA damage in vivo was evaluated in pairs of male and female rats by alkaline elution, 6 hours after a single oral treatment with 500 mg/kg bw of bisphenol A diglycidyl ether (Ciba-Geigy product batch KA 2/LP, purity not stated) as a 20% DMSO solution by gavage. MMS (300 mg/kg bw) by gavage was the positive control. A biological relevant increase in DNA damage was not observed[32] (cited in EFSA[3] and ECHA[4]).

Liver DNA damage was examined in pairs of male and female rats by alkaline elution 6 hours after a single oral gavage treatment with 500 mg/kg bw EPIKOTE 828 (no specification supplied) as a 20% solution in DSMO. A biological relevant increase in DNA damage was not observed[33] (cited in EFSA[3]).

A single, major type DNA adduct has been observed in the skin of C3H mice treated subcutaneously 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)[34] cited in IARC[2]). 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 are indeed identical, but that the mouse skin adduct found in the mouse skin 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. (1992)[35] cited in IARC[2]).

4.4 Summary of the genotoxicity studies

Under in vitro conditions, bisphenol A diglycidyl ether was repeatedly shown mutagenic bacteria and mammalian cell lines. Structural chromosome aberrations were also repeatedly shown in mammalian cell lines. The clastogenic effect was not confirmed in in vivo tests for chromosome aberrations both in somatic and germ cells. However, the positive results found in the in vitro gene mutation assays in bacteria and mammalian cells were not confirmed nor ruled out in an appropriate in vivo test on the same genotoxic endpoint. Consequently, a final conclusion on the genotoxic potential of bisphenol A diglycidyl ether cannot be drawn. Next to that, evidence of formation of DNA adducts that appear identical to those formed by its metabolite glycidaldehyde, a substance demonstrated to be carcinogenic to skin*, has been found after in vivo topical application of bisphenol A diglycidyl ether to skin. The level of DNA adducts after skin application of bisphenol A diglycidyl ether is, however, orders of magnitude lower than that observed after application of glycidaldehyde, which renders the biological relevance of this observation questionable, the more so since it was administered by subcutaneous injection.

* Glycidaldehyde is classified by IARC as *possibly carcinogenic to humans* (*Group 2B*). This is based on evidence in experimental animals: the induction of local tumours upon skin application in mice, and upon subcutaneous injection in rats.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No human data on the carcinogenicity of bisphenol A diglycidy ether are available.

Oral administration of pure epoxy resin for two years in rats showed no oncogenic potential in the gastrointestinal tract or in other tissues.

In the carcinogenicity studies with the pure epoxy resin in mice and rats no epidermal tumours were found after topical application. No increased incidence of the only systemic tumours found in one of these studies, thymic lymphosarcomas, was observed in studies with technical grades of this substance. Available carcinogenicity studies with technical-grade bisphenol A diglycidyl ether do occasionally show increased incidences of various tumours, but the incidences are low and appear incidental in nature: i.e. no clear, reproducible target organ can be identified. This suggests that there is no clear relationship with the actual bisphenol A diglycidyl ether when administered via this route.

In contrast to the clastogenicity of bisphenol A diglycidyl ether both in somatic and germ cells, the positive results found in the in vitro gene mutation assays in bacteria and mammalian cells were not confirmed nor ruled out in an appropriate in vivo test on the same genotoxic endpoint. Consequently, a final conclusion on the genotoxic potential of bisphenol A diglycidyl ether cannot be drawn.

Evidence of DNA adduct forming capabilities in vivo have been found but the biological relevance is questionable.

The Committee is aware that the pure (analytical grade) bisphenol A diglycidyl ether is negative for any tumours in a number of animal carcinogenicity studies after oral and dermal exposure. However, the Committee is also aware that not all dermal animal studies completely exclude oncogenicity. In addition, the Committee observes a complete absence of any epidemiological studies. Therefore, the Committee is of the opinion that the available data on the pure substance are insufficient to evaluate the carcinogenic properties (Category 3).

In addition, the Committee observes that technical grades of bisphenol A diglycidyl ether may occasionally induce local and systemic tumours while no clear relationship with the actual bisphenol A diglycidyl ether is suggested. The Committee is of the opinion that exposure to technical grades of bisphenol A diglycidyl ether, e.g. via inhalation, may pose concern for potential carcinogenic effects.

5.2 Recommendation for classification

The Committee concludes that the available data on pure bisphenol A diglycidyl ether are insufficient to evaluate the carcinogenic properties (Category 3).*

* According to the classification system of the Health Council (see Annex G).

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A	Request for advice
B	The Committee
C	The submission letter
D	Comments on the public review draft
E	IARC Monograph
F	Carcinogenicity studies in animals
G	Carcinogenic classification of substances by the Committee

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10-4 and 10-6 per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

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- G.M.H. Swaen
  Epidemiologist, Dow Chemical NV, Terneuzen *(until April 1, 2013);*
  Exponent, Menlo Park, United States *(from August 15, 2013)*
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- G.B. van der Voet, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter

Subject	: Submission of the advisory report *Bisphenol A diglycidyl ether*
Your Reference	: DGV/MBO/U-932342
Our reference	: U-7910/BV/fs/246-Y18
Enclosed	: 1
Date	: October 18, 2013

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to *Bisphenol A diglycidyl ether.*

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on the Classification of Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The advisory report

has been assessed by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,

(signed)
Professor W.A. van Gool,
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in May 2013 for public review. The following organisations have commented on the draft document:

- National Institute for Occupational Safety and Health (NIOSH), Cincinnati, USA
- Epoxy Resins REACH Consortium (ERRC), c/o Dow MF Produktions GmbH & Co. OHG, Rheinmünster, Germany.

Annex **E**

IARC Monograph

Volume 47, 1989 (Excerpt from Some glycidyl ethers, pp. 237-261)

Summary of Data Reported and Evaluation

1 Exposure data

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. 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 their production, during the production of epoxy products and during various uses of epoxy products, but data on exposure levels are sparse.

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.

3 Human data

No data were available to the Working Group.

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 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. The glycidyl ethers were generally mutagenic to bacteria.

5 Evaluation

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

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

For definition of the italicized terms, see Preamble Evaluation.

Subsequent evaluation: Volume 71 (1999) (Bisphenol A diglycidyl ether)

Synonyms for Bisphenol A diglycidyl ether

- Araldite 6005
- Araldite® GY 250
- Araldite® GY 6010
- Bis(4-glycidyloxyphenyl)dimethylmethane
- 2,2-Bis(4-glycidyloxyphenyl)propane
- 2,2-Bis(4-hydroxyphenyl)propane diglycidyl ether
- 2,2-Bis(*para*-glycidyloxyphenyl)propane
- 2,2-Bis(*para*-hydroxyphenyl)propane diglycidyl ether
- 2,2-Bis[4-(2,3-epoxypropoxy)phenyl]propane
- 2,2-Bis[*para*-(2,3-epoxypropoxy)phenyl]propane
- 4,4'-Bis(2,3-epoxypropoxy)diphenyldimethylmethane
- 4,4'-Dihydroxydiphenyldimethylmethane diglycidyl ether
- 4,4'-Isopropylidenebis[1-(2,3-epoxypropoxy)benzene]
- 4,4'-Isopropylidenediphenol diglycidyl ether
- Bis(4-hydroxyphenyl)dimethylmethane diglycidyl ether
- BPDGE
- D.E.R.® 331
- Dian diglycidyl ether
- Diglycidyl bisphenol A
- Diglycidyl bisphenol A ether
- Diglycidyl diphenylolpropane ether
- Diglycidyl ether of 2,2-bis-(4-hydroxyphenyl)propane
- Diglycidyl ether of 2,2-bis-(*para*-hydroxyphenyl)propane
- Diglycidyl ether of 4,4'-isopropylidenediphenol
- Diglycidyl ether of bisphenol A
- *para*,*para*'-Dihydroxydiphenyldimethylmethane diglycidyl ether
- Diomethane diglycidyl ether
- EPI-REZ® 510
- Epikote® 815
- Epikote® 828
- EPON® 828
- EPOTUF® 37-140
- Epoxide A
- Oligomer 340

Volume 71, 1999 (Excerpt from Bisphenol A diglycidyl ether, pp. 1285-1289)

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).

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).

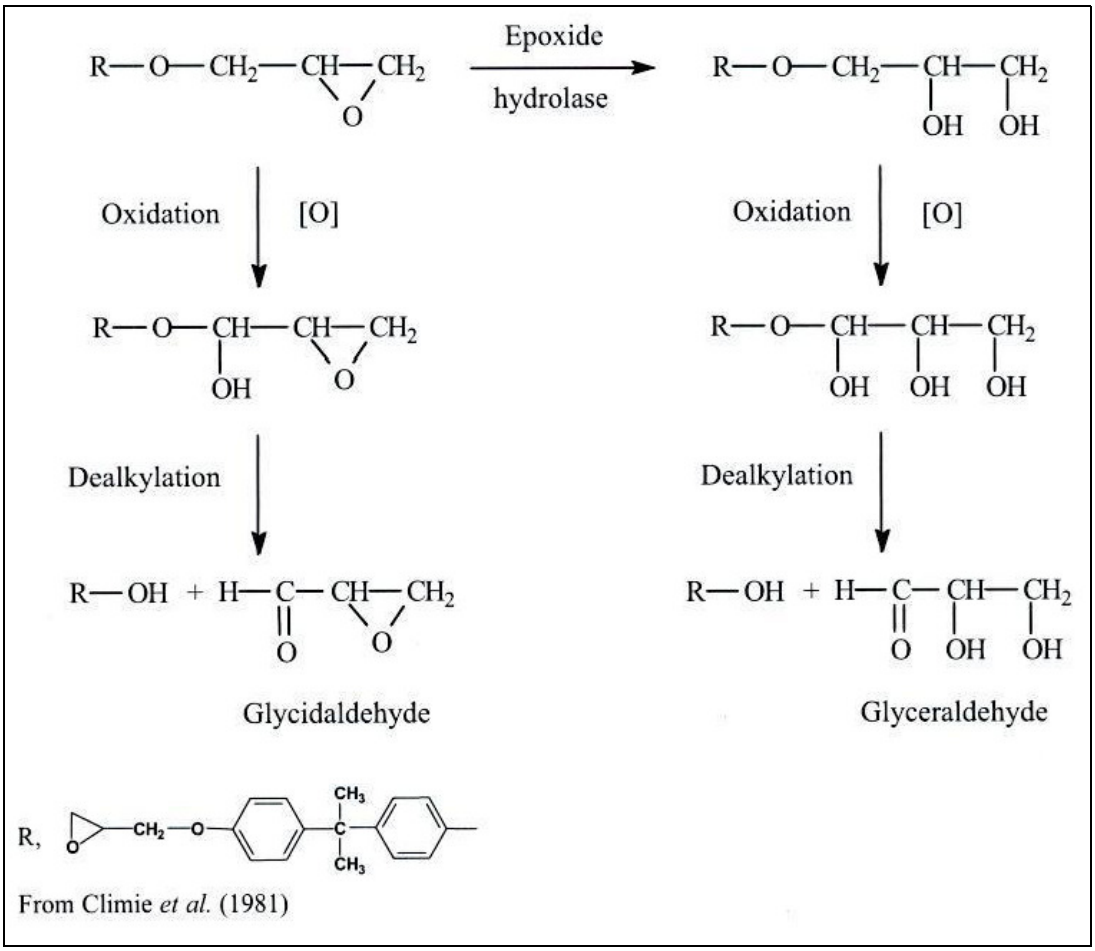

Figure 1 Two possible routes of oxidative dealkylation of the glycidyl moiety of bisphenol A diglycidyl ether.

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 Adiglycidyl ether and

glycidaldehyde with DNA are indeed identical, but that the mouse skin adduct is probably hydroxymethylethenodeoxy-adenosine-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 Adiglycidyl 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)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Volume 47 (1989) (Some Glycidyl ethers)

Synonym

2,2'-[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)]bis(oxirane).

Last updated: 13 April 1999.

Annex **F**

Carcinogenicity studies in animals

Table 1 Incidence of tumours of skin and subcutis in CF1 mice treated with pure (analytical grade) bisphenol A diglycidyl ether and with technical grades EPON 828, and EPIKOTE 828 (Peristianis et al. 1988).[7]

	Males							Females						
	Control	Pure (%)		EPON 828 (%)		Epikote 828 (%)		Control	Pure (%)		EPON 828 (%)		Epikote 828 (%)	
	0	1	10	1	10	1	10	0	1	10	1	10	1	10
Skin (treated site)														
Epidermal tumours														
Squamous-cell carcinoma (M)	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Squamous-cell papilloma (B)	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Basal-cell carcinoma (M)	0	0	0	0	0	1	1	0	0	0	0	0	0	1
Sebaceous-gland adenoma (B)	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Dermal tumours														
Fibrosarcoma (M)	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Haemanchio-sarcoma (M)	0	0	2	0	0	0	0	0	0	0	0	0	0	0
Haemanchio-endothelioma (B)	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Fibroma (B)	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Subcutis (treated site)														
Fibrosarcoma (M)	0	0	1	0	0	0	0	0	0	0	0	1	0	0
Anaplastic sarcoma (M)	0	0	0	0	0	0	0	0	1	0	0	0	0	0

B=benign; M=malignant
The treatment groups consisted of 50 males and 50 females. In the control groups were 99 males and 100 females.

Table 2 Incidence of neoplasms in tissues other than skin in C3H and C57BL/6 mice treated with technical grade bisphenol A diglycidyl ether (Holland et al. 1979).[11]

	C3H mice Dose (mg) 40 animals per sex and dose						C57BL/6 mice Dose (mg) 20 animals per sex and dose					
	0		5		25		0		5		25	
	M	F	M	F	M	F	M	F	M	F	M	F
Site												
Lung	2	1	1	1	3	6	1	0	1	0	1	0
Liver	20	6	21	5	22	3	1	3	5	1	0	2
Reticulum cell sarcoma and lymphoma	4	6	11	5	3	3	3	6	7	7	8	10
Ovary		17		18		15		2		0		1
Breast		11		10		4		0		0		1
Connective tissue	1	1	0	9	1	9	0	0	0	0	0	0
Other mesenchymal	1	1	2	5	0	1	0	1	0	1	0	0

Annex **G**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the committee (GR_{GHS})	Comparable with EU Category	
		67/548/EEC (before 12/16/2008	EC No 1272/2008 (as from 12/16/2008
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be as carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	Not applicable	Not applicable
(4)	The compound is probably not carcinogenic to man.	Not applicable	Not applicable

Source: Health Council of the Netherlands. Guidelines to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[36]

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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