Health Council of the Netherlands

Resorcinol diglycidyl ether

Evaluation of the carcinogenicity and genotoxicity

2016/03

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Resorcinol diglycidyl ether*
Uw kenmerk : DGV/BMO/U-932542
Ons kenmerk : U-915783/DC/fs/246-D25
Bijlagen : 1
Datum : 29 februari 2016

Geachte minister,

Graag bied ik u hierbij het advies *Resorcinol diglycidyl ether* aan.

Dit advies is een herevaluatie van een eerder door de Gezondheidsraad uitgebracht advies voor classificatie als kankerverwekkende stof. De raad is gevraagd om deze herevaluatie omdat de voorgestelde classificatie uit het eerdere advies afwijkt van de classificatie die op dit moment in de Europese Unie wordt gehanteerd. Tevens is de raad gevraagd de stof te classificeren voor mutageniteit. De classificaties in het voorliggende advies zijn gebaseerd op het Europese classificatiesysteem.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. De subcommissie heeft daarbij gebruik gemaakt van commentaren die zijn ontvangen op het openbare concept van dit advies. Het advies is getoetst door de Beraadsgroep Volksgezondheid 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. J.L. Severens,
vicevoorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
E-mail: d.coenen@gr.nl
Telefoon (070) 340 74 73

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Resorcinol diglycidyl ether

Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of the
Dutch Expert Committee on Occupational Safety
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2016/03, The Hague, February 29, 2016

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 and Sport, Infrastructure and the Environment, Social Affairs and Employment, and Economic Affairs. 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.

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

Preferred citation:
Health Council of the Netherlands. Resorcinol diglycidyl ether. Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2016; publication no. 2016/03.

ISBN: 978-94-6281-074-7

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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 de beroepsmatige uitoefening 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. Verder heeft het ministerie aan de Gezondheidsraad gevraagd om een aantal stoffen te herevalueren en daarbij ook een voorstel voor classificatie voor mutageniteit in geslachtscellen te doen. In het voorliggende advies herevalueert de commissie resorcinoldiglycidylether. Resorcinoldiglycidylether wordt gebruikt als epoxyhars en als verdunner in de productie van andere epoxyharsen. Daarnaast wordt het gebruikt als uithardingsmiddel in de productie van polysulfide rubber. De laatste jaren wordt het voornamelijk gebruikt in de luchtvaartindustrie.

De commissie concludeert dat resorcinoldiglycidylether beschouwd moet worden als kankerverwekkend voor de mens, en beveelt aan de stof te classificeren in categorie 1B*. Op basis van de beschikbare gegevens beveelt de commissie verder aan om resorcinoldiglycidylether te classificeren als mutageen voor geslachtscellen in categorie 2 (stof die reden geeft tot bezorgdheid voor de mens

* Zie Annex F (carcinogeniteit) en G (mutageniteit) voor classificatiesysteem.

omdat zij mogelijk erfelijke mutaties in de geslachtscellen van mensen veroorzaakt)*. De stof kan kanker veroorzaken via een stochastisch genotoxisch werkingsmechanisme.

* Zie Annex F (carcinogeniteit) en G (mutageniteit) voor classificatiesysteem.

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 Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In addition, the ministry asked the Health Council to re-evaluate a series of substances, and to include in the re-evaluation a proposal for classification on germ cell mutagenicity. In this report, the Committee re-evaluated resorcinol diglycidyl ether. Resorcinol diglycidyl ether is used as an epoxy resin and as a reactive diluent in the production of other epoxy resins. It is also used as a curing agent in the production of polysulfide rubber. In recent years, it has been primarily used in the aerospace industry.

The Committee concludes that resorcinol diglycidyl ether is suspected to be carcinogenic to man, and recommends classifying the compound in category 1B*. Based on the available data, the Committee furthermore recommends classifying resorcinol diglycidyl ether as a germ cell mutagen in category 2 (Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans)*. The substance acts by a stochastic genotoxic mechanism.

* See Annex F (carcinogenicity and G (mutagenicity) for the classification system.

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). The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex F). In addition to classifying substances on carcinogenicity, the Health Council also assesses the genotoxic properties of the substance in question.

Recently, with reference to the EU Regulation 1272/2008 on classification, labelling and packaging of substances (see Annex G), the ministry of Social Affairs and Employment asked the Health Council to update the evaluations and classification on carcinogenicity of a series of substances, and to propose for these substances a classification on germ cell mutagenicity as well.

In this report, such an update was performed for resorcinol diglycidyl ether. An earlier evaluation of this substance was published in 1995.[1] The re-evaluation now includes a proposal for classification on germ cell mutagenicity.

1.2 Committee and procedure

The evaluation is performed by the Subcommittee on Classifying 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. A submission letter (in English) to the Minister can be found in Annex C.

In 2015 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. The received comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Data

The evaluation and recommendation of the Committee is standardly 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 resorcinol diglycidyl ether, such an IARC-monograph is available, of which the summary and conclusion of IARC (1985) is inserted in Annex E.[2]

Furthermore, if available, relevant data of the European Chemicals Agency (ECHA) were retrieved and included in this advisory report.

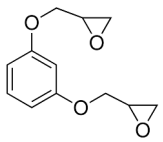
Additional data were obtained from the online databases Medline, Toxline, Chemical Abstracts, and RTECS covering the period up to January 2016, using resorcinol diglycidyl ether as key words in combination with key words representative for carcinogenesis and mutagenesis.

Chapter 2

Identity of the substance

2.1 Name and other identifiers of the substance

Table 1 Substance identity.

EC number	:	603-065-00-9
EU name	:	Resorcinol diglycidyl ether
CAS number	:	101-90-6
IUPAC name	:	1,3-bis(2,3-epoxypropoxy)benzene
Synonyms	:	1,3-diglycidyloxybenzene; 2,2'-(1,3-phenylenebis(oxymethylene)bisoxirane; resorcinol diglycidyl ether; DGRE
Molecular formula	:	$C_{12}H_{14}O_4$
Structural formula	:	
Molecular weight	:	222.2 g/mol

2.2 Composition of the substance

The studies are performed with test substance purities between 80-100%.

2.3 Physico-chemical properties

Table 2 Summary of physico-chemical properties.

Properties	Value	Reference	Comment
State of the substance	Straw yellow liquid		
Melting point	32-33°C	DFG 1992[3]	
Boiling point (0.1 kPa)	172°C	IARC 1985[2]	
Relative density (25°C)	1.21	ICSI 1991[4]	
Vapour pressure (25°C)	Low, 4 x 10^{-5} mm Hg at 25°C	NTP2011[5]	
Surface tension	-		
Solubility	Miscible with acetone, chloroform, methanol, benzene and most organic resins.	ICSC 1991[4]	
Partition coefficient n-octanol/water	No experimental data (1.23 calculated)		
Flammability:			
Flash point	177°C (open cup)	ICSC 1991[4]	
Explosive properties	Reacts with strong oxidants; presumed to perform explosive peroxides	ICSC 1991[4]	
Self-ignition temperature	-		
Oxidising properties	-		
Granulometry	-		
Stability in organic solvents	-		
Dissociation constant (pKa)	-		
Viscosity	-		
Conversion factor (25 °C, 101.3 kPa)	1 mg/m^3 = 0.109 ppm 1 ppm = 9.22 mg/m^3	IARC 1985[2]	

2.4 International classifications

2.4.1 European Commission

Resorcinol diglycidyl ether is classified for carcinogenicity in Annex VI of regulation (EC) No 1272/2008 of the European Parliament as follows: Carc 2 (suspected human carcinogen: H351 suspected of causing cancer), according to the Globally Harmonised System of Classification and Labelling of Chemicals. The substance is also classified for mutagenic activity: Muta. 2 (suspected human mutagen: H341 suspected of causing genetic defects). The classification by the European Commission dates from March 1999.

2.4.2 *The Health Council of the Netherlands*

In 1995, the Dutch Expert Committee on Occupational Standards, a Committee of the Health Council of the Netherlands concluded that resorcinol diglycidyl ether should be regarded as a genotoxic carcinogen.[1] In 1999, it further concluded that the carcinogenicity studies were inappropriate for a quantitative extrapolation for an inhalation based occupational cancer risk value.[6]

2.4.3 *IARC*

In 1985 and 1999, IARC concluded that there are no data on the carcinogenicity of resorcinol diglycidyl ether to humans, but that there is sufficient evidence for the carcinogenicity of a technical grade of resorcinol diglycidyl ether in experimental animals (Annex E). IARC classified resorcinol diglycidyl ether (technical grade) as possibly carcinogenic to humans (Group 2B).[2,7]

Chapter 3

Manufacture and uses

3.1 Manufacture

Not relevant for classification.

3.2 Identified users

Resorcinol diglycidyl ether is used as an epoxy resin and as a reactive diluent in the production of other epoxy resins. It is also used as a curing agent in the production of polysulfide rubber. In recent years, it has been primarily used in the aerospace industry.[5]

Chapter 4

Summary of toxicokinetics

In a study by Seiler (1984), male and female ICR-mice were treated orally (single dose) with ^{14}C labelled resorcinol diglycidyl ether and urine (collected for 1-4 hr after dosing) was analysed for metabolic products (the number of replicates was not reported).[8] Four per cent of the metabolites detected in the urine was the phenol-diol metabolite, 64% was the bis-diol metabolite and 21% of the metabolites could not be identified. The total amount of radioactivity recovered from urine collected up to 4 hours after a single oral dose of 1,000 mg/kg body weight was nearly 50% of the applied dose. In addition, Seiler incubated epoxidase hydrolase containing liver homogenates (S9) with resorcinol diglycidyl ether and measured remaining alkylating activity. Resorcinol diglycidyl ether showed apparent first-order kinetics and a half-life of about 6 minutes. This study indicates that resorcinol diglycidyl ether is rapidly converted to the inactive bis-diol compound.[8]

Chapter 5

Genotoxicity

5.1 Non-human information

5.1.1 *In vitro data*

Data on in vitro mutagenicity testing are presented in Table 3.

Table 3 Summary of in vitro mutagenicity studies.

Method	Cell type	Concentration range	Results - negative + positive	Klimisch score[a]	References
Micro-organisms					
Reverse mutation	*Salmonella typhimurium* *Strains*: TA98, TA100, TA1535, TA1537	*Method*: 5 doses in DMSO using triplicate plates, retest at least one week later *Concentrations (µg/plate)* *Initial study*: 0-333(-S9 mix), 0-2,000(+S9 mix) *Retest*: 0-100(-S9 mix), 0-1,000/1,500(+S9 mix) *Metabolic system*: Liver S9 mix from Aroclor 1,254-induced male Sprague-Dawley rats and Syrian hamsters *Control*: Negative: vehicle; Positive: -S9 mix: sodium azide (TA100, TA1535),	*Outcome*: TA98: negative TA1537: negative TA1535: positive with and without metabolic activation TA100: positive without metabolic activation and with rat S9 mix; equivocal with hamster S9 mix *Cytotoxicity*: Slight clearing of background lawn in the highest and sometimes second to highest dose tested	2	Canter et al., 1986[9]

		9-aminoacridine (TA1537), 4-nitro-o-phenylenediamine (TA98); +S9 mix 2-amino-anthracene (all strains) *Purity*: 87.9% (analyzed; method not reported) *Statistical analysis*: not used			
Reverse mutation	Salmonella typhimurium *Strains*: TA100	*Purity*: >98% (HPLC) *Concentrations*: 0, 50, 100, 200, 500, 1,000 µg/plate *Metabolic system*: not used *Control*: Negative control: not specified, Positive control: not used *Statistical analysis*: not used	*Outcome*: positive Revertant colonies: 116, 438, 609, 772, 117, toxic, for 0, 50, 100, 200, 500, 1,000 µg/plate, for control and lowest through highest concentration, resp. *Cytotoxicity*: In 500 and 1000 µg/plate test	3 (only one strain; no metabolic activation; no information on potential solvent used; no positive control; not specified negative control; number of replicates unknown)	Seiler, 1984[10]
Mammalian cells					
Gene mutation	Mouse lymphoma L5178Y cells, *tk* locus	*Method*: Test performed in duplicate at *tk* *Concentrations*: 0, 0.25, 0.5, 1, 2, 4 µg/ml *Metabolic activation*: not used *Controls*: Negative: dimethylsulfoxide; Positive: ethyl methanesulfonate *Purity*: unknown *Solvent*: unknown *Statistical analysis*: dose-trend test and variance analysis	*Outcome*: Mutant frequency (no. of mutant clones/million viable clones) *Tk*: Positive (5.3 fold increase mutant fraction) respectively: 60, 339, 783 761, lethal, lethal (1st test), 35, 182, 369, 689, 982, lethal (2nd test): *Cytotoxicity*: Relative total growth	2	McGregor et al., 1988[11]
Gene mutation	Mouse lymphoma L5178Y cells, *tk* locus, *hprt* locus	*Method*: Test performed in duplicate at *tk* and *hprt* locus *Concentrations*: 0, 0.1, 0.4, 0.7 µg/ml (first exp.), 0, 0.1, 0.2, 0.4 µg/ml (second exp.) *Metabolic activation*: not used *Controls*: Negative: used, but not specified; Positive: ethyl methanesulfonate *Purity*: unknown *Solvent*: unknown *Statistical analysis*: not used	*Outcome*: Mutant frequency (no. of mutant clones/million viable clones) *Tk*: Positive, respectively: 14, 45, 157, 238 (1st test), 21, 48, 99, 173 (2nd test): *Hprt*: negative, 4, -, 8, 22 (first test), 12, 7, 4, 16 (2nd test) *Cytotoxicity*: Relative total growth	3 (no metabolic activation, no information on potential solvent used, purity unknown, negative control not specified)	McGregor et al., 1996[12]

Chromosome aberration	Chinese Hamster Ovary cells	*Method*: Positive results were repeated *Concentrations* (µg/ml): 0, 0.5, 1.6, 5, 16 (-S9); 0, 5, 16, (25 only in 2nd test), 50 (+S9) *Metabolic activation*: Liver S9 mix from Aroclor 1254-induced male Sprague-Dawley rats *Controls*: Negative: vehicle; Positive: mitomycin C (-S9), cyclophosphamide (+S9) *Purity*: >87.9% (analyzed; method not reported) *Solvent*: DMSO *Statistical analysis*: conducted on slopes of the dose-response curves and on individual dose points	*Outcome*: Positive with and without metabolic activation % cells with aberrations (* indicates statistical significance); 3, 1, 4, 14*, 61* (-S9, 1st test); 0, 5*, 6*, 40*, 69* (-S9, 2nd test); 3, 3,10, 58* (+S9, 1st test); 3, 5, 8, 6, 27* (+S9, 2nd test) *Cytotoxicity*: No information reported	2	Gulati et al., 1989[13]
Chromosome aberration	Chinese Hamster Ovary cells	*Method*: 6 and 24 hours exposure *Solvent*: DMSO *Concentrations*: 2.5, 8, 25 µg/ml *Metabolic system*: not used *Control*: Negative control: not specified, Positive control: not used *Purity*: >98% (HPLC) *Statistical analysis*: estimated with the aid of the tables of Kastenbaum and Bowman (1970)	*Outcome*: Positive; % aberrant metaphases (number of metaphases scored): 1 (100), 8 (100), 24 (33), 44 (25) for 6 hr exposure, 2 (100), 9 (100), 48 (50), 93 (15) for 24 hr exposure for control and lowest through highest concentration, resp. *Cytotoxicity*: high at 8 and 25 µg/ml	3 (no information on check cell line absence of myco-plasma, number of chromosomes); no metabolic activation; no information on potential solvent used, negative control not specified; no positive controls; number of replicates unknown; no standard deviations reported; low numbers of metaphases scored at cytotoxic concentrations)	Seiler, 1984[10]
Other studies					
Sister chromatid exchange	Chinese Hamster Ovary cells	*Method*: Positive results were repeated *Concentrations* (µg/ml): 0, 0.05, 0.16, 0.5, (1.6 only in 1st test) (-S9); 0, 0.5, 1.6, 5, 16 (+S9) *Metabolic activation*: Liver S9 mix from Aroclor 1254-induced male Sprague-Dawley rats	*Outcome*: Positive with and without metabolic activation Number of SCE/cell (* indicates statistical significance): 7.7, 9.7*, 10*, 30*, 71* (-S9, 1st test); 9.1, 8.4, 21*, 49* (-S9, 2nd test); 9.6, 9.8, 10, 13*, 51*	2	Gulati et al., 1989[13]

		Controls: Negative: vehicle; Positive: mitomycin C (-S9), cyclophosphamide (+S9) *Purity*: >87.9% (analyzed; method not reported) *Solvent*: DMSO *Statistical analysis*: conducted on slopes of the dose-response curves and on individual dose points	(+S9, 1st test); 9.4, 8.5, 9.9, 14*, 39* (+S9, 2nd test) *Cytotoxicity*: No information reported		
Alkylating potency using the 4-(4-nitro-benzyl)pyridine assay	Epoxyhydrolase containing rat and mice liver homogenates	*Method*: According to Friedman and Boger (1961) *Concentrations*: 12.5, 25, 50, 100 µg *Control*: Negative control: not specified, Positive control: not used *Purity*: >98% (HPLC) *Solvent*: unknown *Statistical analysis*: no descriptive or comparative statistics reported	*Outcome*: positive; Optical density at 450 nm (measured against negative control): 0.23, 0.55, 1.17, 2.18, respectively	Not applicable	Seiler 1984[10]

[a] See Annex H.

In Table 3 in vitro mutagenicity studies identified in the literature have been summarized. Resorcinol diglycidyl ether was found to be mutagenic in the *Salmonella typhimurium* strains TA100 and TA1535 in the presence and absence of an exogenous metabolic system. Mutagenicity was not observed in strains TA98 and TA1537. Furthermore, in L5175Y mouse cells the mutagenic responses at the heterozygous *tk* locus in the absence of metabolic activation were investigated. A positive response was observed at the *tk* locus (Mc Gregor 1988).[11] Resorcinol diglycidyl ether caused an increase in Chinese hamster ovary cells with chromosome aberrations in the presence and absence of metabolic activation. The results of a 4-(4-nitro-benzyl)pyridine, an alkylating agent, obtained in the present genotoxicity tests indicated that this resorcinol diglycidyl ether binds DNA and has genotoxic potential.[10] Resorcinol diglycidyl ether caused sister chromatid exchanges in Chinese hamster ovary cells in the presence and absence of metabolic activation.[13]
Overall the Committee concluded that resorcinol diglycidyl ether is mutagenic in vitro causing gene mutations and chromosomal aberrations.

5.1.2 *In vivo data*

Data on the in vivo mutagenicity studies are presented in Table 4.

Table 4 Summary of in vivo mutagenicity studies (animal studies).

Method	Cell type	Concentration range	Results - negative + positive	Klimisch score[a]	References
Somatic cell mutagenicity					
Micronucleus	Male B6C3F1 mice, bone marrow	*Method*: 5 animals per dose, test performed in triplicate, intraperitoneal injection on three consecutive days, bone marrow cells sampled 24 hr after last treatment *Concentrations*: 15.2, 30.4, 60.8 mg/kg (first and second test), 30.4, 60.8, 91.2 mg/kg (third test) *Controls*: Negative: vehicle; Positive: dimethylbenzanthracene *Purity*: unknown *Solvent*: corn oil *Statistical analysis*: %PCE[b]: ANOVA; micronucleated PCE: unadjusted one-tailed Pearson chi-square test (pairwise comparison with solvent control group) and one-tailed trend test	*Outcome*: Overall result: negative; first test was positive: dose-related increase in micronuclei (highest dose: p=0.0442, trend: p=0.038), the other two tests were negative *Toxicity*: All animals survived, no cytotoxicity to PCE observed	2	Shelby et al., 1993[14]
Micronucleus (follow up previous test with higher concentrations)	Male B6C3F1 mice; bone marrow cells	*Method*: 5 animals per dose, single intraperitoneal injection, sampled 24 hr after treatment *Concentrations*: 90, 180, 270 mg/kg *Controls*: Negative: vehicle; Positive: dimethylbenzanthracene *Purity*: unknown *Solvent*: corn oil *Statistical analysis*: unadjusted one-tailed Pearson chi-square test (pairwise comparison with solvent control group) and one-tailed trend test	*Outcome*: Positive: dose-related increase in micronuclei (highest dose: p=0.0008, trend: p=0.001) *Toxicity*: no information on survival/clinical signs of toxicity and toxicity to bone marrow	2	Shelby et al., 1993[14]
Micronucleus	ICR mice (male and female)	*Method*: single oral dose, 4 animals per dose *Doses*: 300 mg/kg with 24h fixation time; 600 mg/kg with 24, 48 and 72h fixation time *Control*: Negative control: not specified, Positive control: not used *Purity*: >98% (HPLC) *Solvent*: polyethylene-glycol (PEG 400) *Statistical analysis*: not used		3 (negative control not specified; no positive controls; no information on toxicity to bone marrow, low number of animals)	Seiler, 1984[10]
Other test systems					
Sex-linked recessive lethal induction	*Drosophila melano-gaster*	*Exposure*: 3 days to 50,000 ppm in feeding solution *Controls*: Negative: solvent; Positive: N-nitrosodimethylamine and β-propiolactone *Purity*: 87.9% *Solvent*: 9% ethanol, 1% Tween-80; initial	*Outcome*: Mutagenic: 0.19 and 1.31% lethals for control and exposed groups, resp.	3 (Classification based on studies in mammalians; no OECD guideline anymore)	Valencia et al., 1985[15]; Woodruff et al., 1984[16]

		solution was diluted with aqueous 5% sucrose for feeding *Statistical analysis*: Poisson distribution to correct for spontaneous mutations. Normal test as suggested by Margolin et al. (1983)	*Toxicity*: no mortality or sterility		
Reciprocal translocations induction	*Drosophila melano-gaster*	*Exposure*: three days to 50,000 ppm in feeding solution *Controls*: No concurrent negative controls (results were compared to combined historical control for three laboratories which was very low, namely 0.001%); Positive: N-nitro-sodimethylamine and β-propiolactone *Purity*: 87.9% *Solvent*: 9% ethanol, 1% Tween-80; initial solution was diluted with aqueous 5% sucrose for feeding *Statistical analysis*: Conditional binomial test	*Outcome*: Mutagenic: total reciprocal translocations: 11 in 4,661 tests (0.24%)	3 (Classification based on studies in mammalians; no OECD guideline anymore)	Valencia et al., 1985[15]; Woodruff et al., 1984[16]

[a] See Annex H.
[b] PCE = Polychromatic erythrocytes.

Somatic cells

In Table 4 in vivo mutagenicity studies identified in the literature have been summarized.

In a bone marrow micronucleus study by Shelby et al. groups of five male B6C3F1 mice were exposed to resorcinol diglycidyl ether (up to 91.2 mg/kg body weight/day) by intraperitoneal injection on three consecutive days.[14] The dose levels were selected based on toxic effects (mortality and depression in the percentage of bone marrow polychromatic erythrocytes) observed in a preliminary study. Three independent tests were performed. The initial test was positive, but the two repeat tests were both negative. As toxicity upon repeated exposure prohibited the use of higher doses in the repeated-exposure tests, and hence exposure in these tests may not have been sufficiently high to induce observable genetic toxicity, a fourth micronucleus test was conducted using single exposure and higher doses. In the latter test, groups of five male B6C3F1 mice received a single intraperitoneal dose of 0, 90, 180 or 270 mg/kg body weight resorcinol diglycidyl ether. The results showed a statistically significant, dose-related increase in cells with micronuclei. The micronucleus study performed by Seiler 1984 provided no information on relevant experimental conditions and is therefore considered not to be adequate for the assessment of genotoxicity.[10]

Germ cells

In *Drosophila melanogaster* the induction of sex-linked recessive lethals was determined following treatment of wild-type males with 50,000 ppm resorcinol diglycidyl ether in their feeding solution. These results indicate that resorcinol diglycidyl ether is mutagenic in *Drosophila melanogaster.*[15] However the Committee does not consider this test species relevant for humans and hence not adequate for the assessment of genotoxicity.

Conclusion

In conclusion, the Committee noted the dose-related positive findings of the micronucleus studies of Shelby et al. (1993) in bone marrow in which at triplicate intraperitoneal doses of 60,8 mg/kg bw or single intraperitoneal doses of 270 mg/kg bw statistically significant increases in cells with micronuclei were found.[14] Based on these results, the Committee considers that resorcinol diglycidyl ether may have genotoxic potential.

5.2 Human information

No studies on humans were retrieved.

5.3 Summary and discussion on mutagenicity

Below, only data are summarized of a reliable experimental design according to the Klimisch criteria 1 and 2 (See Annex H).[17]

Germ cell genotoxicity

As no relevant genotoxicity studies of resorcinol diglycidyl ether in germ cells were found, the Committee cannot conclude that resorcinol diglycidyl ether is genotoxic in germ cells.

Somatic genotoxicity

Resorcinol diglycidyl ether was investigated in genotoxicity tests for the 3 endpoints of genotoxicity: gene mutations, structural and numerical chromosome aberrations.

In vitro, resorcinol diglycidyl ether induced gene mutations in bacteria (TA100 and TA1535 strains, with and without metabolic activation) and in mammalian cells (mouse lymphoma study, *tk* locus).[9,11] Exposure to resorcinol diglycidyl ether did also result in an increase in cells with chromosome aberrations with and without metabolic activation.[13] The supporting genotoxicity tests confirmed the positive findings in in vitro tests (Table 3).

In vivo, positive results were found in micronucleus tests at triplicate intraperitoneal doses of 60,8 mg /kg bw and at single intraperitoneal doses of 270 mg/kg bw.[14] Based on these results, the Committee considers that resorcinol diglycidyl ether may have genotoxic potential.

Overall the Committee concludes that resorcinol diglycidyl ether is mutagenic in vivo and in vitro and acts by a stochastic genotoxic mechanism.

5.4 Comparison with criteria

According to the criteria in Annex VI of the European regulation No. 1272/2008 (see Annex G), classification as a mutagen in category 1 is warranted when positive evidence for in vivo heritable germ cell mutagenicity in humans (1A) or mammals (1B) has been reported. No data have been presented on human germ cell mutagenicity, and the test with Drosophila was not relevant for humans. Overall, due to a lack of data the Committee concludes that there is no evidence for in vivo heritable germ cell mutagenicity of resorcinol diglycidyl ether.

In addition, substances may be categorized in 1B if there are "positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells". The latter may be based on a) "supporting evidence from mutagenicity/ genotoxicity tests in germ cells in vivo", or b) "by demonstrating the ability of the substance or its metabolites to interact with the genetic material of germ cells" (see Annex G). Evidence has been found for in vivo mutagenicity testing in mice bone marrow cells. Regarding the second part of the criterion, there is no evidence that resorcinol diglycidyl ether is genotoxic in germ cells. Overall, due to lack of data on germ cell mutagenicity, the Committee is of the opinion that no evidence exists that resorcinol diglycidyl ether has the potential to cause mutations to germ cells.

If substances do not meet the criteria for classification in category 1, they may be classified in category 2 if there is "positive evidence from experiments in

mammals and/or in some cases from in vitro experiments from a) somatic cell mutagenicity tests in vivo, in mammals" or b) "other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays". (see Annex G). As summarized in the previous section, according to the Committee, there is positive evidence from micronuclei experiments in mammals supported by positive in vitro experiments in bacteria and mammalian cells [9,11,13,14]

5.5 Conclusions on classification and labelling

Based on the available data, the Committee recommends classifying the substance as a germ cell mutagen in category 2 (Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans). The substance acts by a stochastic genotoxic mechanism.

Chapter 6

Carcinogenicity

6.1 Non-human information

Data on carcinogenicity are summarized in Table 5.

Table 5 Summary of animal carcinogenicity studies on resorcinol diglycidyl ether exposure.

Species	Design	Exposure levels (X_{po}: observed period; X_{pe} exposure period)	Observations and remarks (Klimisch score)[a]	References
F344/N rats	50 rats per dose/sex	Gavage, 5 times/week, vehicle corn oil, 0, 25, 50 mg/kg bw X_{po}: 103 weeks X_{pe}: 104-105 weeks Purity: 81% Statistical analysis tumour incidences: Fisher's exact test for pairwise comparison, Cochran-Armitage linear trend test for dose response trends. Two methods adjusting for intercurrent mortality using combining contingency tables by Mantel and Haenszel (1959) (llfe table test & incidental tumour test).	Klimisch score: 2 *Survival:* At end of study (week 104-105): males: 84, 10, 0%; females: 74, 32, 2% for control, low, and high-dose respectively. *Adverse effects*: Wheezing and respiratory distress. Body weights: High dose: lower than control after week 30; Low dose: lower than control after week 80 Increased incidence of hyperkeratosis and basal cell hyperplasia in forestomach in both dose groups and both sexes *Tumours*: For control, low, and high-dose respectively Forestomach: squamous cell papillomas: males: 0, 34, 12% (Adjusted for intercurrent mortality: 0, 40.9, 33.5%); females: 0, 14, 2% (Adjusted: 0, 24.2, 14.3%) Forestomach: squamous cell carcinoma: males: 0, 76, 8% (adjusted: 0, 100, 100%); females: 0, 68, 6% (adjusted: 0, 97, 100%)	NTP, 1986[17]; Krishna-Murthy et al., 1990[18]

F344/N rats	50 rats per dose/sex	Gavage, 5 times/week, vehicle corn oil, 0, 12 mg/kg bw X_{po}: 103 weeks X_{pe}: 104-105 weeks Purity: 81% Statistical analysis tumour incidences: Fisher's exact test for pairwise comparison, Two methods adjusting for intercurrent mortality using combining contingency tables by Mantel and Haenszel (1959) (llfe table test & incidental tumour test).	Klimisch score: 2 *Survival*: At end of study (week 104-105): males: 78, 46%; females: 78, 70% for control and treated respectively *Adverse effects*: Increased incidence of hyperkeratosis and basal cell hyperplasia in forestomach in both sexes *Tumours*: For control and treated respectively. Forestomach: squamous cell papillomas: males: 0, 32% (Adjusted for intercurrent mortality: 0, 51.7%); females: 0, 38% (Adjusted: 0, 48.4%) Forestomach: squamous cell carcinoma: males: 0, 78% (adjusted: 0, 92.8%); females: 0, 54% (adjusted: 0, 64%)	NTP, 1986[17]; Krishna-Murthy et al., 1990[18]
$B6C3F_1$ mice	50 mice per dose/sex	Gavage, 5 times/week, vehicle corn oil, 0, 50, 100 mg/kg bw X_{po}: 103 weeks X_{pe}: 104-105 weeks Purity: 81% Statistical analysis tumour incidences: Fisher's exact test for pairwise comparison, Cochran-Armitage linear trend test for dose response trends. Two methods adjusting for intercurrent mortality using combining contingency tables by Mantel and Haenszel (1959) (llfe table test & incidental tumour test).	Klimisch score: 2 *Survival*: At end of study (week 104-105): males: 60, 52, 68%; females: 40, 26, 20% for control, low, and high-dose respectively *Adverse effects*: Body weights: High dose female mice: lower than control after week 20; Other groups were comparable to control. Increased incidence of hyperkeratosis and epithelial cell hyperplasia in forestomach in both dose groups and both sexes *Tumours*: For control, low, and high-dose respectively Forestomach: squamous cell papillomas or papillomatosis: males: 0, 8, 20% (Adjusted for intercurrent mortality: 0, 14, 29.4%); females: 0, 10, 20% (Adjusted: 0, 33.4, 73.1%) Forestomach: squamous cell carcinoma: males: 0, 29, 50% (adjusted: 0, 40.7, 55.5%); females: 0, 24, 47% (adjusted: 0, 53.3, 70.5%) Liver: hepatocellular carcinoma: females: 0, 2, 6% (adjusted 0, 6.3, 25%) Liver: hepatocellular carcinoma and adenoma combined: females: 6, 2, 14% (adjusted 16, 6, 43%)	NTP, 1986[17]; Krishna-Murthy et al., 1990[18]
Swiss-Millerton female mice	30 treated; 60 untreated controls 60 vehicle controls	Dermal application (to clipped dorsal skin) 1% in benzene, three times per week, about 100 mg of solution per application X_{po}: life-span X_{pe}: life-span The study was continued until there were no survivors	Klimisch score: 3 *Survival*: Median survival time: 441, 408 and 491 days for untreated control, vehicle control and treated mice, resp *Tumours*: No tumours observed in any group	Van Duuren et al., 1965[19]

C57/B1 mice	20 treated	Total concentration 0.75 mM Exposure route, frequency and duration, vehicle, purity test material, observation period, method of tumour detection: no data	Klimisch score: 3 (not adequate for carcinogenicity asssessment) *Survival*: 14/20 after 8 months *Tumours*: One skin tumour observed (after 8 months)	Kotin and Falk, 1963[20]
C57/B1 mice		Intrascapular painting three times a week	Klimisch score: 4 Authors state that substance was carcinogenic; organs not mentioned	McCammon et al., 1957[21]
Long-Evans rats		Subcutaneous injection	Klimisch score: 4 Authors state that substance was carcinogenic; organs not mentioned	McCammon et al., 1957[21]

[a] See Annex H.

Table 5 summarizes the carcinogenicity studies in experimental animals. In these studies resorcinol diglycidyl ether was administered orally (gavage), dermally or by subcutaneous injection. No inhalation carcinogenicity studies were available.

The National Toxicology Program (NTP) performed carcinogenicity studies in rats and mice.[17] Groups of 50 F344/N rats of each sex received resorcinol diglycidyl ether (technical grade) in corn oil by gavage 5 days per week for 103 weeks at doses of 0, 25 or 50 mg/kg body weight. Neoplastic lesions are described in detail in Tables 6 and 7. The survival of male and female rats was significantly reduced ($p<0.001$) compared to controls, and the high dose group of each sex had significantly lower survival ($p<0.001$) than the low dose group. At the end of the study (104-105 weeks), 42, 5 and 0 male and 37, 16 and 1 female rats of the control, low dose and high dose groups, respectively, had survived. Most of the early deaths not related to tumour induction were attributable to bronchopneumonia. Clinical signs of toxicity were limited to wheezing and respiratory distress. After week 30, mean body weights of high dose rats of each sex were lower than those of the controls. Mean body weights of low dose males and females were comparable with those of the controls until week 80.

Treatment-related non-neoplastic changes were observed in the forestomach of low and high dose rats of both sexes, namely hyperkeratosis and basal cell hyperplasia. Low and high dose male and female rats had statistically significantly increased incidences of squamous cell papilloma and squamous cell carcinoma of the forestomach. Of the male rats 0/50, 17/50 (34%) and 6/49 (12%) developed squamous cell papilloma in the control, low, and high dose group, respectively. When these numbers were adjusted for intercurrent mortality the incidences were 0, 40.9 and 33.5%, respectively. The incidence of squamous

Table 6 Tumour incidences in forestomach of rats, which were given diglycidiyl resorcinol ether by gavage for 2 years.[17]

Exposure level (mg/kg bw)	0	12[a]	25	50
Male rats				
Fore stomach:				
• Squamous cell papilloma	0/100[b]	16/50(32%) p<0.001	17/50(34%) p<0.001	6/49(12%) p=0.012
• Squamous cell carcinoma	0/100[b]	39/50(78%) p<0.001	38/50(76%) p< 0.001	4/49 (8%) p=0.056
Female rats				
Fore stomach:				
• Squamous cell papilloma	0/99[b]	19/50(38%) p<0.001	7/50(14%) p=0.002	1/50(2%) p=0.125
• Squamous cell carcinoma	0/99[b]	27/50(54%)	34/50(68%) p=0.001	3/50(6%) p=0.125

Fischer exact test.

[a] Dose administered to rats in the supplemental study.
[b] Represents combined incidence of the primary and supplemental studies.

Table 7 Tumour incidences in forestomach and liver of mice, which were given diglycidiyl resorcinol ether by gavage for 2 years.[17]

Exposure level (mg/kg bw)	0	50	100
Male mice			
Fore stomach:			
• Squamous cell papilloma	0/47	4/49(8%) p=0.064	10/50(20%) p=0.001
• Squamous cell carcinoma	0/47	14/49(29%) p<0.001	25/50(50%) p< 0.001
Female mice			
Fore stomach:			
• Squamous cell papilloma	0/47	5/49(10%) P=0.031	10/49(20%) P=0.001
• Squamous cell carcinoma	0/47	12/49(24%) p<0.001	23/49(47%) p<0.001
Liver:			
Hepatocellular carcinoma	0/48	1/50(2%) p=0.510	3/49(6%) p=0.125
Hepatocellular carcinoma and adenoma combined	3/48(6%)	1/50(2%) p=0.294	7/49(14%) p=0.167

Fischer exact test.

cell carcinoma in male rats was 0/50, 38/50 (76%) and 4/49 (8%), respectively (adjusted incidence: 0, 100, 100%). Of the female rats 0/49, 7/50 (14%) and 1/50 (2%) developed squamous cell papilloma in the control, low, and high dose group, respectively (adjusted incidence: 0, 24.2, 14.3%). The incidence of squamous cell carcinoma in female rats was 0/49, 34/50 (68%) and 3/50 (6%), respectively (adjusted incidence: 0, 97, 100%). The lower number of papilloma and carcinoma in the high dose group compared to the low dose group probably resulted from the increased number of early deaths at the high dose.

Because of high early mortality at the high dose (50 mg/kg body weight), a supplemental study exposing rats to 0 and 12 mg resorcinol diglycidyl ether (technical grade)/kg body weight was performed. Except for the dose, the protocol of this study was identical to that of the original study. Survival of the male dosed rats was significantly reduced (p=0.003) compared to controls. Survival of dosed and control female rats did not differ significantly. The numbers of rats that lived to the end of the study were 39 control and 23 dosed males and 39 control and 35 dosed females. Body weight gain was not affected in the dosed rats. The incidence of hyperkeratosis and basal cell hyperplasia in the forestomach was markedly increased in dosed males and females. Regarding tumour development, 32% of the male rats and 38% of the female rats developed squamous cell papilloma (adjusted incidence 51.7 and 48.4%). Squamous cell carcinoma was observed in 78% and 54% (adjusted incidence 92.8 and 64%) of the male and female rats, respectively. These tumours were not observed in the control rats of either sex.

In the mouse study by NTP, groups of 50 $B6C3F_1$ mice of each sex were administered 0, 50 or 100 mg resorcinol diglycidyl ether (technical grade)/kg body weight on the same schedule as the rats. No statistically significant differences in survival were observed between the dosed and control groups, but survival was only 40, 26, and 20% in control, low dose and high dose female mice, respectively. The major cause of death in female mice was a necrosuppurative lesion of the ovary which spread to other areas of the abdominal cavity. Mean body weights of high dose female mice were lower than those of the controls after week 20 of the study. Body weights of the other treated groups were comparable with those of the controls. No compound-related clinical signs were observed. The incidence of hyperkeratosis and epithelial cell hyperplasia in the forestomach was markedly increased in low- and high-dose mice of both sexes. Squamous cell papilloma and squamous cell carcinoma of the forestomach occurred in male and female mice with statistically significant positive trends and the incidences in the high dose groups were significantly higher than those in the controls. Of the male mice 0/47, 4/49 (8%) and 10/50

(20%) (adjusted incidence: 0, 14, 29.4%) developed squamous cell papilloma or papillomatosi in the control, low, and high dose group, respectively. The incidence of squamous cell carcinoma in male mice was 0/47, 14/49 (29%) and 25/50 (50%), respectively (adjusted incidence: 0, 40.7, 55.5%). Of the female mice 0/49, 5/49 (10%) and 10/49 (20%) developed squamous cell papilloma or papillomatosis, respectively (adjusted incidence: 0, 33.4, 73.1%). The incidence of squamous cell carcinoma in female mice was 0/47, 12/49 (24%) and 23/49 (47%), respectively (adjusted incidence: 0, 53.3, 70.5%). Furthermore, a positive trend was observed in the incidence of female mice with hepatocellular carcinoma. The incidences of hepatocellular carcinoma and of hepatocellular adenoma and carcinoma combined were statistically significantly increased in female mice in the high dose group compared to controls (respectively, p=0.041 and 0.030 by life-table analysis). However, the authors conclude that these liver tumours were probably not related to the administration of the test substance because their incidence in females dosed with the test substance was lower than that in historical controls at the same laboratory.

In addition, three other studies were identified by the Committee. However, information on the design and results of these studies was very limited and, therefore, these studies are not adequate for carcinogenicity assessment. In an abstract McCammon et al. (1957) stated that resorcinol diglycidyl ether was carcinogenic in C57/B1 mice treated by intrascapular painting three times a week and in Long-Evans rats exposed to the substance by subcutaneous injection.[21] In a study by Kotin and Falk (1963), 20 C57/B1 mice received a concentration of 0.75 mM resorcinol diglycidyl ether (administration route and duration not reported). One skin tumour was observed after 8 months when 14 mice were still alive.[20] No additional tumours (malignant lymphoma or pulmonary adenoma) were observed in the exposed animals. Van Duuren et al. (1965) exposed 30 female Swiss-Millerton mice to 1% resorcinol diglycidyl ether in benzene by dermal application three times per week for their entire life-span (median survival time: 491 days). No skin tumours (papilloma or squamous epidermoid carcinoma) were observed.[19] The studies published in 1957-1965 have substantial shortcomings in design and reporting and are not adequate for assessment of carcinogenicity. The studies of the NTP were well performed and reported and, therefore, considered suitable for assessing the carcinogenic potential of resorcinol diglycidyl ether. In the NTP studies resorcinol diglycidyl ether was carcinogenic for F344/N rats and B6C3F1 mice of both sexes, causing both benign and malignant neoplasms of the forestomach.

6.2 Human information

No data on carcinogenicity in humans were found.

6.3 Other relevant information

Table 8 Cell transformation studies with resorcinol diglycidyl ether.

Methode	Cell type	Concentration	Results and remarks	(Klimisch score)*	Reference
Transformation	A31-1-13 clone of BALB/c-3T3 cells	*Method*: Tests performed in duplicate *Concentrations*: 0, 2.18, 4.08, 6.26, 9.53 (first trial) 0, 1.36, 2.72, 4.08, 5.44 µM (second trial) *Metabolic activation*: Not used *Controls*: Negative: vehicle; Positive: benzo(a)pyrene *Purity*: unknown *Solvent*: Dissolved in DMSO at a high concentrations and then dispersed in medium supplemented with a non-cytotoxic, nonionic surfactant pluronic F68 (final concentrations max. 0.2% v/v DMSO and 0.25% w/w F68) *Statistical analysis*: (1) ANOVA on $\log_{10}$ transformed data using the F-test, followed by modified Student's t-test (model for unequal or equal variances); Individual treatments were compared with vehicle control by the appropriate unequal variance or equal variance t-statistic	*Outcome*: positive Transformation response (Foci/Vessel; focus type III): 0.348, 3.49 ($p \leq 0.001$), 11.8 ($p \leq 0.001$), 1.51, 0 (1st trial) 0.16, 0.392 ($0.01 < p \leq 0.05$), 0.842 ($0.01 < p \leq 0.05$), 3.45 ($p \leq 0.001$), 3.45 ($p \leq 0.001$) (2nd trial) *Cytotoxicity*: Relative cloning efficiency: 100, 80, 19.4, 0.588, 0% (1st trial), 100, 104, 70.4, 18.9, 2.2% (2nd trial), for control and lowest through highest concentration, respectively	2	Matthews et al., 1993a,b[22,23]

In Table 8 a cell transformation assay was summarised. In both trials of a transformation assay using the A31-1-13 clone of BALB/c-3T3 cells, a statistically significant transformation response was observed.[23]

6.4 Other information on forestomach tumours

A working group of the IARC concluded in 1999 that carcinogens that are DNA reactive and cause forestomach tumours in rodents – even if they only caused tumours at this site – should be evaluated as if they presented a carcinogenic hazard to humans.[7] This conclusion is based on the fact that although humans do not have a forestomach, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. Also, the target

tissues for carcinogens may differ between experimental animals and humans and a forestomach carcinogen in rodents may target a different tissue in humans.

Proctor et al. (2007) reviewed the relevance of rodent forestomach tumours in cancer risk assessment. Substances that cause forestomach tumour through non-genotox mechanisms have typically not been considered relevant for human carcinogenicity because the mode-of-action is specific to the forestomach. Substances that are DNA reactive and cause tumours at multiple sites, in addition to the forestomach, are likely relevant human carcinogens.[24]

6.5 Summary and discussion on carcinogenicity

No data on the carcinogenicity of resorcinol diglycidyl ether in humans are available. In animals, resorcinol diglycidyl ether was carcinogenic for F344/N rats and B6C3F1 mice of both sexes, causing both benign and malignant neoplasms of the forestomach (NTP 1986). Also hepatocellular carcinoma and adenoma in mice were observed; which were not considered to be related to treatment (NTP 1986).[17]

In vitro studies showed that resorcinol diglycidyl ether induced gene mutations in bacteria, and mouse lymphoma cells (*tk* locus) and structural chromosomal aberrations in cultured mammalian cells with and without metabolic activation, which suggests a stochastic genotoxic mechanism. In vivo dose-related positive findings of the micronucleus studies of Shelby et al. (1993) in bone marrow at triplicate intraperitoneal doses of 60,8 mg /kg bw or single intraperitoneal doses of 270 mg/kg bw statistically significant increases in cells with micronuclei were found. [14]

The metabolism study performed by Seiler (1984) showed that resorcinol diglycidyl ether is rapidly inactivated within the body, which might explain why in vitro studies showed clear genotoxic effects whereas not all in vivo results were conclusive. This rapid metabolization to genetically inactive compound and the in vitro results indicating that this substance does not require metabolic activation might also explain why resorcinol diglycidyl ether-induced tumours were observed only at the site of contact (the forestomach) in the oral (gavage) carcinogenicity studies performed by the NTP, because the compound is not distributed to other tissues in significant amounts.[8] Furthermore, the review by Proctor et al. (2007) indicated that chemicals that are DNA reactive and cause tumours at multiple sites, in addition to the forestomach, are likely relevant human carcinogens.[24] Because resorcinol diglycidyl ether has a genotoxic

potential, the Committee considered the forestomach tumours caused by exposure to resorcinol diglycidyl ether as relevant for humans. The Committee further indicates that tumour development at other sites via other routes of exposure cannot be excluded. Based on these findings, the Committee concludes that there is sufficient evidence for carcinogenicity of resorcinol diglycidyl ether in animals.

6.6 Comparison with criteria

No information is available regarding carcinogenicity in humans. Therefore category 1A is not applicable.

Classification in category 1B requires a causal relationship between the substance and an increased incidence of malignant neoplasms in two or more species. Adequate studies on carcinogenicity in experimental animals were available for the oral route. In these studies resorcinol diglycidyl ether was carcinogenic for rats and mice of both sexes, causing benign and malignant neoplasms of the forestomach. The forestomach tumours are considered relevant for humans based on the mutagenicity in vitro of resorcinol diglycidyl ether. According to the CLP criteria, resorcinol diglycidyl ether should, therefore, be classified as “presumed to be as carcinogenic to humans”, which corresponds to classification in category 1B. Supporting evidence is that the substance is mutagenic in vivo and in vitro and acts by a stochastic genotoxic mechanism.

6.7 Conclusions on classification and labeling

The Committee concludes that resorcinol diglycidyl ether is “presumed to be carcinogenic to man”, and recommends classifying this substance in category 1B.

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A	Request for advice
B	The Committee
C	The submission letter (in English)
D	Comments on the public review draft
E	IARC evaluation and conclusion
F	Carcinogenicity classification
G	Classification on mutagenicity
H	Criteria for testing reliability of animal and in vitro studies

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

- R.A. Woutersen, *chairman*
  toxicologic pathologist, TNO, Zeist; professor of translational toxicology, Wageningen UR
- J. Van Benthem
  Genetic toxicologist, RIVM, Bilthoven
- P.J. Boogaard
  toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  emeritus professor of toxicology, Leiden University
- M.J.M. Nivard
  molecular biologist and genetic toxicologist, LUMC, Leiden
- G.M.H. Swaen
  epidemiologist, Maastricht University, Maastricht
- E.J.J. van Zoelen
  professor of cell biology, Radboudumc, Nijmegen
- T.M.M. Coenen, *scientific secretary*
  Health Council of the Netherlands, The Hague

With respect to the data presentation and interpretation, the Committee consulted an additional expert, Mr. J.A.A. Muller, toxicologist from Bureau Reach, National Health Institute for Public Health and the Environment, Bilthoven.

The first draft of the present advisory report was prepared by Dr. M.A.C. Schults and Dr. D. Jonker from TNO by contract with the Ministry of Social Affairs and Employment.

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 (in English)

Subject : Submission of the advisory report *Resorcinol diglycidyl ether*
Your Reference: DGV/BMO/U-932542
Our reference : U-915783/DC/fs/246-D25
Enclosed : 1
Date : February 29, 2016

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to resorcinol diglycidyl ether.

This advisory report is a re-evaluation of an advisory report on the classification as a carcinogenic substance that has earlier been published by the Health Council. The Council is asked for a re-evaluation because the proposed classification differs from the classification that applies in the European Union. In addition, the Council is asked to also propose a classification for mutagenicity. The classifications are based on the European classification system.

The conclusions in the advisory report were drawn by a subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The subcommittee has taken comments into account from a public review, and

included the opinions by the Health Council's Standing Committee on Public Health.

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 J.L. Severens,
Vice President

Annex **D**

Comments on the public review draft

A draft of the present report was released in 2015 for public review. The following organization and persons have commented on the draft document:

- T.J. Lentz, P. Joseph, National Institute for Occupational Safety and Health (NIOSH), USA.

Annex **E**

IARC evaluation and conclusion

Diglycidyl resorcinol ether

Vol.: 36 (1985) (p181-188).[2]

Summary of Data Reported and Evaluation.

Exposure data

Diglycidyl resorcinol ether has been produced since at least 1974. It has only limited application, principally in the aerospace industry.

Experimental data

Diglycidyl resorcinol ether (of technical grade) was tested for carcinogenicity by intragastric intubation in mice of one strain and in rats of one strain. It induced squamous-cell carcinomas and papillomas of the forestomach in animals of both species. In female mice, an increased incidence of hepatocellular tumours was observed. In one experiment in mice, no skin tumour was observed after skin application. Diglycidyl resorcinol ether (technical grade) was mutagenic to bacteria.

Human data

No case report or epidemiological study of the carcinogenicity of diglycidyl resorcinol ether to humans was available to the Working Group.

Evaluation

There is sufficient evidence for the carcinogenicity of a technical grade of diglycidyl resorcinol ether to experimental animals. No data on the carcinogenicity of diglycidyl resorcinol ether to humans were available to the Working Group.

Diglydicyl resorcinol ether

Vol.: 71 (1999) (p1417-1420).[4]

Experimental data

Additional genotoxicity data were available and showed that diglycidyl resorcinol ether (technical grade) was mutagenic at the *tk* locus but not the *hprt* locus of cultured mouse lymphoma cells. It induced chromosomal aberrations in Chinese hamster ovary cells, but did not increase the proportion of micronucleated cells in mouse bone marrow.

Evaluation

No epidemiological data relevant to the carcinogenicity of diglycidyl resorcinol ether were available. There is sufficient evidence for the carcinogenicity of a technical grade of diglycidyl resorcinol ether in experimental animals.

Overall evaluation

Diglycidyl resorcinol ether (technical grade) is possibly carcinogenic to humans (Group 2B).

Annex **F**

Classification on carcinogenicity

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

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category[a]	
		(before 16 December 2008)	(as from 16 December 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

[a] See Section 3.6 (Carcinogenicity) of Regulation No. 1272/2008 of the European Parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances.

* Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[25]

Annex **G**

Classification on mutagenicity

Source: Section 3.5 (Germ cell mutagenicity) of Regulation No. 1272/2008 of the European Parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances.

3.5.1 Definitions and general considerations

3.5.1.1 A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

3.5.1.2 The more general terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

3.5.2 Classification criteria for substances

3.5.2.1 This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from

mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

3.5.2.2 For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

3.5.2 Specific considerations for classification of substances as germ cell mutagens

3.5.2.3.1 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in in vitro tests shall also be considered.

3.5.2.3.2 The system is hazard based, classifying substances on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of substances.

Table 3.5.1 Hazard categories for germ cell mutagens.

Categories		Criteria
CATEGORY 1:		Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
	Category 1A:	The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.
	Category 1B:	The classification in Category 1B is based on: • positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or • positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or • positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

CATEGORY 2:	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: • positive evidence obtained from experiments in mammals and/ or in some cases from in vitro experiments, obtained from: • somatic cell mutagenicity tests in vivo, in mammals; or • other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. *Note*: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

3.5.2.3.3 Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in Regulation (EC) No 440/2008 adopted in accordance with Article 13(3) of Regulation (EC) No 1907/2006 ('Test Method Regulation') such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.4 In vivo heritable germ cell mutagenicity tests, such as:

- rodent dominant lethal mutation test;
- mouse heritable translocation assay.

3.5.2.3.5 In vivo somatic cell mutagenicity tests, such as:

- mammalian bone marrow chromosome aberration test;
- mouse spot test;
- mammalian erythrocyte micronucleus test.

3.5.2.3.6 Mutagenicity/genotoxicity tests in germ cells, such as:

a mutagenicity tests:
   - mammalian spermatogonial chromosome aberration test;
   - spermatid micronucleus assay;

b genotoxicity tests:
   - sister chromatid exchange analysis in spermatogonia;
   - unscheduled DNA synthesis test (UDS) in testicular cells.

3.5.2.3.7 Genotoxicity tests in somatic cells such as:

- liver Unscheduled synthesis test (UDS) in vivo;
- mammalian bone marrow Sister Chromatid Exchanges (SCE);

3.5.2.3.8 In vitro mutagenicity tests such as:

- in vitro mammalian chromosome aberration test;
- in vitro mammalian cell gene mutation test;
- bacterial reverse mutation tests.

3.5.2.3.9 The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the substance compared to the route of human exposure shall also be taken into account.

3.5.3 Classification criteria for mixtures

3.5.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.5.3.1.1 The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2 Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.

	Concentration limits triggering classification of a mixture as:		
Ingredient classified as:	Category 1A mutagen	Category 1B mutagen	Category 2 mutagen
Category 1A mutagen	≥ 0,1 %	-	-
Category 1B mutagen	-	≥ 0,1 %	-
Category 2 mutagen	-	-	≥ 1,0 %

Note. The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.3.2 Classification of mixtures when data are available for the complete mixture.

3.5.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical

analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.5.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles.

3.5.3.3.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.4 Hazard communication

3.5.4.1 Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.3 Label elements of germ cell mutagenicity.

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201, P202, P281	P201, P202, P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

3.5.5 Additional classification considerations

It is increasingly accepted that the process of chemical-induced tumourigenesis in humans and animals involves genetic changes for example in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of substances in somatic and/or germ cells of mammals in vivo may have implications for the potential classification of these substances as carcinogens (see also Carcinogenicity, section 3.6, paragraph 3.6.2.2.6).

Annex **H**

Criteria for testing reliability of animal and in vitro studies

To assess the reliability of animal and in vitro studies, the committee uses the criteria set by Klimisch et al. 1997.[26] A summary of the criteria of the reliability scores is given below. Only studies with a reliability score of 1 or 2 are considered in assessing genotoxicity and carcinogenicity.

Reliability 1 (reliably without restriction)

For example, guideline study (OECD, etc.); comparable to guideline study; test procedure according to national standards (DIN, etc.).

Reliability 2 (reliable with restrictions)

For example, acceptable, well-documented publication/study report which meets basic scientific principles; basic data given: comparable to guidelines/standards; comparable to guideline study with acceptable restrictions.

Reliability 3 (not reliable)

For example, method not validated; documentation insufficient for assessment; does not meet important criteria of today standard methods; relevant methodological deficiencies; unsuitable test system.

Reliability 4 (not assignable)

For example, only short abstract available; only secondary literature (review, tables, books, etc.).

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.

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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?

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